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Recent developments in regioselective ring opening of aziridines

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Contents

1. Introduction

The aziridine moiety, or alternatively recognised as an azaethylene or ethylenimine unit, is one of the most important three-membered ring functionalities in organic synthesis.[1,2] Structurally, aziridines are analogous to epoxides with the nitrogen group replacing the oxygen. The chemistry of aziridines has been increasingly researched over the last few decades and their application has been greatly broadened.[3–5] Aziridines have become important building blocks in synthetic chemistry, especially for nitrogen-containing bioactive natural compounds.[6–8]

The utility of aziridines is profoundly dependent on their ability to undergo nucleophilic ring opening, both stereo- and regioselectively.[9] It is widely accepted that aziridines with nitrogen-bearing, electron-withdrawing substituents, such as sulfonyl, sulfinyl, phosphoryl, phosphinyl and carbonyl, are more reactive towards ring opening than their nitrogen-unsubstituted counterparts.[10]

Regarding the regiochemistry, the intrinsic properties of the aziridine and the nature of the incoming nucleophile can both affect the outcome.[11] In general, 1,2-disubstituted aziridines mirror the similarly substituted epoxides, in that they suffer attack at the less substituted 3-position. This regioselectivity may be changed when the two C–N bonds are polarised unsymmetrically and there is significant positive charge development at the 2-carbon atom, e.g. 2-phenyl-substituted aziridines in acidic media. When both carbon atoms are substituted, competing steric and electronic effects may be such that the regioselectivity of nucleophilic ring opening is eroded, although many examples of selective reactions are documented.[1,9,10,12]

In general, 2-phenyl substituents are powerful directing groups for regioselective ring opening of aziridines by both carbon and hetero nucleophiles. Two possible mechanisms may be proposed, as outlined in Figure 1. Firstly, as mentioned above, there is a partial positive character developed on C-2 induced by the electron-withdrawing phenyl group, as shown in structure **1**. Secondly, the resulting C-2 p orbital of the nucleophilic ring-opening transition state is stabilised through overlapping with the aromatic system of the phenyl ring, as depicted in structure **2**.

A comprehensive review on the subject of nucleophilic ring opening of aziridines was offered by Hu,[13] together with many others.[6,9,11] The following review intends to give an overview of the regioselective ring opening of aziridines organised by class of nucleophile, and focused mainly on reports from the year 2000 onwards.

2. Carbon nucleophiles

Regioselective ring opening of aziridines by carbon nucleophiles has become a competitive strategy for constructing carbon–carbon bonds.[1,6] With more and more robust and simple methods for the

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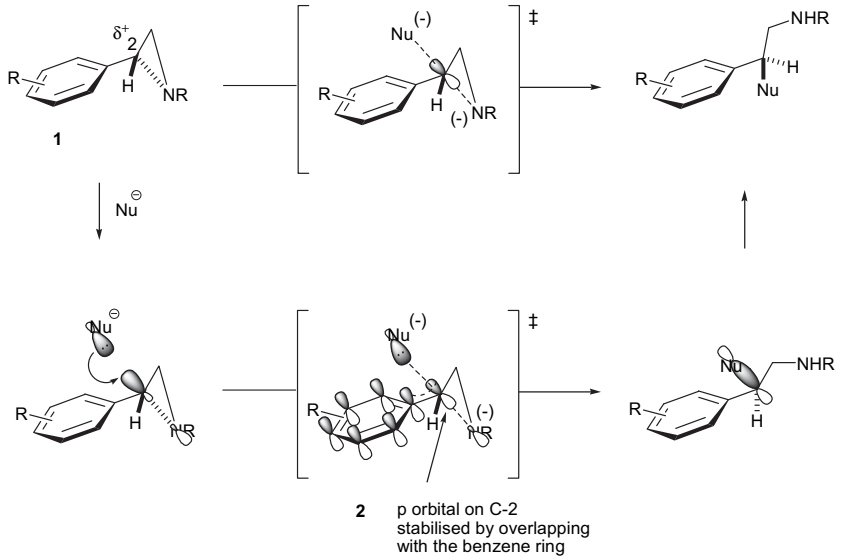


Figure 1. Nucleophilic ring opening of 2-benzyl-substituted aziridines.

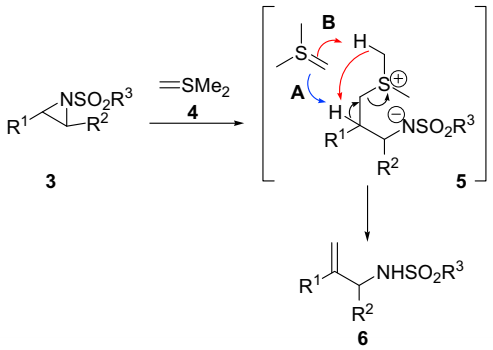
synthesis of aziridines being developed, especially stereoselectively, its impact is set to grow.[6,14,15]

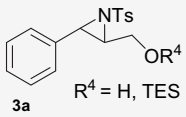
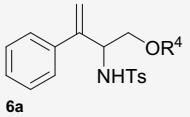
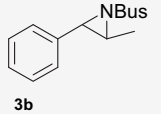
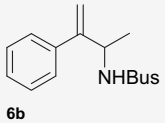
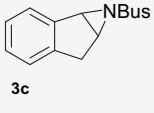
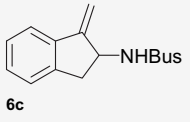
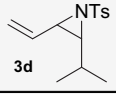
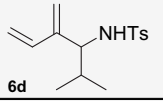
Allylamines are important building blocks in synthetic chemistry.[16,17] Hodgson and co-workers have established a general process to access allylic *N*-sulfonylamines by the regiocontrolled opening of 2,3-disubstituted *N*-sulfonylaziridines with dimethylsulfonium methylide **4**[18] (Table 1).[19] Initial attack on the benzylic or allylic carbon of the aziridines **3a–d** by **4** generated the intermediates **5**, which could then undergo elimination to give the desired products **6a–d** through either path **A** or **B** with another equivalent of **4**.

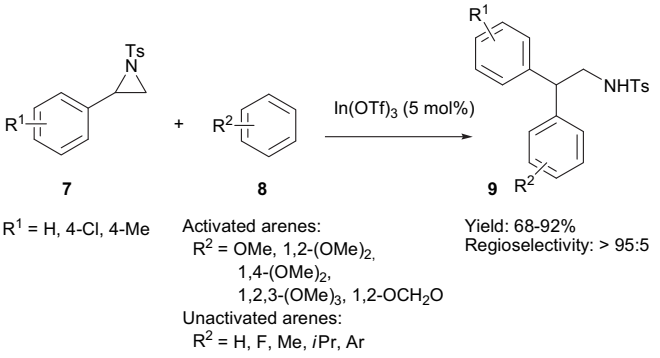
As shown in Table 1, both *N*-Ts and *N*-Bus (Bus=*tert*-butylsulfonyl) aziridines gave the corresponding allylic amines in good yields. With the exception of substrate **3b** that gave the other regioisomer in 12% yield, all others produced exclusively the expected compounds. Diene **6d** is also potentially useful for cycloaddition chemistry.[19]

The use of Lewis acids, such as Cu, Zn, B, Sc, In, Bi, Ce, Au and Ag, in promoting aziridine ring opening has attracted much attention.[13] Yadav et al. examined the use of $In(OTf)_3$ as a catalyst in the reaction of arylaziridines **7** and arenes **8** (Scheme 1).[20] This was the first report on regioselective aziridine ring opening with arenes. Despite the fact that there is no substitution on C-3, nucleophilic additions almost exclusively occur on C-2. With short reaction times of 1–2 h for activated arenes, and slightly longer for unactivated arenes (4–6.5 h), β-diaryl amines **9** were prepared in high yields and excellent regioselectivity. In addition, they also investigated other metal triflates and found that 5% $Sc(OTf)_3$ and 10% $Yb(OTf)_3$ gave similar results for activated arenes, but $In(OTf)_3$ was the only catalyst effective for unactivated arenes. Additionally, without the use of a catalyst, no reaction was observed.

Table 1
Regioselective ring opening of *N*-sulfonylaziridines with dimethylsulfonium methylide

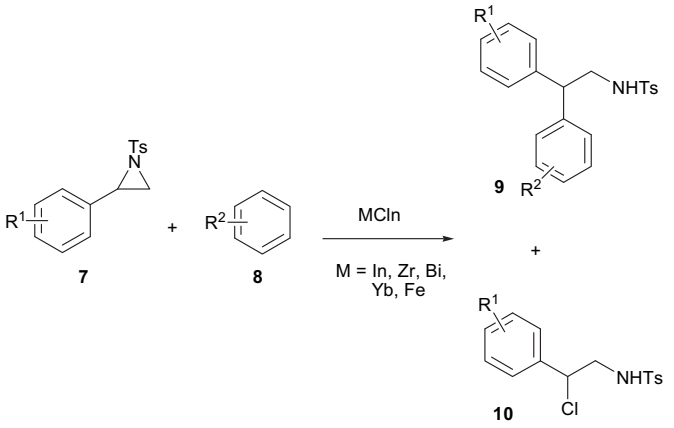


Entry	Aziridine	Product	Yield (%)
1			R^4=H,85 TES,79
2			81
3			95
4			75



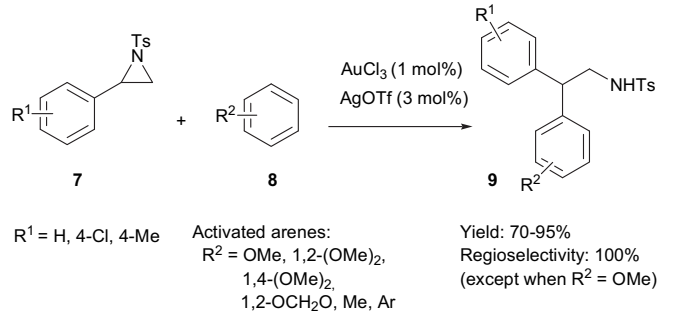
Scheme 1.

Interestingly, when metal halide catalysts were used, a 1:1 mixture of β-diaryl amines **9** and β-chloro amines **10** was obtained (Scheme 2).



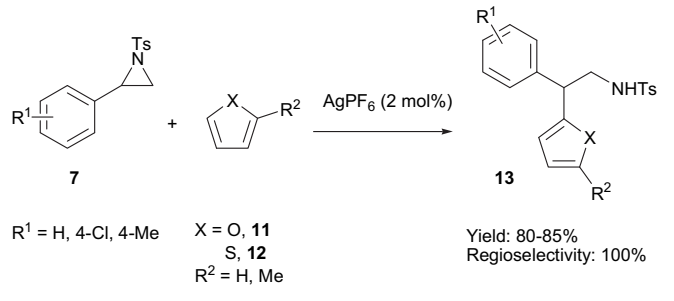
Scheme 2.

This methodology was extended by Wu et al.[21] and Roy et al.[22] In their interesting studies on applying gold and silver catalysts in organic synthesis, Wu et al. demonstrated that the combination use of $AuCl_3$ and AgOTf gave similar results to those of Yadav (Scheme 3), whereas poor yields resulted when only one of these reagents was used. Except when R^2=OMe, providing a selectivity of 5.2:1, all other reactions gave 100% regioselectivity. However, when switching R^2 to electron-withdrawing groups such as Cl, CF_3 and NO_3, complex, unidentified mixtures were obtained.



Scheme 3.

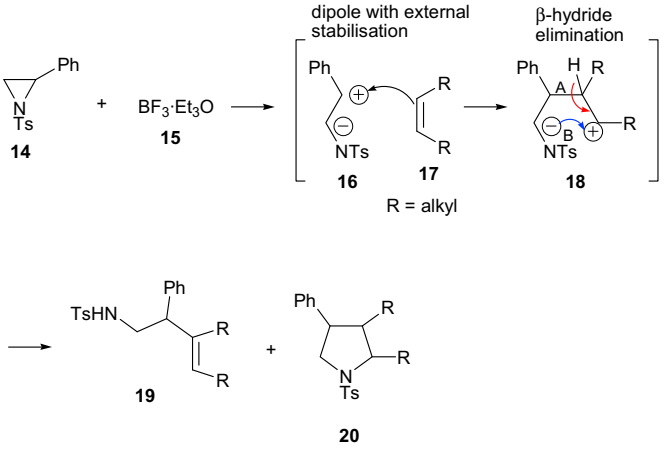
This type of process is not restricted to arenes. Heteroarenes are also susceptible to Lewis acid-mediated nucleophilic addition to aziridines. In addition to Yadav's earlier work,[23] Roy and Bera recently showed that, in the presence of $AgPF_6$, furans **11** and thiophenes **12** are good nucleophiles for the regioselective ring opening of aziridines **7** to yield exclusively **13** (Scheme 4).[22] The authors believed that the well-known binding ability of Ag(I) towards arenes[24–26] and aziridines[27] might contribute to such reactivity.



Scheme 4.

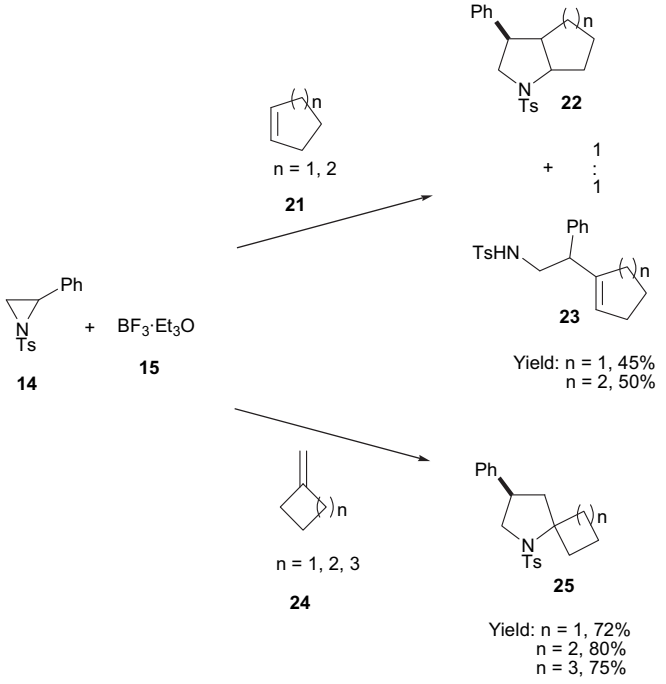
Aziridines have also been found to undergo ring-opening reactions with nonactivated alkenes in the presence of $BF_3 \cdot Et_2O$ (**15**). This remarkable work was published by Mann et al. (Scheme 5).[28,29]

They described this process as a formal [3+2] cycloaddition involving a 1,3-dipole 2-phenylaziridine precursor. Building on the success of reacting aziridine **14** with allylsilanes,[28] they were able to extend this methodology to a variety of other alkenes.[29] They suggested that the reaction occurred via a rather unusual zwitterionic 1,3-dipole, as depicted in the intermediate **16**, stabilised externally by the aromatic ring and the tosyl group. It is so electron deficient that it can react with nonactivated alkenes such as **17** to generate **18**. The intermediate **18** can then undergo either β-hydride elimination, mechanism A, to give **19** or nucleophilic attack of the nitrogen anion on the carbocation, mechanism B to afford pyrrolidine **20**.



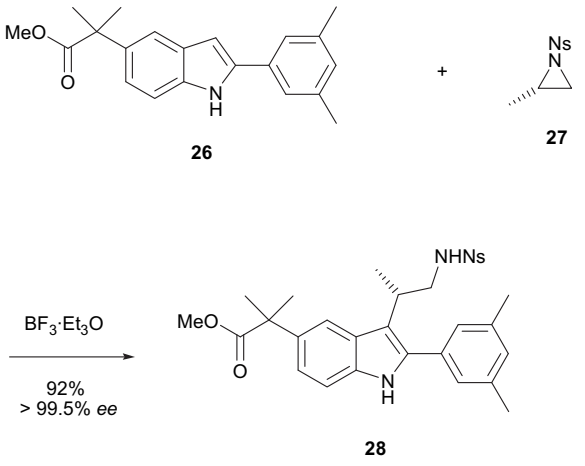
Scheme 5.

The results showed that the ratio of **19** and **20** depends on the stability of the carbocation of **18** (Scheme 5). When cyclopentene and cyclohexene **21** were used, a 1:1 mixture of **22** and **23** was observed (Scheme 6). The yields of these two reactions were low, which was probably also due to the stability of the carbocation. This hypothesis was supported by the outcome of the reactions using geminal disubstituted alkenes **24**, in which more stable tertiary carbocations were formed. As shown in Scheme 6, only the cyclised products **25** were prepared in good yields.



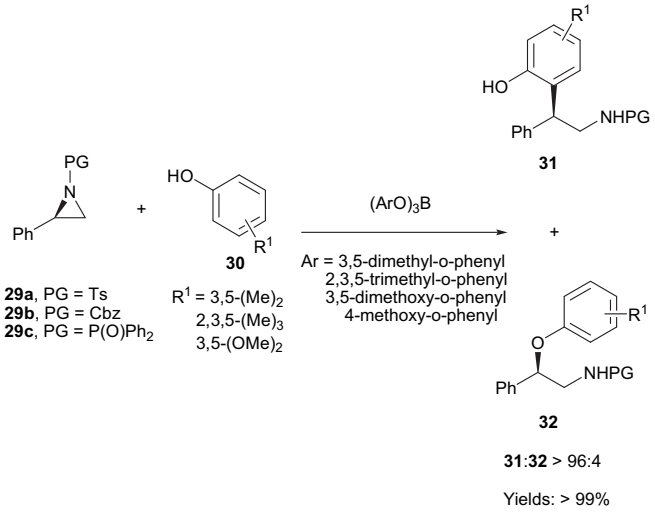
Scheme 6.

Boron trifluouride etherate (**15**) is an excellent Lewis acid for mediating regioselective aziridine ring openings. A key step in Farr's synthesis of the GnRH antagonist GnRH-1 is the unprecedented $BF_3 \cdot Et_2O$-catalysed enantio- and regioselective reaction between 2-arylindole **26** and nosyl aziridine **27** (Scheme 7).[30] The use of $BF_3 \cdot Et_2O$ resulted from the screening of a series of Lewis acids. Indole **26** was prepared in a nine-step sequence, starting from 4-nitrophenyl acetic acid, involving a palladium-catalysed coupling of iodo aniline with phenyl acetylene followed by a 5-*endo-dig* indole formation triggered by CuI. Aziridine **27** could be obtained in a one-step transformation by treating L-alaninol with 2.1 equiv of nosyl chloride in the presence of triethylamine. As illustrated in Scheme 20, the reaction of **26** with **27** gave a very good yield of **28**, with perfect regio- and enantioselectivity. The stereochemistry of **28** was determined by direct comparison with that previously prepared by Walsh.[31]



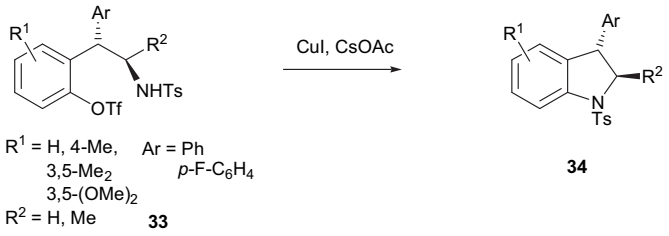
Scheme 7.

The effective boron-based Lewis acids are not limited to just $BF_3 \cdot Et_2O$. Pineschi et al. adopted the use of electron-rich aryl borates to achieve highly chemo-, stereo- and regioselective carbon–carbon bond formations from aziridines **29a**–**c** and phenols **30** (Scheme 8) with retention of configuration at C-2 of the aziridines.[32] When Ar is phenyl, a 1:1 mixture of C- and O-alkylated products **31** and **32** was obtained. Interestingly, the amount of the C-alkylated product was dramatically increased when Ar was more electron rich, with a ratio of >95:5 over the O-alkylated counterpart. Changing the protecting groups of the aziridine had very little effect on the outcome. During all these transformations, no alternative regioisomer was observed.



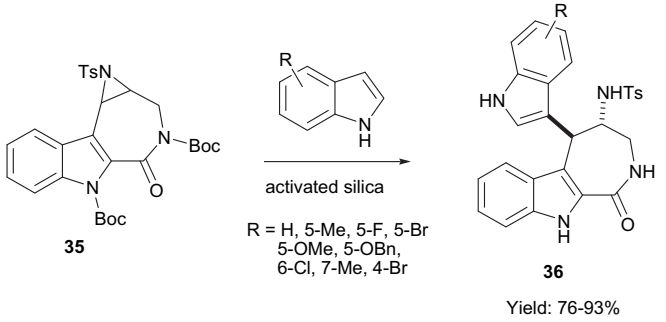
Scheme 8.

Having successfully accessed aminophenol derivatives **31**, Pineschi also managed to convert them into arylindolines **34** using intramolecular amination of aryl triflates **33** with CuI and CsOAc (Scheme 9).



Scheme 9.

Another group of substrates capable of directing regioselective attack on the benzylic carbon of the aziridine is α-indole aziridines. Tse et al. have developed a very efficient method of furnishing highly functionalised bisindoles **36** from **35** on a solid support under solvent-free conditions (Scheme 10).[33] The advantage of employing activated silica as the solid support was not only enhanced regioselectivity, but it also cleaved the two *N*-Boc groups, whereas clay (Montmorillonite K-10) gave both regioisomers and neutral alumina only yielded a small amount of the deprotected products.



Scheme 10.

Many functionalities on the indole nucleophile, including halides, alkoxy groups and esters, were tolerated under these conditions. However, 5-nitroindole only gave a poor yield of less than 20% and 5,6-dimethylindole yielded a substantial amount of the undesired regioisomer.

In addition to indole carbon nucleophiles, others such as *N*-, *O*- and *H*-nucleophiles, also gave similar results.

In addition to investigations of regioselective nucleophilic additions at the aziridine C-2 centre, interest in C-3 attack has also been aroused. Unsurprisingly, when R is alkyl, ring opening on the 3-carbon is favoured, due to steric factors (Fig. 2).

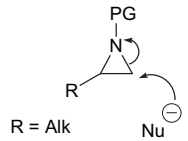
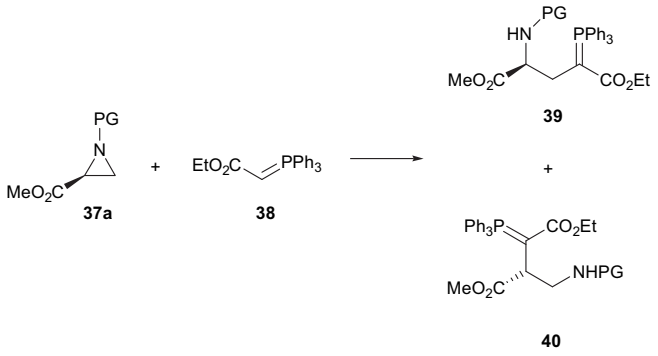


Figure 2. Nucleophilic attack on C-2 alkyl-substituted aziridines.

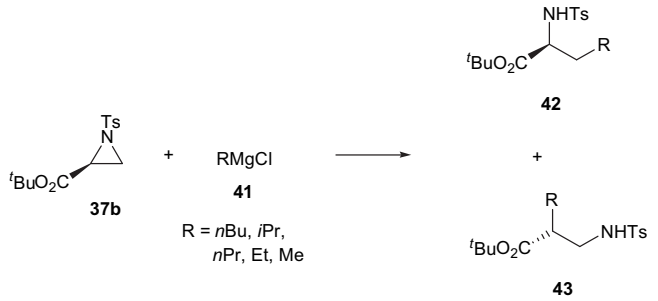
However, this limits the synthetic utility of the ring-opening product, considering the difficulties of further functionalising the R group α to the resulting amine. Introduction of other functionalities

will complicate the electronic effect and, as a result, both C-3 and C-2 attack are possible, due to steric and electronic reasons. For example, when using 2-carboxylate ester aziridines in the course of their study to provide new amino acids, Baldwin et al. observed some interesting regioselectivities (Scheme 11).[34] When the carbonyl-stabilised reagent **38** was used to react with aziridine **37a** and the protecting group of the nitrogen was either of the strongly electron-withdrawing groups, $-COC_6H_4NO_2$ and –Ts, both isomers **39** and **40** were obtained, with the C-3–N-1 cleavage product **39** being favoured, whereas, when the protecting group was $-COCH_2C_6H_4NO_2$ or $-COCH_2Ph$, only **39** was isolated with yields of 30%.



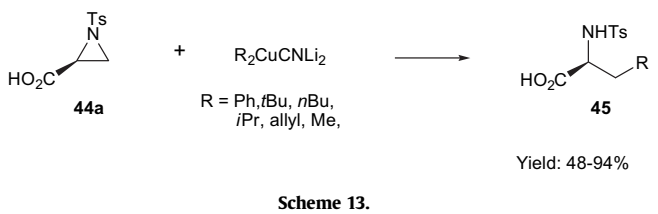
Scheme 11.

They also tested organolithium and Grignard reagents, such as **41**, in the reactions with aziridine **37b** and found that nucleophilic attack on both carbons took place (Scheme 12).[35,36] The ratio between products **42** and **43** is affected by the size of the nucleophile. When R is methyl, compound **43** was obtained as the major isomer at a ratio of 4:1. However, when R is isopropyl, only compound **42** was observed.

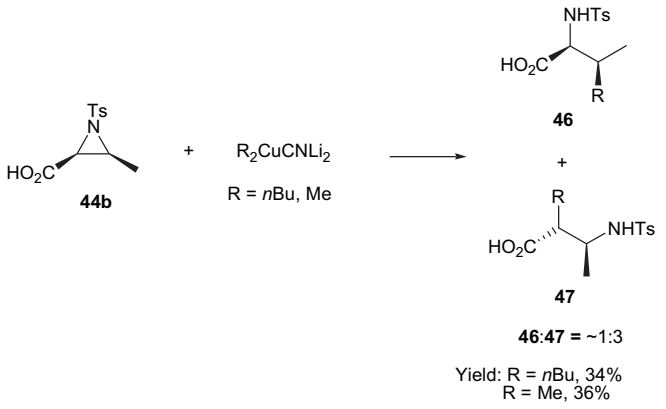


Scheme 12.

To overcome this problem, Young et al. examined the reaction of 2-carboxylic acid aziridine **44a** with a variety of organocuprate nucleophiles, where completely regioselective C-3 attack was achieved to furnish α-amino acids **45** (Scheme 13).[37] Nevertheless, the reaction of 3-methyl-substituted aziridine **44b** gave a ~1:3 mixture of isomers **46** and **47**, with the β-amino acid as the preferred product (Scheme 14).



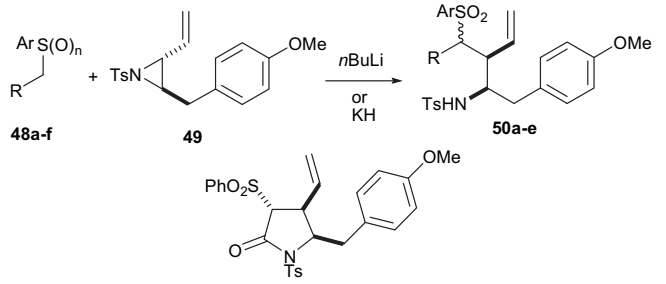
Scheme 13.



Scheme 14.

Another important category of regiochemistry of aziridine ring opening is the direct attack by carbanionic nucleophiles without any additives.[38–42] This area of chemistry was enriched by the results published by Craig and co-workers, as illustrated in Table 2.[12] Remarkably, when 2,3-disubstituted vinylaziridine **49** was treated with the sulfur-stabilised carbanion of **48a–f**, derived from *n*BuLi or KH deprotonation, it underwent complete regioselective ring-opening on the vinylic position to give the corresponding products **50a–e** and **53**. γ-Lactam **51** was synthesised from the KH-deprotonated sulfonyl acetate **50f** after its regioselective attack on the aziridine followed by a lactamisation in one pot.

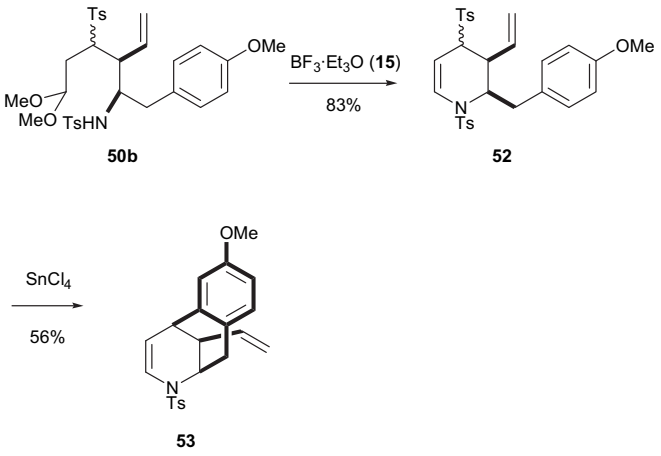
Table 2
Regiocontrolled nucleophilic attack on vinylaziridine 49 by sulfur-stabilised nucleophiles



Entry	Ar	R	*n*	Ratio 50:51	Yield (%)	dr
a	Tol	H	2	2	74	—
b	Tol	$(MeO)_2CHCH_2$	2	1.5	90	3:1
c	Ph	*E*-PhCH=CH	2	1.3	45	10:1
d	Ph	H_2CCH	0	1.1	76	5:1
e	Ph	HCC	0	1.2	76	2:1
f	Ph	MeO_2C	2	1	89	1:0

These reactions demonstrate the powerful directing effect of the vinyl group on regioselective ring opening of aziridines, similar to that of a phenyl group. Craig et al. believed that this may be rationalised in terms of selective weakening of the allylic C–N bond of the aziridine by $\pi_{C=C}$–σ^*_{C-N} overlap.

The products from these reactions are valuable building blocks, owing to their ability to undergo further transformations. Compound **50b**, for instance, was converted into a mixture of tetrahydropyridines **52** when treated with $BF_3 \cdot Et_2O$ (**15**). Upon exposure to $SnCl_4$, **52** underwent an intramolecular desulfonylative cyclisation to give the tricyclic product **53** (Scheme 15).



Scheme 15.

In addition to the vinyl-substituted aziridine **51**, the same workers also discovered that hydroxymethyl-substituted aziridines **54** and **55** exhibited similar regioselectivities when treated with sulfur-stabilised carbanions, where they were attacked on the C-2 positions (Fig. 3).

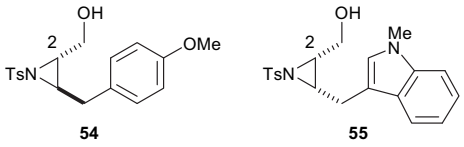
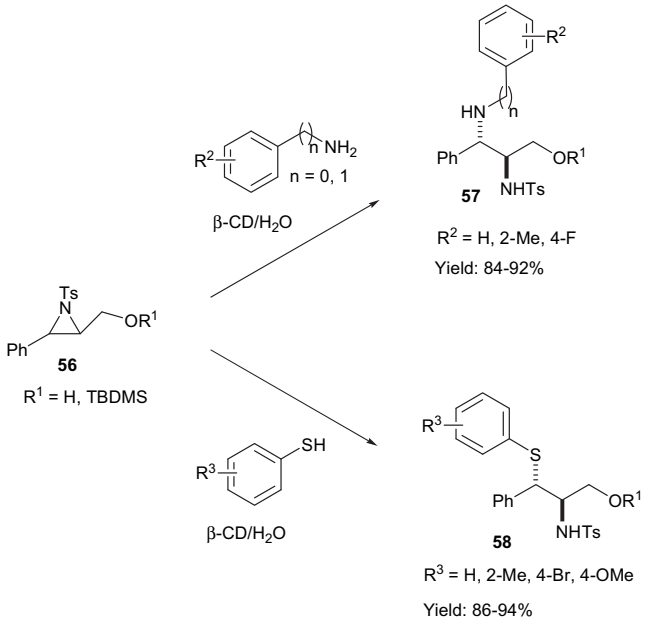


Figure 3. Hydroxymethyl-substituted aziridines that are capable of undergoing regioselective nucleophilic addition on C-2.

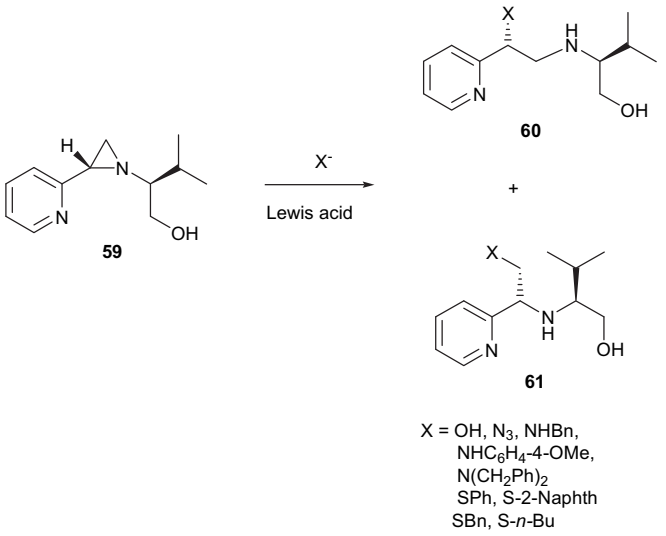
3. Heteroatom nucleophiles

2-Phenylaziridines are also often used to effect regioselective attack by heteroatom nucleophiles, similar to carbon nucleophiles, on the benzylic carbon.[43–46] Diamines and amino sulfides are biologically and synthetically important classes of compounds in the pharmaceutical industry.[47] Rao et al. have devised an approach to synthesise these two groups of substrates (Scheme 16).[46] In the presence of β-cyclodextrin (β-CD) in H_2O, the reaction of hydroxy phenylaziridine **56** and amines/sulfides yielded only single regioisomers **57** and **58**. β-Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively.



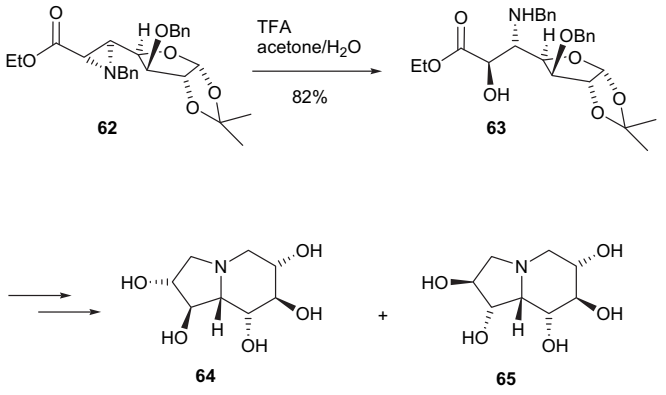
Scheme 16.

Ring opening of a pyridyl-substituted aziridine with *N*-, *S*- and *O*-nucleophiles was tested by Savoia et al. (Scheme 17).[48] Intriguingly, in contrast to phenyl-substituted aziridines, it did not produce good selectivity. Prepared by the addition of chloromethyllithium to the pyridineimine derived from (*S*)-valinol, aziridine **59** was allowed to react with a series of nucleophiles in the presence of Lewis acids. Except when NaN_3 was used, which gave 100% of the C-2 addition isomer **60**, all other reagents gave mixtures of **60** and **61** with ratios varying from 96:4–40:60.



Scheme 17.

Nucleophilic addition of heteroatoms to carboxylate aziridines is of particular interest, due to the ease of accessing the precursor natural or unnatural amino acids, which are useful building blocks for synthesis. In their work towards indolizidine alkaloid syntheses, the Dhavale group developed an efficient approach for the synthesis of pentahydroxylated indolizidine derivatives by using regioselective ring opening of aziridine **62** with H_2O to give **63**, promoted by TFA (Scheme 18).[49] Following a six-step sequence from **63**, compounds **64** and **65** were prepared.

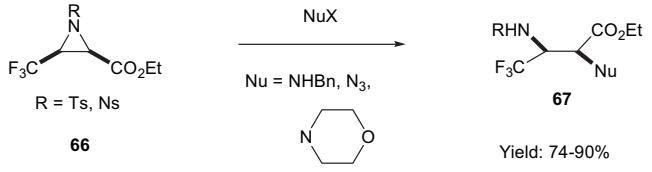


Scheme 18.

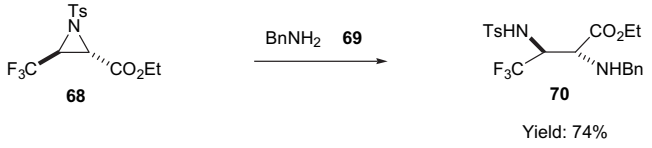
The importance of fluorinated compounds has been well documented.[50] This class of substrates has attracted increasing attention in recent years, especially in the pharmaceutical industry.[49–52] The introduction of fluorine atoms into organic molecules often results in profound changes in their chemical and biological properties.[50,53] One important family is fluorine-substituted amino acids.[54] Many

methods for their preparation have been reported.[50,53] However, few methodologies for the synthesis of fluorinated diamino acids have been developed.[55–57]

Bonnet-Delpon et al. have achieved the synthesis of fluoroalkyl α,β-diamino acids by ring opening of 2-carboxy-3-trifluoromethylaziridines **66** and **68** with nitrogen nucleophiles (Schemes 19 and 20).[58] The 2,3-*cis*-aziridines **66** were prepared from CF_3-imines reacting with ethyl diazoacetate in the presence of a sub-stoichiometric amount of $BF_3 \cdot Et_2O$.[59] When treated with amines or NaN_3, ring-opening products **67** were obtained with complete stereo- and regioselectivity without Lewis acid catalysis (Scheme 19). The 2,3-*trans*-aziridine **68** was synthesised by bromination of (*E*)-ethyl 4,4,4-trifluorobut-2-enoate followed by aminative cyclisation with tosylamine.[60] Regioselective nucleophilic attack of **68** was accomplished with benzylamine **69** to give the α,β-diamino ester **70** (Scheme 20). The stereochemistry of **70** was determined by X-ray crystallography.



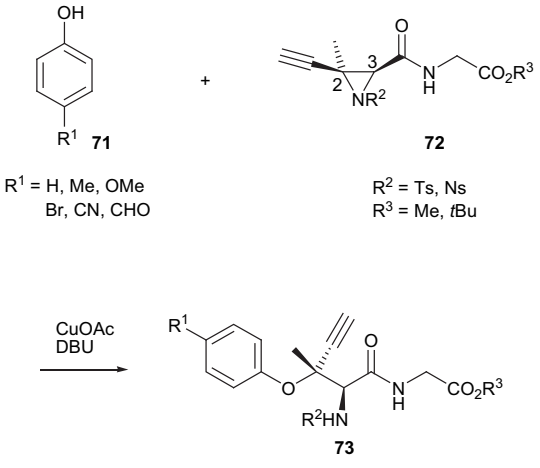
Scheme 19.



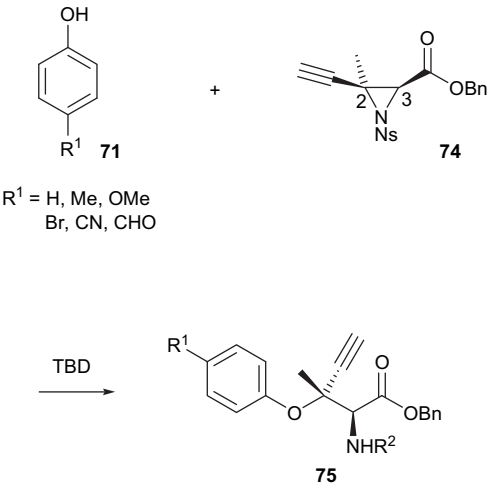
Scheme 20.

Bonnet-Delpon believed that the regioselectivity of these reactions was due to the strongly electronegative nature of the fluorine atoms, resulting in electrostatic repulsion between the trifluoromethyl group and the incoming nucleophiles. Additionally, it may also be explained by the theory that the $-CF_3$ substituent is less able than the –COOEt group to stabilise the p orbital of the transition state on the adjacent carbon in an S_N2 process.

The Joullié group has reported a thorough investigation of ring-opening reactions of highly substituted alkynylaziridines with oxygen nucleophiles (Schemes 21 and 22).[61,62] Remarkably, addition of phenol nucleophiles **71** occurred exclusively on the more



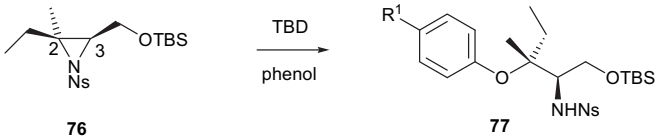
Scheme 21.



Scheme 22.

substituted C-2 of both the aziridine carboxamide **72** and aziridine ester **74**. The yields of the products **73** were low, typically around 50%. It was found that, under these conditions, the sulfonamide anion intermediate further reacted with the terminal alkyne, undergoing a 5-*endo*-*dig* cyclisation to give the corresponding pyrroles. This was avoided when a stronger base TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene or 2,3,4,6,7,8-hexahydro-1*H*-pyrimido[1,2-*a*]pyrimidine) was used in the absence of a copper catalyst. When these optimised conditions were later applied to the reactions of **74**, the yields of the products **75** were dramatically increased.

To probe the mechanism of these reactions, aziridine **76** was used to investigate whether the regioselectivity was dictated by the alkynyl substituent (Scheme 23), as a literature precedent suggested that alkynylaziridine ring opening processes could occur through an allene carbenoid intermediate.[63–65] However, as shown in Scheme 23, with the absence of the C2 alkynyl group, aziridine **76** underwent a regiocontrolled nucleophilic addition with phenol at the more hindered C2 to give **77**. This unanticipated result prompted the authors to carry out computational studies, which showed that, in both alkyl- and alkynyl- aziridines, the C2–N bond was longer than the C3–N bond. Additionally, there was a partially positive charge on C2. An X-ray analysis of aziridine **78** (Fig. 4) confirmed that the C2–N bond length was 1.552 Å, longer than the 1.496 Å of the C3–N, implying that it was indeed the weaker bond. Furthermore, the ethynyl–C2–methyl bond angle is greater than that of a normal tetrahedral carbon, making it more susceptible towards nucleophilic attacks.



Scheme 23.

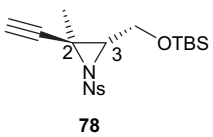
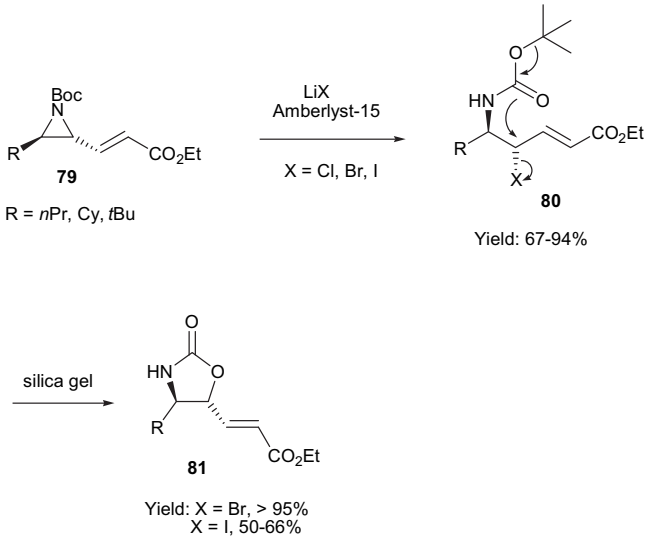


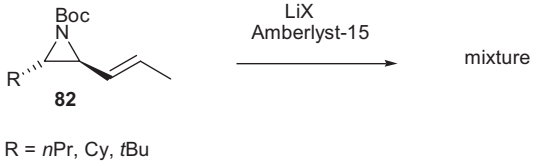
Figure 4. X-ray evidence suggested that C-2 centre is more susceptible towards nucleophilic attacks.

Halides are another good group of nucleophiles in the reactions with aziridines.[66] Righi et al. found that *N*-Boc-alkenylaziridines **79** underwent regioselective ring-opening with lithium halides when catalysed by Amberlyst-15 (Scheme 24).[67] With various R substituents, only single regioisomers **80** were observed. Interestingly, when purified by silica gel column chromatography, the bromo and iodo products underwent intramolecular S_N2 reactions to give the oxazolidinones **81**, whereas no conversion occurred on the chloro derivatives.



Scheme 24.

Nevertheless, when aziridine **82** was used, with a methyl group replacing the carboxylate group of **80**, the reactions gave a complex mixture of products (Scheme 25).

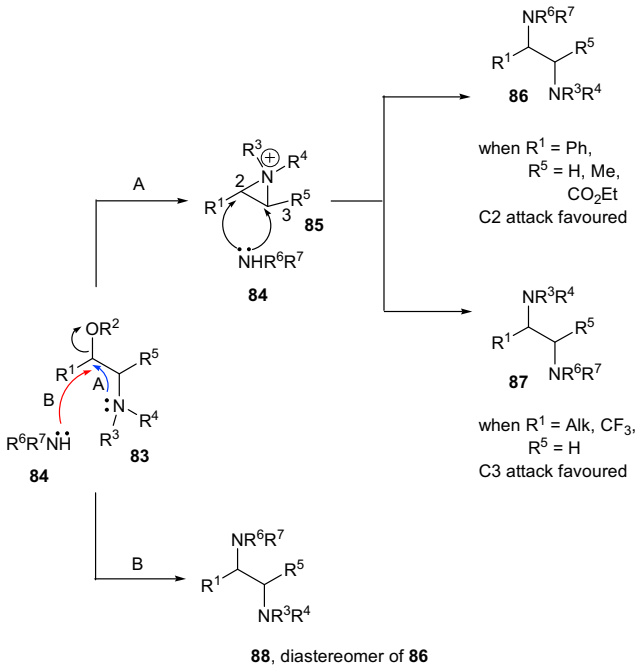


Scheme 25.

4. via Aziridinium ions

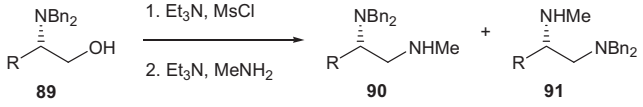
Aziridinium ions have gained increasing interest from synthetic chemists.[68] They are useful intermediates in facilitating aziridine ring-opening processes and have proved to be valuable for the synthesis of chiral diamines.[68] A general strategy in forming aziridinium ions such as **85**, as shown in path A in Scheme 26, relies on an intramolecular S_N2 reaction of hydroxyamine **83**.[68–71] Subsequent regioselective attack of **85** with amine **84** will give C2 and/or C3 addition adducts **86** and/or **87**. The regioselectivity depends on the R^1 and R^5 substituents, or sometimes the nucleophiles.[68,69,72–75]

However, as illustrated in path B, direct intermolecular S_N2 reaction of **83** with amine **84** can occur under the same conditions. This gives diamine **88**, which is diastereomeric to **86**. Owing to the difficulties in differentiating between **86** and **87** by common analytical techniques, such as NMR, questions arise whether the aziridinium intermediates have indeed been formed during the reaction.



Scheme 26.

The O'Brien group has probed the evidence for aziridinium ion formation using a novel deuterium substitution approach.[76] During their investigation of the synthesis of 1,2-chiral diamines, they observed that varying the R group of **89** affected the regioselectivity (Scheme 27). When R=Me, Bn or *i*Pr, **90a–c** were favoured against **91a–c** (Table 3), whereas, when R=Ph, **91d** was synthesised with an excellent regioselectivity. They argued that the formation of **91d** must have proceeded via an aziridinium ion intermediate, whereas it was not conclusive for the formation of **90a–c**, since direct S_N2 substitution on **89a–c** with $MeNH_2$ would also give **90a–c**.

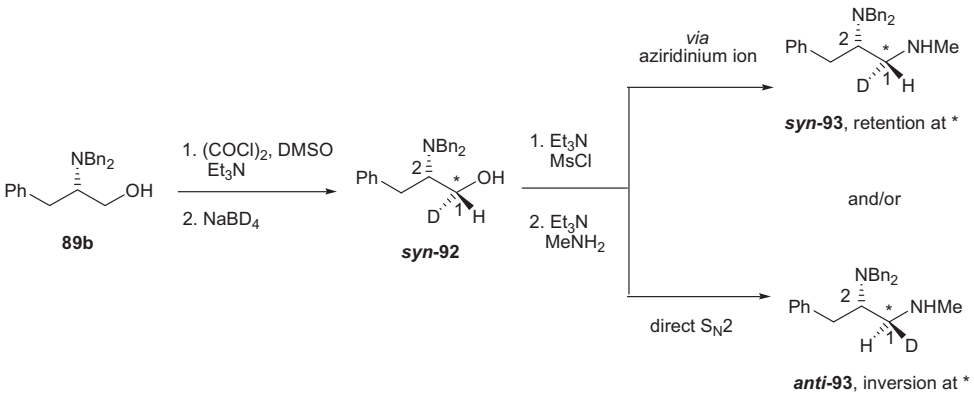


Scheme 27.

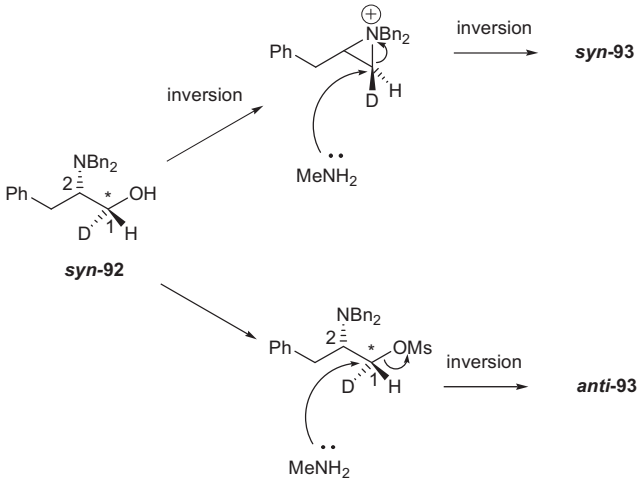
Table 3
Regioselectivity of 1,2-chiral diamines synthesis affected by the R substituents of **89a–d**

Starting material	R	Yield (%)	**90a–d**:**91a–d**
89a	Me	78	70:30
89b	Bn	70	94:6
89c	*i*Pr	62	93:7
89d	Ph	78	2:98

To clear up this ambiguity, they prepared the deuterated adduct *syn*-**92** by incorporating a deuterium atom onto the α-hydroxy carbon of **89b** and determined the mechanism of nucleophilic addition of NH_2Me by analysing the stereochemistry of the products. As depicted in Scheme 28, compound *syn*-**92** was prepared via a Swern oxidation of **89b** followed by reduction with sodium borodeuteride. Subsequent methanesulfonate formation with MsCl followed by treatment with $MeNH_2$ gave a 94:6C1/C2 addition regioisomeric mixture with C1 addition product **93** as the major isomer. Further experimental and NMR analyses revealed that **93** consisted of an 85:15 diastereomeric mixture of *syn*-**93** and *anti*-**93**. As illustrated in Scheme 29, the retention of the C1 stereocentre of *syn*-**93** indicated that this process went through an aziridinium ion intermediate, whereas the C1 inversion conformation of *anti*-**93** came from a direct S_N2 process.

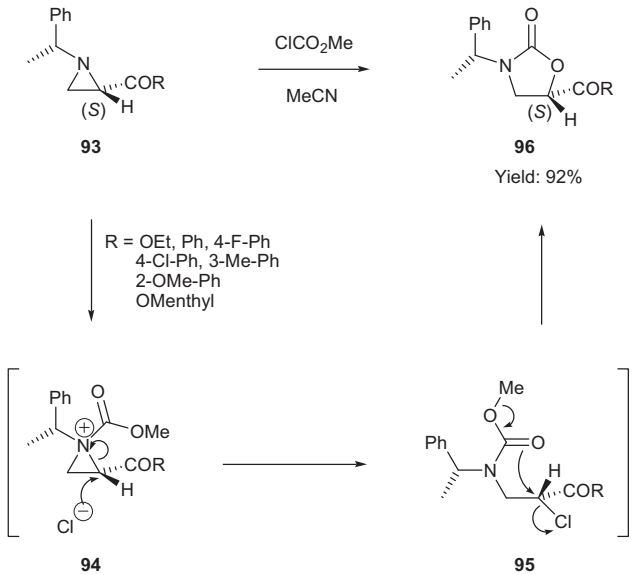


Scheme 28.



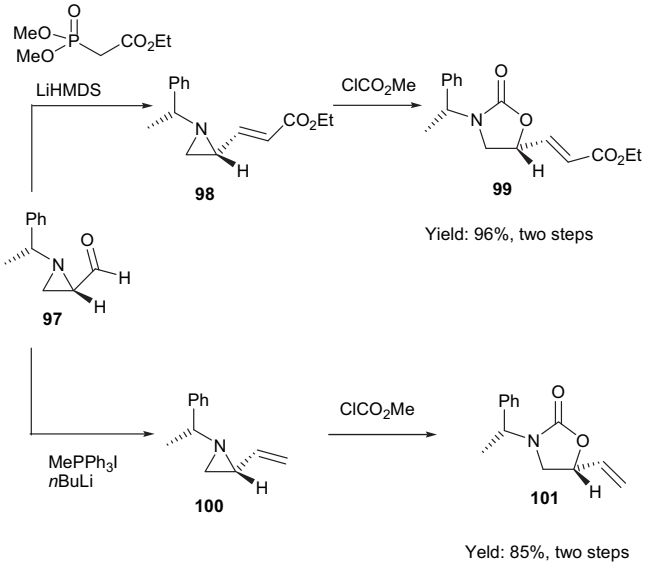
Scheme 29.

Ha et al. have reported a novel synthesis of oxazolidinones via aziridinium ion species (Scheme 30).[77] Acylation of the nucleophilic nitrogen of carboxylate aziridines **93** gave aziridinium ions **94**, which were more reactive and regioselectively attacked by the resulting chloride anion to give the chlorides **95**. Chloro-substituted intermediates **95** were then converted into oxazolidinones **96** through intramolecular S_N2 reactions. The formation of the aziridinium intermediate was also evidenced by the isolation of compound **95** when the reaction was performed in toluene instead of acetonitrile. Furthermore, when **95** was heated under reflux in acetonitrile, it gave oxazolidinone **96** in excellent yield.



Scheme 30.

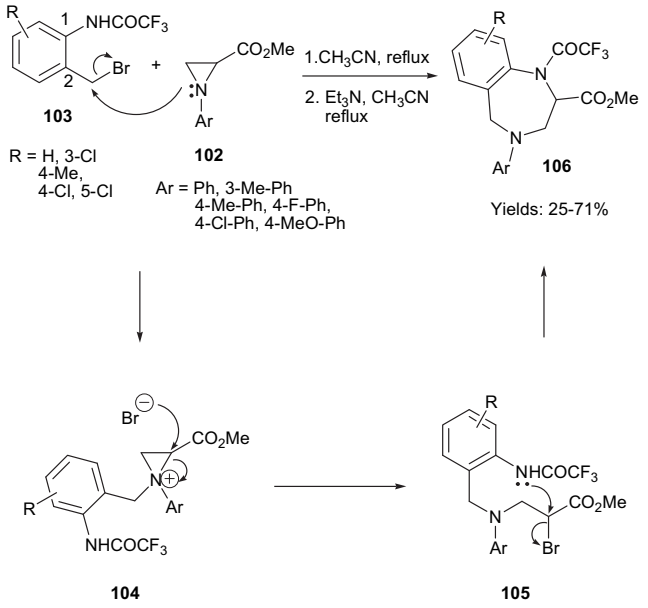
In addition to carboxylate aziridines, Ha also investigated vinylaziridines **98** and **100**, prepared from aldehyde **97** via a Horner–Wadsworth–Emmons reaction and a Wittig reaction, respectively (Scheme 31). When exposed to standard conditions, oxazolidinones **99** and **101** were isolated in good yields and with excellent regioselectivity.[77]



Scheme 31.

Wang et al. extended this methodology to the synthesis of 1,4-benzodiazepine derivatives **106** (Scheme 32).[78] This process began with N-benzylation of aziridines **102** with benzyl bromides **103** followed by a highly regioselective ring opening of the aziridinium intermediates **104** by the resulting bromide anion to generate the bromoesters **105**. The regioselectivity was ca. 10:1, as determined by ^{1}H NMR, in favour of attack on the more substituted carbon adjacent to the ester group. Although the compounds **105** could be isolated by silica gel column chromatography, they were used in a one-pot process by the addition of triethylamine under reflux to

furnish the desired products **106**. The overall yield was respectable, typically around 50–60%, with the exception of R=3-Cl and Ar=phenyl, giving a yield of 25%. This tandem method provides an efficient way of preparing 1,4-benzodiazepines with easy availability of starting materials and a simple procedure.



Scheme 32.

5. Conclusions

Regioselective ring opening of aziridines has a unique value in constructing carbon–carbon bonds and incorporating nitrogen into molecules. In general, phenyl substituents are particularly effective for directing regioselective attack, both for carbon and heteroatom nucleophiles. The presence of Lewis acids proved to be essential in some cases and their effects were fascinating. Recent developments also demonstrated that adjacent olefin or hydroxymethyl substituents have a similar effect. Some interesting results with carboxylate-substituted aziridines have been observed, where the control elements are less obvious. Finally, aziridinium chemistry has significant potential in directing regio- and stereo-controlled attack, which allows the rapid formation of a variety of heterocycles.

Acknowledgements

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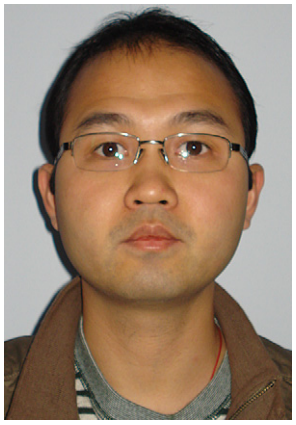
Biographical sketch



Pengfei Lu received his B.Sc. in pharmaceutical sciences in 2002 from the Guangdong Pharmaceutical University in China. He then moved to the UK and obtained his M.Sc. in Drug Chemistry in 2004 from the University of Newcastle upon Tyne. He started his Ph.D. at Imperial College London in 2005 under the supervision of Professor Donald Craig, where he worked on approaches based on aziridine and metathesis towards alkaloid synthesis. Upon completion in 2009, he joined the group of Dr Igor Larrosa at Queen Mary University of London as a postdoctoral research assistant, where he is currently based. His research focuses on C–H activation using transition metals.