
Ana L. Cardoso[a] and Teresa M. V. D. Pinho e Melo*[a]

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Chemistry based on ring opening of aziridines has been widely studied in organic synthesis. However, it has mainly been centered on ring opening by nucleophiles and on cycloaddition of azomethine ylides generated by carbon–carbon bond cleavage. In recent years, significant effort has been dedicated to study of the participation of aziridines in formal [3+2] cycloadditions, which provide routes for the construction of a wide variety of functionalized five-membered heterocycles. Here we review the most relevant aspects of the reactivities and selectivities of aziridines as masked zwitterionic 1,3-dipoles generated through C–N bond cleavage.

Introduction

Aziridines are valuable strained small heterocycles of interest in preparative organic synthesis. Chemistry based on ring opening of aziridines has been used for an impressive range of synthetic applications.[1] Aziridines 1 (Scheme 1) undergo electrocyclic ring opening upon irradiation or thermolysis to give azomethine ylides 2, via C–C bond cleavage, and these participate in 1,3-dipolar cycloadditions to give five-membered nitrogen heterocycles.[1] In the presence of Lewis acids, on the other hand, aziridines typically bearing electron-withdrawing N-substituents undergo C–N bond cleavage to afford zwitterionic 1,3-dipoles 3 (Scheme 1, or synthetic equivalents), which react with alk-
enes, alkynes, ketones, aldehydes, nitriles, and heterocumulenes to afford formal 1,3-dipolar cycloadducts.[2]

It has also been reported that the nonactivated aziridine 4 (Scheme 2) reacts with acetylenecarboxylates to afford dipolar intermediates 5, followed by intramolecular attack of the carbanion on the aziridine ring to give the formal 1,3-dipolar cycloaddition products 6 through C–N bond cleavage.[3] A sequential S_N2/cycloaddition approach to indolizines 10 starting from nonactivated aziridines has also been developed,[4] as well as the preparation of pyrrole derivatives 11 through reactions between 2-benzoylaziridines and allenoates.[5–7] In each case the main pathway involves a formal [3+2] cycloaddition through aziridine C–N bond cleavage.

2. Formal [3+2] Cycloadditions of Aziridines

2.1 Reactions with Alkenes and Alkynes as Dipolarophiles

The formation of the uncommon zwitterionic 1,3-dipole 13 (Scheme 3), generated from 2-phenyl-N-tosylaziridine (12a) by C–N bond cleavage in a process induced by the addition of a stoichiometric amount of boron trifluoride etherate, was first investigated by Mann and co-workers.[8–11] In contrast with classical 1,3-dipoles, which are internally stabilized by delocalization, the substitution pattern of 13 allows external stabilization by both the aromatic and the tosyl groups.

The reactivity of this zwitterionic intermediate was explored with a variety of non-activated and electron-rich alkenes, affording the corresponding substituted pyrrolidines. The reactions between aziridine 12a and either dihydro-
pyran 14a or tetrahydropyridine 14b each resulted in the formation of only one regioisomer (15a or 15b, respectively) in good yield. However, the products were obtained as 1:1 mixtures of endo and exo cycloadducts. It was later demonstrated that the reaction between 12a and dihydropyran 14a could also be achieved with Cu(OTf)₂ catalysis, leading to a 2:3 mixture of exo and endo bicyclic pyrroline derivatives 15a, although the combined overall yield was lower (45%).[12] The cycloadditions are presumed to occur by a stepwise pathway, as indicated by the reactions with cyclopentene (18a) and with cyclohexene (18b), from which the corresponding cycloadducts 20 are isolated together with the noncyclized derivatives 21 (Scheme 3). Both product types would arise from the initial reactions between the dipolarophiles and zwitterions 13 to afford intermediates 19.

Clearly, the stabilities of the carbocations in the 1,5-zwitterionic intermediates strongly influence the regioselectivities and the yields. Indeed, the reaction between aziridine 12a and olefin 16, containing a geminally disubstituted alkene group, under the same reaction conditions led only to the formation of spiropyrrolidine 17 and no elimination products were observed (Scheme 3). Heterocyclization therefore seems to be favoured over elimination if the lifetime of the 1,5-zwitterionic intermediate is long enough.[8–12]

The synthesis of bicyclic proline analogues through intramolecular formal [3+2] cycloadditions involving aziridines and allylsilanes was reported by Bergmeir and co-workers.[13] Enantiomeric aziridines 22 and 26 (Scheme 4) reacted in the presence of BF₃·OEt₂ (15 mol-%) to afford the corresponding cycloadducts. The reactions of aziridines 22a and 26a were diastereoselective, giving the cis-bicycles 23a and 27a, respectively, in good yields. Along with these cycloadducts, olefins 25a and 29a were also isolated in low yields. Cyclization of aziridines 22b and 26b under the same reaction conditions resulted in a different outcome, with the more flexible nature of the precursors allowing the formation of both cis and trans cycloadducts in addition to the formation of the corresponding olefins (25b and 29b). In both cases the trans cycloadducts (24b and 28b) were the major products.

The bicyclic heterocycles were used to prepare proline analogues by oxidation of the silyl group to the acid, followed by deprotection of the nitrogen as illustrated by the example shown in Scheme 5.

Scheme 5. Synthesis of proline analogue 30.

Yadav et al. demonstrated that Sc(OTf)₃ can also be used as Lewis acid to generate zwitterionic 1,3-dipoles from N-tosylarylaziridines.[14] When the reactions were carried out in the presence of cyclic enol ethers the corresponding pyrroline derivatives were obtained in high yields and with high regioselectivities (Scheme 6). Arylaziridines 12a-c thus reacted smoothly with 2,3-dihydrofuran (32) and 3,4-dihydro-2H-pyran (14a) in the presence of catalytic amounts of Sc(OTf)₃ (3 mol-%) to give the corresponding cycloadducts 27a-c and 27d-e/15a, respectively, in good yields as 1:1 mixtures of diastereoisomers (Scheme 6). These Sc(OTf)₃-mediated [3+2] cycloadditions can also occur with cyclopentene and 1H-indene, to afford the corresponding cycloadducts in good yields.

The synthetic potential of this methodology is demonstrated by its application to the total synthesis of the medicinally relevant physostigmine, in which the key step involves the reaction between 1,3-dimethylindole (35) and N-(benzoylcarbonyl)aziridine (34) in the presence of Sc(OTf)₃ (Scheme 7).[15] Several Lewis acids were tested, but only Sc(OTf)₃, EtAlCl₂ and Et₂AlCl were found to promote the reaction, albeit with low yields. It was observed that the
Scheme 6. Sc(OTf)₃-catalysed reactions between N-tosylaziridines 12 and cyclic enol ethers.

use of chlorotrimethylsilane in combination with Sc(OTf)₃ resulted in a significant enhancement of the yield. The desired pyrrolo[2,3-b]indole 36 was thus obtained in 90% yield and converted into physostigmine (37) in two steps.

Scheme 7. Synthesis of physostigmine from N-(benzyloxycarbonyl)aziridine.

There are several examples of alkynes acting as highly efficient dipolarophiles in formal [3+2] cycloadditions with aziridines in the presence of catalytic quantities of various Lewis acids.[16,17] A variety of arylalkynes (e.g., 39a–e, Scheme 8) were employed in FeCl₃-catalysed reactions with arylaziridines (e.g., 12a) to afford the corresponding functionalized 2-pyrrolines in moderate to high yields.[16] The reactions were more efficient with alkynes bearing electron-donating substituents on their aromatic rings (e.g., 39c leading to 2-pyrroline 41c in 82% yield), whereas with (p-nitrophenyl)acetylene or pyridylacetylene no reaction was observed. The authors observed that aziridines without a tosyl group (such as aziridines 42) or alkylaziridines (e.g., 43) did not react with phenylacetylene in the presence of FeCl₃. These results confirmed the requirement for external stabilization of the zwitterionic 1,3-dipole 38 generated in situ in order to participate in formal cycloadditions. Dipole 38 is attacked by the arylacetylenes to generate aryl-substituted alkenyl cations 40, followed by intramolecular cyclization to give the desired functionalized 2-pyrrolines 41.

Scheme 8. Formal [3+2] cycloadditions of arylaziridine 12a with alkynes, in the presence of catalytic amounts of FeCl₃.

Wender and co-workers reported Ag-catalysed reactions of a wide range of nonsymmetrical alkyl- and arylalkynes in combination with aziridines (e.g., 12) to afford various substituted 2-pyrrolines with complete regioselectivity (Scheme 9).[17] The reactions tolerate the presence of a methyl ether, a pivaloic ester (46), a cyclopropyl or a cyclohexenyl (48) group in the alkyne. In fact, high chemoselectivity is observed in the reaction between aziridine 12a and 1-ethylnylcyclohex-1-ene (48). Furthermore, N-nosylphenylaziridine also participates efficiently in the reaction with phenylacetylene, leading to the corresponding N-nosyl cycladduct in high yield, thus providing options for easier deprotection. Brønsted acids, such as TfOH (5 mol-%), can also be used as catalysts in this process, offering a metal-free alternative.

Interestingly, the authors demonstrated that the method is not limited to arylaziridines. Aziridine 50 (Scheme 10), with an α-tert-butyldiphenylsilyl group as a cation-stabilizing system, reacts with phenylacetylene in the presence of AgSbF₆ to form 52 in 84% yield.[17]

Formal [3+2] cycloadditions of alkynyltungsten complexes with tethered aziridines in the presence of BF₃·OEt₂ have been reported.[18] The reactions were stereoselective, affording bicyclic tungsten-enamines (e.g., 55, Scheme 11), which were efficiently converted into cis-fused bicyclic lactams (e.g., 56) by decomplexation with I₂, followed by hydrolysis. Of several Lewis acids, BF₃·OEt₂ was found to be the most efficient, whereas AlCl₃ and TiCl₄ gave the products in low yields (22–23%). Cyclization of complex 53 in the presence of BF₃·OEt₂ (50 mol-%) thus gave bicyclic tungsten-enamine 55 in 69% yield. This process is believed to involve the cyclization of tungsten-vinylidenonium interme-
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Scheme 9. Ag-catalysed reactions between arylaziridine 12a and nonsymmetrical alkyl- and arylalkynes to afford substituted 2-pyrrolines.

Scheme 10. Reaction between aziridine 50 and phenylacetylene in the presence of AgSbF6.

diate 54, arising from opening of the aziridine ring by SN2 attack of the tungsten fragment. Oxidative demetallation of 55 afforded cis-fused bicyclic lactam 56 and CpW(CO)3I in 88% and 94% yields, respectively (Scheme 11). Formal [3+2] cycloaddition is also applicable to the synthesis of tungsten-enamines containing five- and six-membered oxacyclic rings and five- and six-membered carbocyclic rings, all of which can be converted into the corresponding bicyclic lactams in high yields.

A disadvantage of this method is that it is limited to trans-aziridine derivatives. All attempts to promote the cyclization with cis-aziridine derivatives failed, leading to a different outcome. Treatment of cis-aziridine derivative 57 (Scheme 12) with BF3·OEt2 (50 mol-%) led to the formation of the alcohol 60 in 82% yield, presumably as a result of initial C–O ether bond cleavage. These observations can be interpreted by considering that steric hindrance due to the positioning of the propyl group would strongly disfavour the tungsten-alkynyl group SN2 attack at the aziridine ring.[18]


Scheme 12. Treatment of cis-aziridine derivative 57 with BF3·OEt2 resulting in the formation of alcohol 60.

Shipman and co-workers recently reported the first examples of Lewis-acid-promoted cycloadditions of methyleneaziridines.[19] The intramolecular BF3·OEt2-mediated reactions led to the formation of cis-octahydrocyclopenta[e]pyrroles (e.g., 62 and 63, Scheme 13) and 2,4,5,6-tetrahydrocyclopenta[e]pyrroles (e.g., 67) through reactions with tethered alkenes and alkynes, respectively. Carrying out the intramolecular formal cycloaddition of (E)-61 (Scheme 13, a) in the presence of excess BF3·OEt2 (150 mol-%) in dichloromethane at 30 °C, followed by slow warming to room temperature over 15 h, led to the formation of iminium ion 64 as essentially a single diastereoisomer. Further reductive workup provided the separated diastereoisomers 62 and 63 in a combined yield of 48%. Aziridine (Z)-65 (Scheme 13, b), bearing a single methyl group on the exocyclic double bond, reacted under the same conditions to afford pyrrole 67 in 38% yield, through spontaneous isomerisation of bis-enamine 66. Experimental evidence suggests that these reactions most probably proceed in an asynchronous manner, with the major reaction pathway involving planar 2-aminoallyl cations.[19]

The stereocontrolled synthesis of substituted pyrrolidines (e.g., 70 and 71, Scheme 14) and its application in the formal synthesis of (–)-α-kainic acid (72) has also been reported.[20] The key step in this synthesis involves the reaction of methyl vinyl ketone (69) with enantiomerically pure vinylaziridine 68 under palladium catalysis conditions. It
was observed that addition of $n$Bu$_4$NCl (1 equiv.) to the reaction medium resulted in higher yields of products, due to the increased reactivity of the Pd complex formed in situ. Of the several phosphanes and solvents tested, the most sterically hindered ($o$-tolyl)$_3$P and a pentane/TBuOMe (TBME) mixture were found to lead to the highest diastereoselectivity. Aziridine 68 reacted with methyl vinyl ketone (69) under the optimized reaction conditions to give a 93:7 diastereoisomeric mixture of pyrrolidines 70 and 71 in moderate yield (66%). The single pure diastereoisomer 70 was further converted into (-)-$\alpha$-kainic acid (72) in six steps.[20]

2.2 Reactions with Nitriles as Dipolarophiles

Formal [3+2] cycloadditions between N-tosylaziridines and nitriles involving C–N bond breaking are especially useful for the preparation of substituted imidazolines, and so tremendous efforts have been devoted to devising catalytic versions for this reaction. Several Lewis acids, including BF$_3$·OEt$_2$,[21–26,28] Cu(OTf)$_2$,[12] ZnX$_2$ (X = Cl, Br, I),[27] Zn(OTf)$_2$,[28] Sc(OTf)$_3$,[29] and Bi(OTf)$_3$,[30] have been employed as catalysts in reactions of this type.

Hiyama and co-workers reported reactions between acetonitrile or benzonitrile and N-alkoxycarbonylaziridines (e.g., 73, Scheme 15, a) in the presence of boron trifluoride etherate for the preparation of imidazolines in good yields.[21] These BF$_3$·OEt$_2$-mediated transformations required harsh conditions such as high temperatures and use of the nitriles as solvents and were limited to acetonitrile or benzonitrile. It has been proposed that the reported methods proceed in a Ritter fashion by an initial SN2-type aziridine ring-opening to give zwitterionic intermediates (e.g., 74).

A similar reaction was also reported by Zwanenburg and his group (Scheme 15, b).[22] The observed regioselectivity resulted from exclusive SN2-type attack at C-3 of the aziridines 77, also leading to inversion of configuration, induced by the cis stereochemical relationship between the hexyl and ester groups. The imidazolines thus obtained were very unstable and easily hydrolysed into the corresponding 1,2-diamine derivatives (e.g., 76 and 79).

A different outcome was observed by Tomasini and co-workers in the BF$_3$·OEt$_2$-catalysed reaction between N-benzoylaziridine 80 and acetonitrile (Scheme 15, c). In this case, an 89:11 regioisomeric mixture of the cis-4,5-dihydro-1H-imidazoles rac-81a and rac-81b was obtained.[23]

Some of the above limitations were successfully overcome by Singh and co-workers, who reported the formal [3+2] cycloadditions of N-tosylarylaziridines (e.g., 12a) with a range of nitriles, in the presence of BF$_3$·OEt$_2$ or Et$_3$OBF$_4$, at room temperature and with very short reaction times (Scheme 16).[24] Good yield of imidazolines (e.g., 83a, 72%) were thus obtained with aliphatic nitriles, whereas aryl nitriles and chloro- or bromo-substituted acetonitriles gave the cyclized products only in moderate yields. The method was extended to a variety of N-tosylarylaziridines with acetonitrile and benzonitrile, although the corresponding imidazoline derivatives were formed only in modest yields. Lewis acids such as Zn(OTf)$_2$[28] and Cu(OTf)$_2$[12] have also been reported to promote this type of reaction efficiently.

The BF$_3$·OEt$_2$-mediated reaction between chiral aziridine ($R$)-(-)12a and benzonitrile gave the racemic product 85 (Scheme 17), consistently with the mechanistic proposal involving the formation of highly stabilized benzyl carbocation 84, which induces the observed regioselectivity.[24]
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Scheme 15. Formal [3+2] cycloadditions between aziridines and nitriles in the presence of BF₃·OEt₂.

Scheme 16. Formal [3+2] cycloadditions between N-tosylarylaziridine 12a and a range of nitriles in the presence of BF₃·OEt₂.

Scheme 17. The BF₃·OEt₂-mediated reaction between chiral aziridine R⁻(-)-12a and benzonitrile.

Yadav and co-workers cleverly used tert-butyl diphenylsilylmethyl-substituted (TBDPS-substituted) aziridines 50 in formal [3+2] cycloaddition with nitriles in the presence of BF₃·OEt₂. The presence of silicon stabilizes the α-carbon and allows the formation of the stable zwitterionic intermediates 51 (Scheme 18), thus providing an alternative to the typical aryl stabilizing groups.[25] Furthermore, because the silylmethyl moiety can be considered a masked hydroxymethyl substituent, this methodology offers the opportunity to carry out subsequent functional group transformations. Cycloadditions between aziridine 50a and both aromatic and aliphatic nitriles gave the 2-imidazolines in high yields (e.g., 86a-c). The reactions are stereospecific: aziridine cis-50b reacted with acetonitrile to form the cis cycloadduct 86e exclusively, whereas trans-50b gave mainly the trans cycloadduct 86f. In the case of trans-50b, however, it was observed that stereoselectivity was greatly affected by the temperature. With an increase in the reaction temperature from –78 °C to 25 °C, the cis cycloadduct 86f became the major product (25:75 to 56:44, cis/trans).

Enantiopure 2-(1-aminoalkyl)aziridines (e.g., 87, Scheme 19) react with nitriles in a Ritter fashion in the presence of BF₃·OEt₂ to afford enantiopure tetrasubstituted imidazolines (e.g., 92) with total regio- and stereoselectivity.[26] The reactions can be performed with a variety of amino aziridines (derived from leucine, phenylalanine and serine) and nitriles (aromatic, aliphatic and alkoxyl-functionalized), allowing the preparation of a range of functionalized imidazolines in moderate to high yields. The observed stereoselectivity was explained by considering that the Lewis acid selectively coordinates to the aziridine nitrogen, thus promoting the intramolecular attack of the dibenzyl amino group at C-2. This results in aziridine ring opening with consequent inversion of configuration to give the reactive aziridinium salt 89. Attack of the nitrile at C-3 of this intermediate 89 leads to cationic intermediate 90 with inver-
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Scheme 18. Formal [3+2] cycloadditions between aziridines 50 and nitriles in the presence of BF$_3$·OEt$_2$.

N-Cyclization of 90, followed by debenzylation promoted by a second molecule of nitrile, affords the corresponding 2-imidazolines 92 and intermediates 93, which after hydrolysis give the corresponding N-benzylamides 94.

Formal [3+2] cycloadditions between N-tosylarylaziridines and nitriles under solvent-free conditions have also been reported. Several Lewis acids such as Dy(OTf)$_3$, Ag(OTf), In(OTf)$_3$, Sc(OTf)$_3$, Yb(OTf)$_3$ and Zn(OTf)$_2$ were tested in catalytic amounts, with the best result being achieved with Sc(OTf)$_3$. The Sc(OTf)$_3$-catalysed reactions between N-tosylarylaziridines 12a–c and aliphatic and aromatic nitriles, under solvent-free conditions in air, thus led to the formation of imidazolines 98 in good yields (Scheme 20). It is suggested that the reactions proceed via cationic intermediates 96 rather than stable benzylic carbocation intermediates 97. This was supported by the observation that the reaction between chiral (R)-(−)-12a and acetonitrile under the same conditions afforded a nonracemic imidazoline. Singh and his group demonstrated that solvent-free reactions of this type can also be achieved with Zn(OTf)$_2$ catalysis, although the corresponding imidazolines were obtained in lower yields.[28]

The aziridino-cyclohexane 43 undergoes Cu(OTf)$_2$-mediated cycloadditions with nitriles to yield bicyclic imidazolines 100 (Scheme 21).[12] Formation of cycloadducts 100 with trans ring junctions suggests that the reactions proceed through an SN2-type pathway. This method can also be applied to N-tosyl-2-alkylaziridines 101 (Scheme 22), which react with nitriles in a regioselective fashion under Cu(OTf)$_2$ catalysis conditions to afford products 102 as the major cycloadducts, along with 103 as the minor regioisomers.[13] In fact, with N-tosyl-2-octylaziridine (101b) the corresponding cycloadducts 102c and 102d, resulting from the reactions with acetonitrile and benzonitrile, respectively, were isolated as single products. In this case, the formation of zwitterionic 1,3-dipole intermediates was also ruled out by the observation that enan-
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Scheme 21. Cu(OTf)2-mediated cycloadditions between N-tosylaziridino-fused cyclohexane 43 and nitriles.

titomerically pure (R)-2-phenyl-1-(toluene-4-sulfonyl)aziridine reacted with nitriles to give nonracemic imidazolines.


More recently, Bi(OTf)3-promoted [3+2] cycloadditions between substituted N-tosylaziridines 12 and a variety of nitriles to afford the corresponding imidazolines (e.g., 104a–d, Scheme 23) in good to excellent yields were described.30 In reactions with acetonitrile, aziridines bearing electron-withdrawing groups gave better results than those with electron-donating groups (e.g., 104e and 104g vs. 104c). With benzonitrile, somewhat lower yields were obtained with aziridines possessing electron-donating groups (e.g., 104e vs. 104d). This method was also efficiently applied to aromatic aziridines with condensed rings.

2.3 Reactions with Carbonyl Groups as Dipolarophiles

Traditional methods for the preparation of 1,3-oxazolidine derivatives start from 1,2-amino alcohols and carbonyl substrates and usually require high temperatures, have limited scope and can lead to many side products. Although Lewis-acid-mediated [3+2] cycloadditions between aziridines and carbonyl groups offer a more attractive strategy for the construction of these heterocycles, there are only a few reports on reactions of this type, with use of BF3·OEt2,25 Cu(OTf)2,12 Zn(OTf)2,28 Sc(OTf)3,31 and AgSbF6,32 as catalysts.

tert-Butylphenylsilylmethyl-substituted aziridines 50 can also participate in BF3·OEt2-mediated [3+2] cycloadditions with carbonyl species, via the stable zwitterionic intermediate 51 (see Scheme 18).25 The reactions are very fast under mild conditions and both aromatic and aliphatic carbonyl compounds react with aziridines 50 to generate the desired products in good yields (e.g., 106, Scheme 24).

The reactions are diastereoselective: aziridine cis-50b reacted at low temperature with propanal to form predominantly the cis cycloadduct 107a, whereas trans-50b gave mainly the trans cycloadduct 107b. Once again, the stereoselectivity outcomes of these reactions are greatly affected by the temperature. In the reaction of trans-50b, raising the reaction temperature from –78 °C to 25 °C resulted in increased formation of the cis cycloadduct 107b (from 20:80 to 47:53, cis/trans).

Scheme 23. Bi(OTf)3-promoted formal [3+2] cycloadditions between N-tosylaziridines 12 and nitriles.

Almost simultaneously, two different groups reported formal [3+2] cycloadditions between 2-aryl-N-tosylaziridines and carbonyl compounds in the presence of Zn(OTf)$_2$\cite{28} or Cu(OTf)$_2$\cite{12} to afford a range of oxazolidines (e.g., 109a–h, Scheme 25) in moderate to good yields. Under Zn(OTf)$_2$ catalysis conditions 2-phenyl-N-tosylaziridine reacted more rapidly with aliphatic symmetrical ketones (e.g., 109a–b, 30 min) than with aliphatic and aromatic aldehydes (e.g., 109c–d, 4 h, Scheme 25). The reaction between chiral (R)-2-phenyl-N-tosylaziridine and cyclohexanone under the same reaction conditions resulted in the formation of the corresponding racemic oxazolidines, indicating that in this case the reaction proceeds via a benzyl carbocation intermediate. Cu(OTf)$_2$-mediated reactions between 2-aryl-N-tosylaziridines 12 and carbonyl species proceeded very smoothly and the corresponding substituted oxazolidines (e.g., 109e–h) were obtained in good yields in very short periods of time (5 min) (Scheme 25).\cite{12} The reactions were found to be highly diastereoselective when aldehydes were used, affording mainly cis-1,3-oxazolidines (e.g., 109f and 109h).

Scheme 25. Formal [3+2] cycloadditions between 2-aryl-N-tosylaziridines 12 and carbonyl compounds in the presence of Zn(OTf)$_2$ or Cu(OTf)$_2$.

This method was extended to cycloadditions between enantiomerically pure (R)-2-phenyl-N-tosylaziridine (12a) and several aliphatic and aromatic carbonyl compounds; in all cases non-racemic 1,3-oxazolidines (e.g., 110b–d) were obtained in good yields with moderate to good ee values.\cite{12} This observation is an indication that these Cu(OTf)$_2$-mediated cycloadditions proceed by an SN$_2$-type pathway. The reactions with aldehydes performed at 0 °C showed high diastereoselectivity in most cases (e.g., 110d–e). In fact, when (R)-12a reacted with benzaldehyde, cycloadduct 110e was formed as a single diastereoisomer (dr > 99% cis/trans), although with moderate ee (62%, Scheme 26). Nevertheless, the cis/trans selectivity was found to depend strongly on the aldehyde and the reaction conditions, especially the temperature. The reduced enantioselectivity observed in all cases was attributed to partial racemization of the starting aziridine (R)-12a before the nucleophilic ring opening step. Furthermore, the observed preferred inversion of stereochemistry supports the evidence for an SN$_2$-type mechanism. 1,3-Oxazolidines 110 could be transformed into the corresponding non-racemic 1,2-amino alcohols 111 in quantitative yields, although with slightly decreased enantioselectivity in relation to the starting oxazolines.

Scheme 26. Reactions between enantiomerically pure (R)-2-phenyl-N-tosylaziridine (12a) and several carbonyl compounds with Cu(OTf)$_2$ catalysis.

Chiral disubstituted N-tosylaziridines 112 underwent Zn(OTf)$_2$-mediated cycloadditions with cyclohexanone to afford spirooxazolidines 113 and 114 (Scheme 27) with excellent diastereoselectivities and in high yields.\cite{28} The formation of isomers cis-113 as the major diastereoisomers results from attack of the carbonyl oxygen on the benzylic carbon atom from the less hindered side (i.e., away from the methyl group).

Scheme 27. Zn(OTf)$_2$-mediated cycloadditions between chiral disubstituted N-tosylaziridines 112 and cyclohexanone.

Nguyen and co-workers described an efficient and general Sc(OTf)$_3$-catalysed synthesis of 5-alkyl-1,3-oxazolidines from 2-alkyl-N-tosylaziridines (e.g., 115, Scheme 28) with either aldehydes or ketones.\cite{31} 2-Methyl-N-tosylaziridine...
(115) reacted with several aldehydes in the presence of catalytic Sc(OTf)$_3$ to form a wide range of 5-alkyl-1,3-oxazolidines (e.g., 117a–g) with moderate regioselectivity. Unlike those of typical 2-aryl groups, the weak electronic effect of the methyl group at C-2 of aziridine 115 does not favour regioselectivity, and mixtures of the two isomers were always obtained. The best results were achieved in reactions with 2-furaldehyde (116f), m-methoxybenzaldehyde (116e) and m-hydroxybenzaldehyde (116g). It is suggested that the higher regioselectivities observed in these cases were the result of coordination of these substrates to the (OTf)$_2$Sc-(2-methylaziridine) intermediate through the secondary sites of the aldehydes (furyl, methoxy, and hydroxy groups, respectively). With non-bulky aldehydes 1:1 mixtures of two diastereoisomeric products were obtained (e.g., 117a, 117b and 117d). It was observed that the diastereoisomeric ratios start out high and degrade over time. Evidence of partial racemization in the reaction medium comes from the fact that a sample of cis-enriched 117d (8:5:1, cis/trans) was readily isomerized to a 1:1 mixture (cis/trans) within 15 min in the presence of Sc(OTf)$_3$. Aziridine 115 also reacts both with acyclic aliphatic ketones (e.g., 108a and 108b) and with cyclohexanone to afford the corresponding 2,2-disubstituted 1,3-oxazolidines (e.g., 108a and 108b) in good yields, although requiring longer reaction times (Scheme 28).[31]

Electron-deficient aldehydes generally afforded the target cycloadducts in better yields than electron-rich benzaldehydes (e.g., 120d vs. 120c), whereas sterically demanding benzaldehydes required longer reaction times (e.g., 120e, 23 h). This method could also be applied to linear and branched aliphatic aldehydes (e.g., 120g), naphthaldehydes (e.g., 120f), heteroaromatic aldehydes and α,β-unsaturated aldehydes. A major disadvantage of this methodology is that it is limited to aldehydes; all attempts to promote AgSbF$_6$-mediated cycloadditions of aziridine 119 with ketones failed. The exclusive formation of a single isomer in each of the reactions is attributed to the powerful electronic and steric effect of the CF$_3$ group at C-2 of aziridine 119 in relation to those of 2-aryl or 2-alkyl groups. As for the observed cis stereoselectivity, it can be explained by considering that it avoids the severe steric repulsion between the bulky tosyl group and the two substituents at the carbon on both sides.

Scheme 29. AgSbF$_6$-promoted cycloadditions between 2-trifluoromethyl-N-tosylaziridine and several aldehydes.

2.4 Reactions with Heterocumulenes as Dipolarophiles

Oxazolidinones are an important class of heterocyclic compounds showing a large range of application as chiral auxiliaries, intermediates in organic synthesis and building blocks for the synthesis of biologically active compounds. During the last decade the development of highly efficient methods for chemical fixation of CO$_2$ and its efficient utilization as a C1 building block has been attracting great interest in organic synthesis and in the chemical industry. Of the various strategies investigated so far, the coupling of CO$_2$ with aziridines to form oxazolidinones has emerged as an attractive and efficient synthetic methodology for chemical fixation of CO$_2$. In this regard, the use of a variety of catalysts such as alkali metal halides,[33–38] (tetraalkylammonium halide systems,[34] DBN,[37] phenol/DMAP,[39] iodine,[40–42] naturally occurring amino acids,[43] (salen)-Cr$_3$[44] DMAP,[44] zirconyl chloride,[45] quaternary-ammonium-functionalized polyethylene glycol,[46] polystyrene-supported amino acids,[47] polyethylene-glycol-functionalized phosphonium salts,[48] and ionic liquids (ILs)[49,50]...
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has been reported. An electrochemical procedure has also been described.[51] More recently, catalyst-free cycloadDITIONS of aziridines and carbon dioxide have also been reported.[52]

Cycloaddition of methylaziridine (121, Scheme 30, a) with carbon dioxide was successfully catalysed by alkali metal halides or tetraalkylammonium halides at atmospheric pressure and room temperature to afford the corresponding 2-oxazolidinones (e.g., 122) regioselectively.[34] The lithium-halide-catalysed reaction of aziridine 121 with CS2 gave the target five-membered cyclic dithiourea 123 regioselectively. The catalyst efficiency in these reactions was largely dependent on the counter anion, with the best results being achieved with bromide.[34] 2-Aryl-N-tosylaziridines 121 were found to react with carbon dioxide under lithium bromide catalysis conditions at 100 °C under atmospheric pressure to give the substituted oxazolidinones 126 in good yield (Scheme 30, b).[35] It was observed that the presence of an electron-withdrawing group in the para-position of the aromatic substituent leads to a decreased reactivity (e.g., 126b). The observed regioselectivity results from exclusive attack of bromide anion at C-3 of the aziridine to form the anionic intermediate 124 through a ring opening reaction. Reaction with CO2 gives intermediate 125, which undergoes cyclization leading to the desired products 126 (Scheme 30, b).

Scheme 30. Formal [3+2] cycloadditions between aziridines and CO2 or CS2 catalysed by alkali metal halides or tetraalkylammonium halides.

Different outcomes were observed by Pinhas and co-workers in cycloadditions between unactivated aziridines (e.g., 127, Scheme 31) and CO2 catalysed by alkali metal halides.[33,37] The regioselectivities of the lithium-iodide-mediated reactions between aziridines 127 and CO2 were heavily dependent on the substituents on the aziridines.[33] When both substituents were alkyl groups the corresponding 4-substituted oxazolidinones (e.g., 128a, 128b) were obtained as 1:2 mixtures of regioisomers, with the major isomers being the 4-substituted derivatives. The isomeric ratios of these reactions were significantly improved by the addition of hexamethylphosphoramide (HMPA), a potent lithium-complexing agent, as a co-solvent (e.g., 128a, isomer ratio 1:2 to 3:97). In contrast, with N-benzyl-2-phenylaziridine (42b) the reaction almost exclusively afforded the 5-substituted adduct 128c (isomeric ratio > 99:1), whereas with N-phenylaziridines 127c and 127d no reaction at all was detected (Scheme 31).

Scheme 31. Cycloadditions between unactivated aziridines and CO2 catalysed by alkali metal halides.

Unactivated 2-methylaziridine 127a can also be converted into the corresponding oxazolidinone 128a under ammonium iodide catalysis conditions (Scheme 31).[37] This process requires a low pressure of carbon dioxide (4 atm), a low temperature, no co-solvent and a short reaction time. When the reaction was carried out at room temperature for 40 min, oxazolidinone 128a was obtained in high yield (96%) and with good regioselectivity (isomeric ratio 9:91). The major 4-substituted isomer was the result of the insertion of CO2 into the less substituted C–N bond.

Nguyen and co-workers demonstrated that the coupling of CO2 and unactivated aziridines can also be efficiently achieved with a (Salen)chromium(III)/DMAM catalyst system.[44] This catalyst system showed high activity for a wide range of N-aryl- and N-alkylaziridines, affording the 5-substituted oxazolinones 130 selectively in high yields (Scheme 32, a). It was observed that increasing steric hindrance of the N-substituent leads to a decrease in reaction rate. This is consistent with the mechanistic proposal, which involves the coordination of the aziridine to the (Salen)Cr metal centre before the nucleophilic ring-opening by the Lewis base co-catalyst at the more substituted...
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carbon. Bulky aziridines would therefore be expected to coordinate poorly, leading to longer reaction times (e.g., 130f, reaction time 120 h).

![Scheme 32](image)

Scheme 32. Coupling of CO₂ with unactivated aziridines in the presence: a) of a (Salen)chromium(III)/DMAM catalyst system, or b) of an organic Lewis acid (p-methoxyphenol)/Lewis base (DMAP) co-catalyst system.

Fang and co-workers carried out computational studies, using the experimental results of Pinhas[33] and Nguyen[44] as a guide, to explain the reaction mechanisms and regioselectivity associated with the ring-opening conversions of alkyl-substituted aziridines to oxazolidinones in the presence of CO₂ and LiI.[36] They found the presence of both I⁻ and Li⁺ to be necessary for the correct modelling of the reaction. The computational studies suggest the formation of a complex composed of one molecule each of aziridine and carbon dioxide, together with I⁻ and Li⁺, prior to the ring-opening of the aziridine. It was also demonstrated that the regioselectivity was greatly dependent on aziridine ring-carbon substitution. Monophenyl substitution led to the formation of a single product resulting from the breaking of the more highly substituted C–N bond. In contrast, when the aziridine carbon substituent was a methyl group the three-membered heterocycle underwent ring-opening preferentially through the less substituted carbon-nitrogen bond.

An efficient system for CO₂ incorporation into aziridines co-catalysed by an organic Lewis acid (p-methoxyphenol) and a Lewis base (4-dimethylaminopyridine, DMAP) without any metal catalyst has also been reported.[39] Aziridines 131a–d (Scheme 32, b) react with CO₂ in the presence of this catalytic system to give the corresponding 4-substituted oxazolidinones 132a–d selectively in moderate to good yields. A different outcome was observed with aziridine 42a, with a phenyl group at the 2-position, with which a 1:1 isomeric mixture of the 4-substituted and 5-substituted oxazolidinones 132e was obtained.[39]

More recently, N-functionalized 2-oxazolidinones (e.g., 136a–e, Scheme 33) were efficiently prepared through the reactions between aziridines 133a–c and CO₂ at atmospheric pressure in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as catalyst and LiI as an additive.[38] Reactions carried out in the absence of DBN resulted in lower yields, which suggests that the organocatalyst must be involved in the cycle of CO₂ fixation. A mechanistic proposal involves CO₂ fixation by DBN to afford intermediate 138 (Scheme 33), which then reacts with aziridines 133 to generate 134. Ring-opening of aziridinium compounds 134 promoted by LiI followed by intramolecular ring closure gives the desired products 136 in good yields.

High regioselectivity was observed in carbon dioxide fixation by 2-substituted aziridines 42a and 121 to afford 2-oxazolidinones 139 and 140 (Scheme 34) in the presence of iodine under supercritical CO₂ conditions.[41] The reaction of aziridine 121 produced only 4-methyloxazolidin-2-one (139), whereas 5-phenyloxazolidin-2-one (140) was formed regiospecifically when aziridine 42a was used under the same reaction conditions. The observed regioselectivity can be explained in terms of two different mechanisms – Pathway A and Pathway B – for the formation of oxazolidinones 139 and 140, respectively.

Aziridine 121 reacts with carbon dioxide directly at the nitrogen atom to give carbamic acid 141. Attack of 141 at the β-carbon atom of a second aziridine molecule affords 142, which leads to oxazolidinone 139 by intramolecular ring closure (Scheme 34, Pathway A).
In the case of aziridine 42a, with a phenyl group at the 2-position, the exclusive formation of 140 could be attributed to the generation of zwitterionic 1,3-dipole 143, which would then react with scCO$_2$ to afford 144 through Pathway B.

The yield of 139 increases greatly with increasing pressure, reaching its maximum (66%) at the near critical pressure of 11.8 MPa. This is likely to be the result of the increase in CO$_2$ density leading to a shift in the equilibrium in favour of the generation of 142, resulting in the formation of oxazolidinone 139 in higher yield (Scheme 34, Pathway A). In contrast, the yield of 140 decreases with increasing pressures (76% at 2.1 MPa vs. 33% at 11.8 MPa), corroborating the proposed mechanism because the formation of zwitterionic 1,3-dipole 143 would not be expected to be favoured under the less polar supercritical conditions (Scheme 34, Pathway B).

Many of the previously described methodologies require the use of toxic organic solvents, high reaction temperatures and co-catalysts to achieve higher yields and in some cases offer a limited substrate scope. In the last few years, significant advances have been made in this area with the development of more efficient, environmentally benign and recyclable catalysts for the synthesis of oxazolidinones from CO$_2$ and aziridines under very mild reaction conditions. Liang-Nian He’s group has extensively investigated transformations of this type and reported several efficient and recyclable catalysts for these reactions under solvent-free conditions. Formal cycloadditions between aziridines 42, 129 and 145 and CO$_2$ with zirconyl chloride catalysis under solvent-free conditions afforded a variety of 5-aryloxazolidin-2-ones with high chemo- and regioselectivities and in high yields (Scheme 35, Method A). This methodology was successfully applied to several N-alkyl-2-phenylaziridines, although increasing steric hindrance of the N-substituent led to lower activities and the requirement for longer reaction times to provide the corresponding oxazolidinones in good yields [e.g., 146a (2 h, 86%) vs. 130f (19 h, 71%)]. The regioselectivities were heavily dependent on the nature of the group at the 2-position of aziridine. When R$^2$ is an aryl group, formation of the 5-substituted isomer is favoured (e.g., 146a, 146b, 130d, 130f and 128c) whereas if...
R² is an alkyl group the main cycloadduct formed is the 4-substituted derivative (e.g., 146c, isomeric ratio 3:97) (Scheme 35, Method A). A significant advantage of this approach is the fact that the catalyst can easily be recovered from the reaction mixture simply by filtration and can be reused over five times without significant loss of activity. Alternatively, the coupling of aziridines 42, 129 and 145 with CO₂ can be efficiently achieved with use of a quaternary ammonium bromide covalently bound to polyethylene glycol as catalyst under solvent-free conditions (Scheme 35, Method B).[46] The same pattern of reactivity was observed with the selective formation of 5-substituted oxazolidin-2-ones when R² is an aryl group and of 4-substituted oxazolidin-2-ones (e.g., 146d) when R² is an alkyl group. The catalyst can be effectively recycled with retention of high catalytic activity and regioselectivity, but organic solvents are required for the separation of products and catalyst. More recently, a polyethylene-glycol-functionalized phosphonium salt (Br⁻Ph₃⁺PPEG₆₀⁺P⁺Ph₃Br⁻) has been reported as an efficient and recyclable catalyst for this solvent-free reaction, producing a range of 5-aryloxazolidin-2-ones (e.g., 146a, 146b, 128c, 130d and 130f) with high regioselectivities and in good yields (Scheme 35, Method C).[48] The lower reactivities observed with aziridines 129f and 129d, bearing a bulkier N-tert-butyl and N-cyclohexyl group, respectively, is consistent with the previously observed reactivity and was overcome by use of an increase in temperature and reaction time.

Jiang and co-workers described successful incorporation of CO₂ into aziridines 42a, 42b, 129b, 129d, 129f, 147a and 147b catalysed by naturally occurring α-amino acids under solvent-free conditions without the need for any additives (Scheme 36, Method A).[43] Almost all naturally occurring α-amino acids (e.g., L-histidine) were efficient catalysts for the reactions, producing the corresponding oxazolidinones (e.g., 128c, 130b, 130d, 130f, 140, 148a and 148b) in good yields and with high regioselectivities (isomeric ratios from 87:13 to 100:0). However, the activities of the catalytic systems were strongly dependent on temperature and CO₂ pressure. Although regioselectivities was not influenced by variation of temperature or pressure, higher yields of oxazolidinones were obtained when reactions were carried out at 110 °C at about 8 MPa, close to the critical pressure of CO₂. The observed regioselectivities are the result of Lewis acid activation through hydrogen bonding followed by Lewis base nucleophilic attack on the aziridines by the different amino acids. A disadvantage of this method is the fact that it still requires organic solvents to separate the catalysts from the products without decomposition of the catalyst or formation of byproducts. That limitation, however, was successfully overcome by the development of poly-styrene-supported amino acid catalysts (e.g., polystyrene-supported threonine, PS-Thr), which show high catalytic activities for the coupling of aziridines and CO₂ and can also be easily separated from the products and reused.[47]

Treatment of aziridines 42a, 42b, 129b, 129d, 129f, 147a and 147b with CO₂ in the presence of these catalytic systems under solvent-free conditions afforded the corresponding oxazolidinones 128c, 130b, 130d, 130f, 140, 148a and 148b in good yields and with high regioselectivities (isomeric ratios from 85:15 to 100:0, Method B, Scheme 36). The reactions followed the previous pattern, with the product ratios depending mainly on the N-substituents, in which increasing steric hindrance leads to enhancement of the regioselectivity.[47]

Liang-Nian He and his group reported the first example of the synthesis of 5-aryloxazolidin-2-ones from aziridines and CO₂ catalysed by a Lewis basic ionic liquid under solvent-free conditions.[49] Several DABCO-derived ILs ([C₄DABCO]Br) were tested to investigate the effects of different anions (e.g., Br⁻, OH⁻, Cl⁻, BF₄⁻, TF₂N⁻) on the reaction outcome. The best result was achieved with the [C₄DABCO]Br catalytic system. [C₄DABCO]Br-mediated reactions of 2-arylziridines 42b, 129a, 129c, 129d, 145a, 147a, 149a and 149c with CO₂ under solvent-free conditions led to the formation of the corresponding 5-arylox-

Scheme 36. Formal cycloaddition between aziridines and CO₂ under solvent-free conditions.

The same researchers demonstrated that solvent-free reactions of this type can also be achieved from aziridines under compressed CO₂ conditions, in the absence of any catalyst.[52] It was observed that reaction outcome could be controlled simply by tuning CO₂ pressure. Coordination of CO₂ with the aziridine to generate a zwitterionic adduct in situ was detected by in situ FT-IR under CO₂ pressure. This zwitterionic adduct is believed to be the reaction catalyst and its formation is favoured near-critical CO₂ conditions. The mechanistic proposal involves ring opening through nucleophilic attack on this zwitterionic adduct by the partially anionic oxygen of a second zwitterionic adduct. Intra-molecular cyclization of this intermediate leads to the product and regenerates the adduct. The reactions between aziridines and CO₂ at 120 °C and about 9 MPa thus afforded the corresponding oxazolidinones in good yields and with high regioselectivities (isomeric ratios from 86:14 to 97:3, Scheme 38, a). Aziridines with electron-withdrawing or -donating groups on their aryl rings gave higher regioselectivities (e.g., 150b, I/II = 97:3), whereas substrates with bulkier N-substituents exhibited poorer performances (e.g., 130d).

Replacing R¹ by an alkyl group led to 4-substituted oxazolidinone 146b as the main product with high regioselectivity (I/II = 3:97), in agreement with the previously reported reactivity, whereas with N-phenyl- and N-tosylaziridines no reaction was observed (Scheme 38, a).[52] Drawbacks of this method are the high temperatures and CO₂ pressures required to achieve good results.

These limitations were successfully overcome by Pinhas and co-workers through the use of a high-speed ball milling (HSM) technique in the solvent-free and catalyst-free reactions between unactivated 2-alkyl- and 2-arylaziridines and CO₂ at room temperature (Scheme 38, b and c).[53] The mechanical energy from HSM gives rise to higher yields and increased rates of chemical reactions, especially in those

azolidin-2-ones in good yields and with high regioselectivities (isomeric ratios from 96:4 to 99:1, Scheme 37, Method A). It was observed that aziridines bearing alkyl groups at their nitrogen atoms reacted smoothly, although increasing steric hindrance of the N-substituents resulted in lower activities (e.g., 130c and 130d, 6% and 16%, respectively). On the other hand, the presence of an electron-donating substituent on the 2-phenyl group led to higher activity than in derivatives bearing aryl groups with electron-withdrawing substituents (e.g., 150b vs. 150c). The mechanistic proposal involves CO₂ activation through the tertiary nitrogen in the cationic part of the ionic liquid, which can be recycled for over four times without loss of yield or selectivity.[49]
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Scheme 38. Catalyst-free formal cycloadditions between aziridines and CO₂.

carried out in the absence of any solvent. Treatment of aziridines 42a and 121 with dry ice under HSBM reaction conditions afforded the corresponding oxazolidinones 129c and 129a, respectively, in nearly quantitative yields and with the formation in each case of only one regioisomer (Scheme 38, b). It was observed that performing the reactions under shaking/mechanical energy conditions resulted in decreases in reaction times from a week to overnight (17 h). However, with N-phenylaziridines substituted at the 2-position by a phenyl group (e.g., 129d) or an alkyl group, no reaction was detectable even after shaking for an extended period of time (43 h), whereas with mildly electron-withdrawing substituents such as the m-chlorophenyl group only trace amounts of product were generated (e.g., 155). On the other hand, N-benzyl-7-azabicyclo[4.1.0]heptane (156, Scheme 38, c) gave the corresponding cis-oxazolidinone 157 in nearly quantitative yield, showing that these reactions proceed with net retention of stereochemistry as previously observed for the LiI-catalysed reactions.[53]

More recently, palladium-catalysed insertion of CO₂ into vinylazirides to afford a range of 5-vinyloxazolidinones 159 (Scheme 39) in high yields and with good regio- and stereoselectivities has been described.[54] The process involves very mild reaction conditions such as ambient atmosphere of carbon dioxide and low temperatures. In some cases, the use of a halide salt (tetrabutylammonium chloride, TBAT) as additive was necessary to prevent isomerization of the starting aziridines. Under optimized reaction conditions, trans-vinylaziridines 68 and 158a–c underwent Pd-catalysed carboxylation to give the corresponding trans-vinlyloxazolidinones 159 selectively in high yields (Scheme 39). The ratios of trans- to cis-vinlyloxazolidinones 159 reflected those in the initial trans- and cis-aziridine reactants, indicating that the reaction proceeds without loss of stereoselectivity.

Scheme 39. Palladium-catalysed insertion of CO₂ into vinylazirides.

An alternative synthetic methodology for 2-oxazolidinones that mimics the direct insertion of CO₂ has also been reported.[55] This strategy proceeds without use of CO₂ but involves initial conversion of aziridines 42a and 161a–c into their N-ethoxycarbonyl derivatives 162 (Scheme 40). These were converted under flash vacuum pyrolysis (FVP) conditions into the corresponding 2-oxazolidinones 140 and 163a–c in yields ranging from 47% to 88%. The reactions were regiospecific with the exception of that of the tert-butyl derivative 162d, which afforded an isomeric mixture of products containing the 5-substituted isomer (79%) together with its 4-substituted counterpart (21%). The thermal transformation of cis-aziridine 162c gave 2-oxazolidinone 163b as a 1:3 mixture of cis and trans isomers in 86% yield. The reactions proceed through intermediates 164, which could be isolated from the pyrolysates at temperatures below 600 °C. These intermediates are then converted into the products by thermal elimination of ethylene.[55]

N-Tosylaziridines undergo tributylphosphane-catalysed cycloadditions with carbon disulfide and isothiocyanates to produce 1,3-thiazolidine derivatives, which are commonly used as useful intermediates in pharmaceutical chemistry and organic synthesis.[56] Aziridines 43 and 165 (Scheme 41, a) react with CS₂ in the presence of tributylphosphane under reflux conditions to give the target trans products 166a–e, regioselectively, in yields ranging from 41% to 98%. Re-
Scheme 40. Flash vacuum pyrolysis of N-(ethoxycarbonyl)aziridines 162.

Regioselectivity was also observed in the reactions of aziridines 43 and 165 with phenyl isothiocyanate, which afforded the corresponding heterocycles 167a–e in moderate yields. A plausible mechanism involving phosphane attack on CS$_2$ to form a zwitterionic intermediate, which then reacts with aziridines to generate ring-opened intermediates, was proposed. These intermediates undergo ring closure to give the desired products 166 with regeneration of the organophosphane catalyst.$^{[56]}$

Cycloadditions between aziridines 168 (Scheme 41, b) and heterocumulenes (phenyl isothiocyanate, carbon disulfide and carbon dioxide) in the presence of catalytic amounts of organoantimony(V) halides such as Ph$_4$SbI, Ph$_3$SbBr, Ph$_3$SbBr$_2$, and Ph$_3$SbCl$_2$ have also been reported.$^{[57]}$ All the organoantimony catalysts tested proved effective and gave the corresponding cycloadducts selectively in moderate to good yields (e.g., 169a–c and 170). The reaction between aziridine 168a and phenyl isothiocyanate under Ph$_3$SbBr catalysis conditions thus gave adduct 169a regioselectively in 67% yield. Performing the same reaction with Bu$_3$SnI as catalyst resulted in the formation of 169a in lower yield (57%) along with the corresponding piperazine (23%) obtained from aziridine dimerization. The Ph$_3$SbBr-mediated reactions between aziridines 168b–e and CO$_2$ gave the desired products 169b–e selectively in good yields (Scheme 41, b). When Bu$_3$NBn was used as the reaction catalyst, isomeric mixtures of products containing the 5-substituted (major) and 4-substituted isomers (minor) were obtained. On the other hand, the reaction between aziridine 168c and carbon disulfide required a higher reaction temperature (180 °C) and although the corresponding thiazolidinethione was identified as the major product in the crude sample, after workup only oxazolidinethione 170 could be isolated, in 60% yield (Scheme 41, b)$^{[57]}$

Alper and co-workers described reactions between aziridines and carbodiimides or sulfur diimides catalysed by bis(benzonitrile)palladium dichloride, forming imidazolidenimides (e.g., 173a–d) and imidazolidinethiones (e.g., 175), respectively, in moderate to good yields (Scheme 42)$^{[58,59]}$ Aziridines 129f and 171 reacted with carbodiimides (e.g., 172a–b) under palladium catalysis conditions in toluene at 100 °C to afford the corresponding imidazolidenimides (e.g., 173a–d, 61–95%) regiospecifically, in a process involving the cleavage of the more substituted

Scheme 41. Formal [3+2] cycloadditions between aziridines and heterocumulenes: a) with tributylphosphane catalysis, or b) with organoantimony(V) halide catalysis.
ring carbon-nitrogen bond (Scheme 42, a).[58] The reactions between aziridine 129f and sulfur diimides (e.g., 174) under the same reaction conditions afforded imidazolidinethiones (e.g., 175) instead of the expected thiadiazolidinethiones (Scheme 42, b).[59] Experimental evidence shows that these imidazolidinethiones do not originate from cycloadditions between aziridines 129f and aryl isothiocyanates generated in situ, but that the thiocarbonyl carbon of 175 instead derives from a second molecule of the aziridine reactant 129f through a metathesis pathway. In fact, treatment of an aziridine labelled with $^{13}$C at one of the ring carbon atoms with di-$p$-tolylsulfur diimide resulted in incorporation of the label at the 2- and 5-positions of the imidazolidinethione.[59] 

This work was further extended to Pd$^{II}$-catalysed reactions between 1,2,3-trisubstituted aziridines (e.g., 176, Scheme 43, a) and heterocumulenes such as aryl isocyanates, isothiocyantes and carbodiimides, providing a simple and efficient methodology for production of a range of five-membered heterocycles (e.g., 177a-c).[60] These reactions proceed with both regio- and stereospecificity, with retention of the stereochemistry of substituents in the aziridine ring. The reaction between cis-aziridine 176 and phenyl isocyanate in the presence of a catalytic amount of bis(benzonitrile)palladium dichloride (10 mol-%) in toluene at 120 °C over 20 h thus resulted in the formation of the corresponding cis-imidazolidinone 177b in 72% yield (Scheme 43, a). 

This catalytic system was also applied to reactions between enantiomerically pure $N$-alkyl-2-phenylaziridines (e.g., 178a-b and 180a-b, Scheme 43, b) and heterocumulenes to afford the corresponding chiral five-membered heterocycles (e.g., 179a-c and 181a-c) in high yields with retention of configuration.[60] Indeed, the palladium-mediated reaction between ($S$)-(+)2-butyl-phenylaziridine (178a) and phenyl isocyanate gave (+)-1-butyl-3,4-diphenylimidazolidin-2-one (179b) in 82% yield. Similarly, the (–)-enantiomer 181b was obtained in 81% yield from the reaction between (R)-(+)180b and phenyl isocyanate under the same reaction conditions.[60] 

A major disadvantage of this catalytic system is that it requires high temperatures for the reactions to proceed to completion. A much milder catalytic system consisting of palladium acetate (2 mol-%) and PPh$_3$ (10 mol-%) was later developed and showed high activity in catalysed cycloadditions between 2-vinylaziridines (e.g., 182, Scheme 43, c) and several heterocumulenes.[61] Reactions were carried out...
at room temperature and isocyanates, isothonocyanates and carbodiimides were employed as heterocumulenes, leading to imidazolidinones (e.g., 183a, 89% and 183b, 82%), imidazolidinethiones (e.g., 183c, 60%), and imidazolinedineimines (e.g., 183d, 96%), respectively, as products (Scheme 43, c). For isocyanates, the reactions were complete after only 2 h, whereas carbodiimides and isothiocyanates usually required longer reaction times (20 h). From experimental evidence these transformations are likely to occur through (π-allyl)palladium complex intermediates.[61] The first examples of asymmetric versions of these reactions were reported by Trost and co-workers, who obtained high yields and high enantioselectivities in (η-C5H5PdCl2)-catalysed cycloadditions between isocyanates and vinylaziridines (e.g., 184) in the presence of the Trost ligand (Scheme 44, a).[62] It was observed that addition of acetic acid to the reaction medium was required to achieve increased enantioselectivity. In general, reactions of vinylaziridine 184 furnished the corresponding chiral imidazolidinones 186 in high yields and enantiomeric excesses ranging from 13% with benzoyl isocyanate to 95% with benzyl isocyanate. Imidazolidinones 186 were efficiently further converted into their corresponding chiral diamines.[62]

A different asymmetric version employing Pd3(dba)2, CHCl3, (S)-BINAP and CeCl3 as the catalytic system has also been reported.[63] The formal cycloadditions between 1-alkyl-2-vinylaziridines 182 and 187 and several isocyanates in the presence of that catalytic system afforded the corresponding imidazolidinones 183a and 188a-c in yields of up to 89% and with ee values of up to 83% (Scheme 44, b). The highest ee was obtained for adduct 188a, resulting from the reaction between aziridine 182 and o-chlorophenyl isocyanate. In contrast, the reactions between aziridine 187 and the same isocyanates gave imidazolidinones 188 in higher yields, but with lower enantiomeric excesses (e.g., 188b, 51% ee and 188c, 66% ee). The observed enantioselectivity was explained as a result of the fact that the presence of CeCl3 might increase the rate of equilibration of the diastereoisomeric π-allyl palladium intermediates, thus leading to the formation of the enantiomeric products.[63]

3. Formal [3+2] Cycloadditions via Aziridinium Ions

Mattay and co-workers described formal [3+2] cycloadditions between nonactivated aziridines 4 and activated acetylene derivatives (e.g., 189, Scheme 45, a) under mild thermal conditions to give the formal cycloadducts such as 191 through C–N bond cleavage.[3] Several side products were formed, which led to isolation of 191 in only 13% yield. The proposed mechanism involves the formation of dipolar intermediate 190, which affords the target product 191 through an intramolecular attack of the carbanion on the aziridine ring. When methanol was used as solvent instead of acetonitrile, the intermediate 190 could be trapped, leading to highly substituted enamines (e.g., 192, 70%).[3] N-Alkenylaziridines 193 (Scheme 45, b) also reacted with dimethyl acetylenedicarboxylate (DMAD) under thermal conditions to generate mixtures of regioisomeric pyrrolines 194 and 195 through formal [3+2] cycloadditions.[64] The reaction between aziridine 193a and DMAD in toluene at 60 °C gave a 1:1 mixture of 194a and 195a in 80% combined yield after 24 h. Application of the same reaction conditions to aziridine 193b resulted in the formation of the corresponding regioisomers 194b and 195b in a 1:3 ratio and 65% combined yield.[64]

A sequential S+2/formal [3+2] cycloaddition approach to polystituted indolizidines (e.g., 200 and 201, Scheme 46) starting from nonactivated aziridines 42a and 197 has also been reported.[4] After initial S+2 reactions between 7-iodohept-2-ynoate 196 and N-unsubstituted aziridines, dipoles 198 are formed. Reaction with iodide anion then leads to the opening of the aziridine ring followed by a third S+2 reaction to afford the corresponding indolizidines 200 in good yields. Furthermore, the reaction between iodide 196 and enantiopure aziridine (S)-42a (>99% ee) furnished bicyclic product (S)-201 in 92% yield and with an ee identical to that in the starting aziridine, thus indicating that the last two S+2 reactions proceed stereospecifically.[4]

The reactivity of buta-2,3-dienoates towards 2-benzoyl-3-phenylaziridines has recently been described (Schemes 47

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**Scheme 44.** Palladium-catalysed cycloadditions between isocyanates and vinylaziridines.
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Scheme 45. Formal [3+2] cycloadditions between aziridines and DMAD under thermal conditions.

Scheme 46. A sequential SN2/formal [3+2] cycloaddition approach to polysubstituted indolizidines 200 and 201.

Scheme 47. The reactivity of buta-2,3-dienoates towards 2-benzoyl-3-phenylaziridines under MW irradiation conditions.

In contrast, performing the same reactions under scCO2 conditions exclusively affords pyrroles 11, in yields ranging from 51% to 79% (Scheme 48).[7] The exclusive synthesis of pyrroles at pressures close to the critical pressure of scCO2 (90–110 bar) was observed. A plausible mechanism based on experimental evidence was proposed for the formation of pyrroles 11. It involves nucleophilic addition of the aziridines 202 to the activated double bonds in allenoates 203 to give intermediates 205. These then undergo intramolecular attack of the carbanion centres on the aziridine rings to produce 207, bearing hydroxybenzyl side chains. The final products 11 and benzaldehyde are obtained from pyrroles 208 through a retro-aldol-type fragmentation. In one case a pyrrole derivative containing a hydroxybenzyl side chain formed from intermediate 207 could indeed be isolated as a minor product, thus reinforcing the proposed mechanism.
**Scheme 48.** The reactivity of buta-2,3,3-dienoates towards 2-benzoyl-3-phenylaziridines under supercritical CO2 conditions.

**Conclusions**

The formal [3+2] cycloaddition reactions of aziridines discussed in this review have demonstrated the potential of this methodology as an approach to a wide variety of five-membered heterocyclic compounds. However, despite the results thus far achieved, issues relating to selectivity must still be addressed. Particularly interesting is the coupling of CO2 with aziridines to form oxazolidinones, useful building blocks in organic synthesis, as an attractive and efficient synthetic methodology for chemical fixation of CO2.

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A. L. Cardoso, T. M. V. D. Pinho e Melo

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Aziridines in Formal [3+2] Cycloadditions

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