Aziridines: epoxides' ugly cousins?

J. B. Sweeney

Department of Chemistry, University of Reading, Reading, UK RG6 6AD.
E-mail: j.b.sweeney@rdg.ac.uk

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Aziridines, the nitrogenous analogues of epoxides, have until recently excited far less interest amongst synthetic organic chemists than their oxygenated counterparts, with some justification. A range of reviews concerned with the physical properties,[1] synthesis (asymmetric[2] and otherwise[3]), reactions[4] and utility of aziridines exists; this review briefly summarizes the similarities and differences between oxiranes and their nitrogenated analogues, concentrating on the underlying properties of aziridines and recent developments in their chemistry. In addition to descriptions of the physical nature of aziridines, especially those features which underpin their utility as synthetic intermediates, the sections beneath describe reactions involving alkylative ring-opening and synthesis of aziridines.

1 Physical properties of aziridines

Aziridine (**1**), also known as *ethyleneimine*, the simplest of the class of three-membered saturated nitrogen-containing heterocycles is a water-soluble, colourless, distillable liquid (b.p. 57 °C).

(**1**)

Joe Sweeney was born in Liverpool in 1963 and he graduated from Imperial College in 1984; he carried out his DPhil studies under the supervision of Professor Jack Baldwin in the Dyson Perrins Laboratory at the University of Oxford. After completing his doctorate in 1987, Joe was a Royal Society Fellow in the laboratories of Professor Steve Benner at the ETH in Zürich, where he carried out research in the area of anti-sense nucleic acids. Joe took up a lectureship in chemistry at the University of Leicester in 1989 and moved to the University of Bristol the following year. In 1996 he took up his present position as Reader in Biological Organic Chemistry at the University of Reading. The research interests of the Sweeney group are diverse: asymmetric synthetic methodology and organometallic chemistry have been mainstays of their research effort and the group is currently engaged in the study of the Neocarzinostatin protein complex from both synthetic and biological aspects.

The compound undergoes ready polymerization, *via* nucleophilic ring-opening (*vide infra*), explosively so when treated with acids. Aziridine exhibits weaker basicity than alkylamines, but stronger basicity than arylamines (the aziridinium ion has pK_a = 7.98), and reacts in a similar fashion to secondary amines with alkylating agents. Aziridines differ from other secondary amines, however, in that the additional bond strain caused by the geometric constraints of the trigonal ring makes the barrier to inversion at nitrogen considerably higher than in acyclic analogues. Thus, the activation enthalpy of the N-inversion of 2-methylaziridine is, at approximately 70 kJ mol^{-1}, considerably greater than that of a typical secondary amine but still not enough of a retardation to prevent racemization at room temperature. If, however, an electronegative substituent is present on nitrogen the inversion barrier is much augmented such that, for instance, 1-chloro-2-methylaziridine (in which the inversion barrier $\Delta G^{\ddagger}$ = 112 kJ mol^{-1}) can be separated into diastereomers which are stable at room temperature, and (+)-(*S*)-1-chloro-2,2-bis(methoxycarbonyl)aziridine can be prepared by enzymatic hydrolysis of the racemic compound. The amide derivative, **2**, of this compound (whose structure has been analysed by X-ray crystallography, Fig. 1) exists exclusively in the (*Z*)-conformation, which is the dominant form even when a solution of **2** is heated to 50 °C.[5]

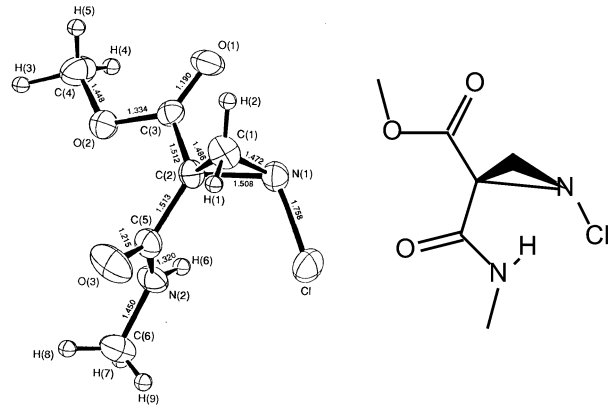


Fig. 1 (−)-*E*-1-Chloro-2-methoxycarbonyl-2-methylcarbamoylaziridine (**2**).

2 Biological properties of aziridines

As powerful alkylating agents, aziridines have an inherent *in vivo* potency, often based primarily on toxicity rather than specific activity. There are, however, several classes of aziridine-containing natural products which marry potency with selectivity, of which perhaps the best-known are the Mitosanes (Fig. 2).[6] The Mitosanes were first isolated from soil extracts of *Streptomyces verticillatus* and they exhibit both anti-tumour and antibiotic activity: structure–activity relationships have

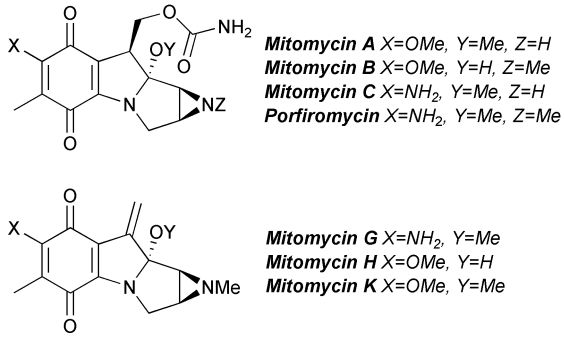
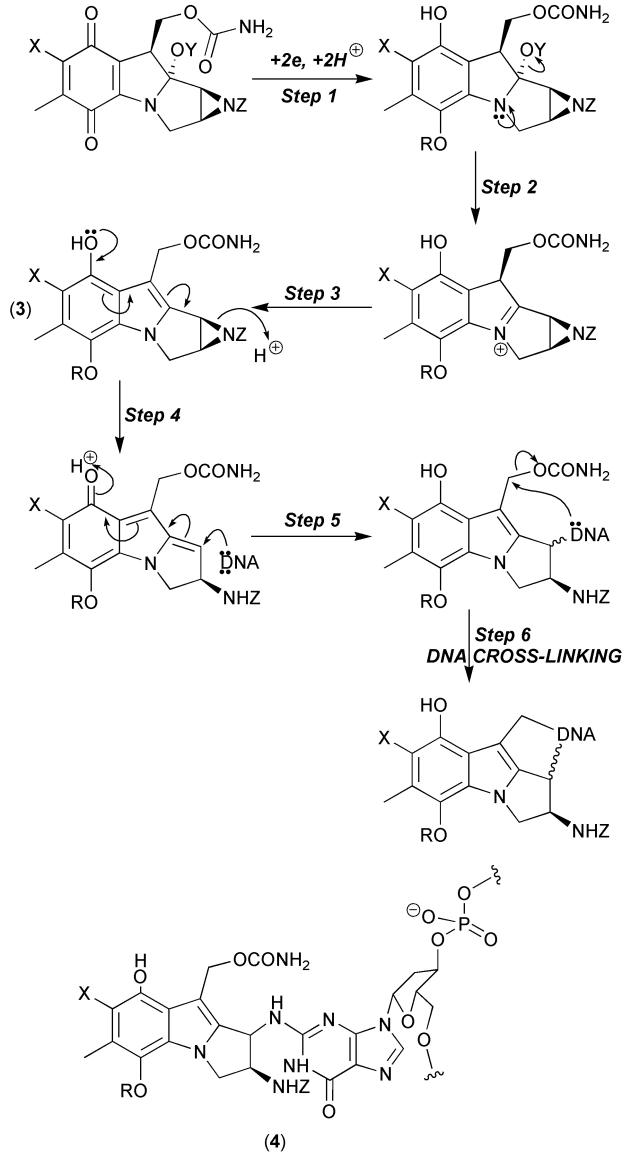


Fig. 2 The Mitosanes

identified the aziridine ring as being essential for such anti-tumour activity, and a large amount of work has concentrated on synthesizing derivatives of these natural products with increased potency.

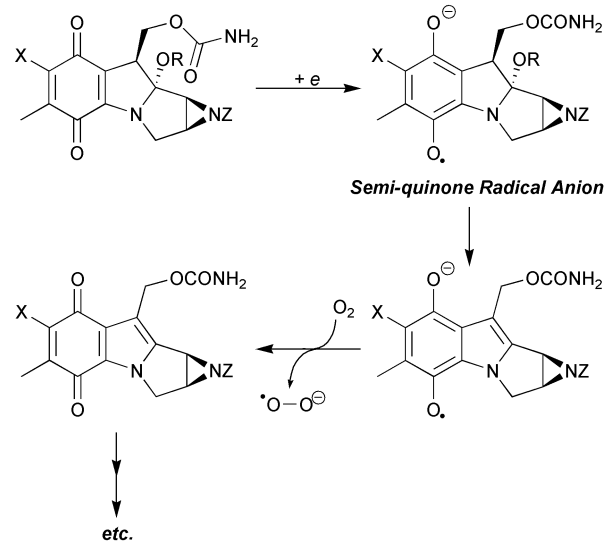
These natural products represented one of the first classes of bioactive compounds to rely on a *bioreductive activation* to provide a means for DNA alkylation. Thus, in the first step of the postulated mechanism of action, the natural products are converted from the native quinone form to the hydroquinone (Scheme 1); secondly, formation of indoloaziridine **3** occurs.



Scheme 1 Mode of action of Mitosanes.

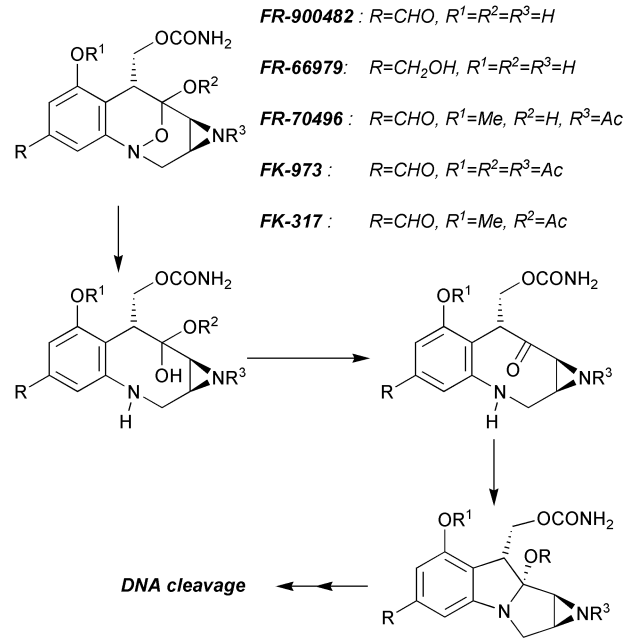
The aziridine ring is next cleaved and DNA is first alkylated (step 5) and then cross-linking occurs (step 6): compounds such as **4** are isolated from cells treated with Mitomycins. The Mitosanes are one of the few classes of naturally-occurring antibiotics to exhibit the same mode of action *in vivo* and *in vitro*.

An alternative mode of action, involving a semi-quinone radical anion as a key intermediate (Scheme 2), has been expounded by Danishefsky and co-workers to explain certain observations which are at odds with the previous mechanism.[7]



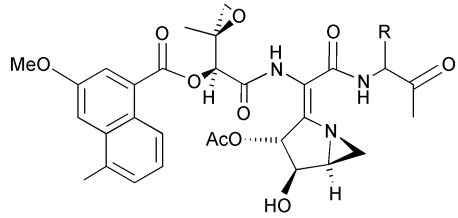
Scheme 2 Alternative mode of action of Mitosanes.

Related compounds which have also shown similar anti-cancer activity are the FR and FK compounds shown below.[8] Consideration of the acetal-like core of these molecules reveals an intimate relationship with the Mitosanes (Scheme 3).



Scheme 3

A structurally-distinct class of naturally-occurring aziridine derivatives possessing potent biological activity, isolated from *Streptomyces grieseofuscus S42227* by Nagaoka and co-workers, is the Azinomycin family (Fig. 3).[9] This class of compounds possesses a wide range of activity against a range of cancers, including solid tumours, and Azinomycin-like structures have been shown to exert cytotoxicity against a variety of

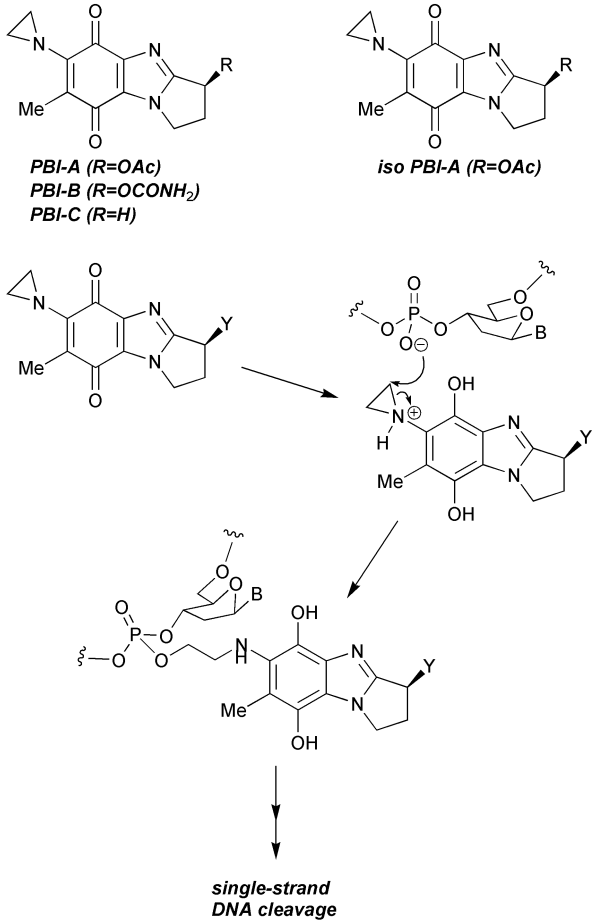


R=H, Azinomycin A
R=CHO, Azinomycin B

Fig. 3

human tumour cell lines. The activity of all of these compounds again lies in their ability to act as DNA cross-linking agents, *via* nucleophilic ring-opening of the aziridine and epoxide moieties by N-7 positions of purines. It is not clear at present which ring-opening reaction takes precedence in the cross-linking event.

The PBI class of natural products represents another type of DNA-alkylating aziridinyl quinone species.[10] In these compounds, however, the aziridine 'warhead' is directly attached to the quinone subunit and undergoes ring-opening by nucleophilic attack of the DNA phosphate backbone, rather than alkylation by a purine nitrogen atom, as in the case of the Mitosanes (Scheme 4).



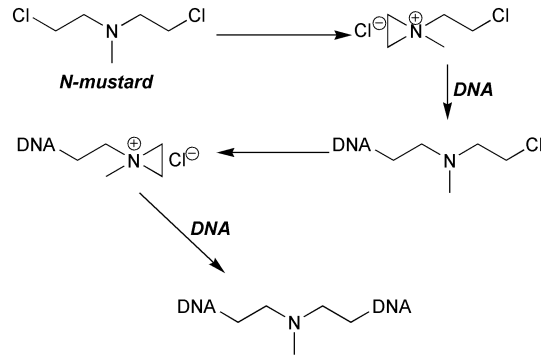
PBI-A (R=OAc)
PBI-B (R=OCONH$_2$)
PBI-C (R=H)

iso PBI-A (R=OAc)

single-strand DNA cleavage

Scheme 4

Finally, in this section a range of synthetic azidirines has been examined for their suitability as pharmaceutical agents, based on the observations in the 1960s that *nitrogen mustards* (such as di(2-chloroethyl)methylamine) were able to reduce the rate of tumour growth in mice models. Nitrogen mustards (so-named due to their close structural resemblance to *sulfur mustard*, di(2-chloroethyl)sulfide, the 'mustard gas' of the First World War) are very active alkylating agents due to their ability to form *aziridinium ions* which are rapidly alkylated by DNA (*inter alia*) (Scheme 5).



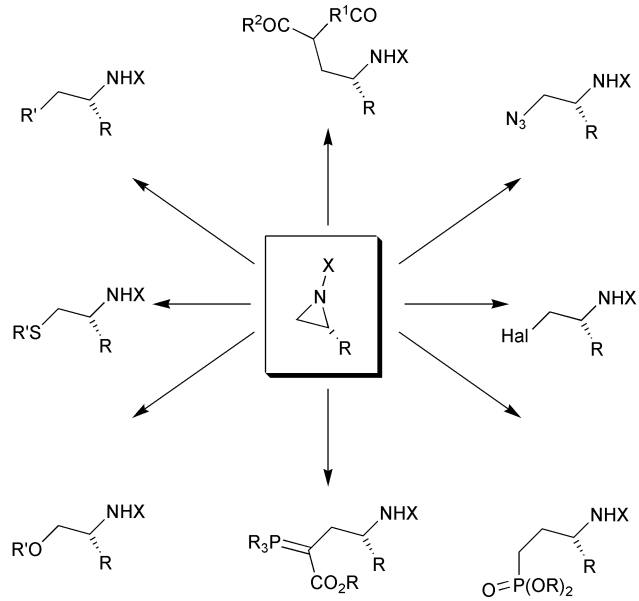
Scheme 5

In particular, N-mustard-based ADEPT (antibody-directed enzyme pro-drug therapy) strategies (in which a protected form of the mustard is directed with high selectivity to a tumour site) have attracted great interest in recent years as potential cancer chemotherapies.[11]

3 Reactions of aziridines

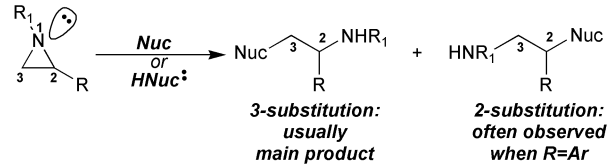
3.1 Ring-opening processes[4]

The combination of Bæyer strain (in aziridine itself estimated at around 111 kJ mol^{-1}, comparable with that of oxirane) inherent in the three-membered heterocycle and the electronegativity of the heteroatom mean that aziridines are willing to undergo ring-cleavage reactions under relatively mild conditions. As might be expected, due to the diminished electronegativity of nitrogen compared to oxygen, ring-opening reactions of these heterocycles are less facile than the corresponding reactions of epoxides, but there is still a wealth of examples of such chemistry (Scheme 6). There are several features of these reactions which are worthy of consideration.



Scheme 6

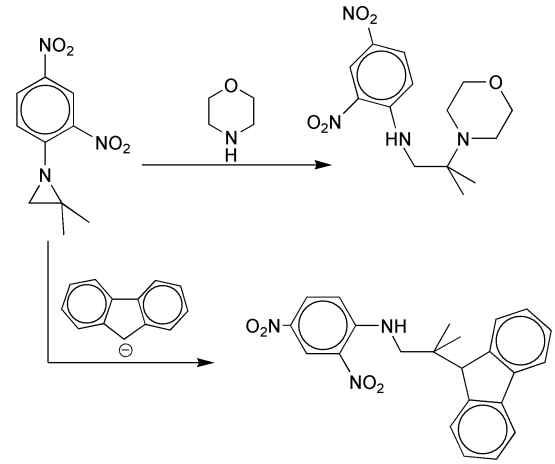
Regioselectivity in ring-opening processes. Ring-cleavage reactions of aziridines proceed by nucleophilic attack at carbon, in an analogous manner to similar reactions of epoxides. Where an aziridine is unsymmetrically-substituted (as would typically be the situation), reaction with a nucleophile can lead to two products of ring-opening (Scheme 7). As would be expected,



Scheme 7

most nucleophiles preferentially direct their attack to the site of lesser substitution, though electronic considerations (for instance in the ring-opening of 2-arylaziridines) may perturb this preference.

An anomalous reactivity profile is occasionally observed where the nucleophile concerned is either hindered or a relatively weak Lewis base *and* the aziridine N-substituent is a relatively weak activator. As shown in Scheme 8, in this situation, attack at a quaternary C atom is preferred over the alternative, less substituted C atom.[4]



Scheme 8

3.2 Effect of Lewis acid

Epoxides are able to act as Lewis bases directly through their non-bonded electron pairs, meaning that the presence of Lewis acids in reactions enhances the rate of ring-opening processes, primarily by weakening the already strained C–O bond. In the case of aziridines, only when there is a non-oxygenated N-substituent can a direct interaction with Lewis acids occur (Fig. 4), and since a polar activating N-substituent is often required to

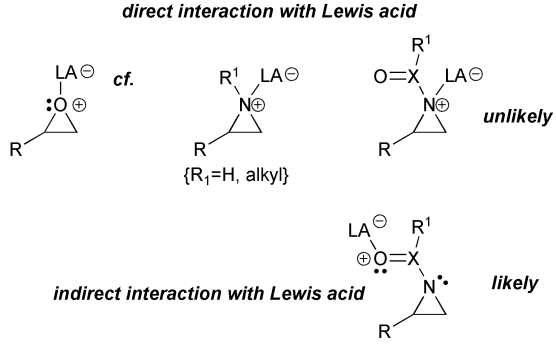


Fig. 4

enable efficient ring-opening of aziridines (*vide infra*), the reactions of aziridines are less dominated by the use of Lewis acid than those of epoxides. Nonetheless, the desirability of a polar, oxygenated N-substituent for ring-opening still allows for some use of this type of activation, *via* coordination of oxygen lone-pairs to Lewis acid.

3.3 The nature of the N-substituent

General points. The chemistry of aziridines is further complicated by comparison to that of epoxides by the presence of an additional valency on the heteroatom. In ring-opening reactions, it is often the case (especially with highly basic, carbon-centred nucleophiles) that the N–H bond of the parent aziridines must be masked to avoid deprotonation as a competitive side-reaction: additionally, the N-substituent should ideally activate the aziridine ring to ring-opening by stabilizing the resultant amide anion arising from a ring-cleavage process. Protonation may activate aziridines to ring-opening by relatively non-basic nucleophiles, but this, simplest, activating method is not appropriate for more basic nucleophiles, especially carbon-centred nucleophiles. Since the mid-1960s, aziridines have been classified as 'activated' or 'non-activated' according to whether or not nucleophilic ring-opening reactions proceed in the absence of positive charge at nitrogen[12] and this classification is intimately related to the nature of the substituent at the nitrogen atom of the heterocycle. The rôle of activating group is often neatly filled by oxygenated substituents such as sulfonyl, sulfinyl, phosphoryl, phosphinyl or carbonyl functional groups (Fig. 5).

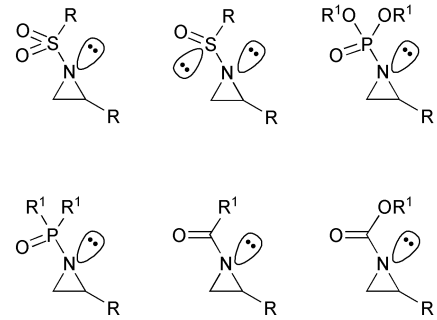
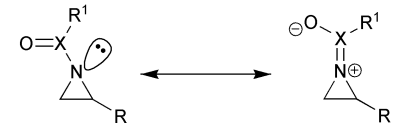


Fig. 5

In these aziridines, there is little resonance interaction between the N non-bonded pair and the X=O bond (*vide infra*), due to the large increase in ring-strain which would be associated with the amidate-like resonance isomers shown in Scheme 9.

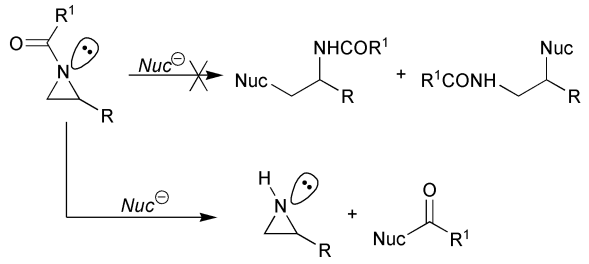


Scheme 9

Thus, the *kinetic* activation provided by these N-substituents relies on inductive effects, leading to an augmentation of the polarization of the C–N bonds, already present due to the larger electronegativity of N *versus* C. There is also a *thermodynamic* effect whereby the amide-like anion produced after ring-cleavage is stabilized: now, in the case of carbonyl substituents, resonance stabilization is highly likely. The stabilization of sulfonamide, phosphonamide and phosphinamide anions is again primarily inductive.

When considering acyl activation of aziridines, the oxidation state of the carbonyl substituent (and, hence, the carbonyl electrophilicity) is crucial: when simple (more electrophilic) acyl groups are present on the aziridine nitrogen, ring-cleavage is frequently *not* observed upon reaction with carbon-centred

nucleophiles. Instead, as shown by several groups, acyl transfer is the typical reaction pathway (Scheme 10); for instance, this is the method of choice for C-acylation of enolates derived from 1,3-dicarbonyl compounds.[13]



Scheme 10

This reaction manifold therefore reinforces the statement made earlier concerning N→C resonance electron-donation. When (less electrophilic) alkoxycarbonyl substituents are employed as aziridine activators, a reactivity more typical of these heterocycles is observed upon reaction with nucleophiles, *viz*. ring-opening is favoured. It should be noted, however, that even in these cases there is often a deacylative side-reaction, and the yields of alkylative ring-opening reactions is often mediocre (*vide infra*).

3.4 *N*-Alkyl aziridines

Eis and Ganem showed that *N*-benzyl aziridines may be ring-opened using organocuprates in the presence of boron Lewis acids and Shipman *et al*. have investigated similar reactions involving methyleneaziridines:[14] other than these reports, there has been little investigation into the ring-openings of simple *N*-alkylated aziridines.

3.5 *N*-Sulfonyl aziridines

Without question, aziridines activated by *N*-sulfonyl substitution are the most widely-employed class used in alkylative ring-cleavage reactions. The sulfonamido group is adept at stabilizing negative charge and this renders nucleophilic ring-cleavage of *N*-sulfonyl aziridines a facile process of general utility. Moreover, *N*-sulfonyl aziridines are relatively easily prepared (*vide infra*), are significantly more stable than the corresponding N–H aziridines and are frequently (in the case of tolylsulfonyl substituents) highly crystalline species, thereby simplifying large-scale preparation. The only significant drawback to the use of such aziridines as synthetic intermediates is the reluctance of the sulfonamide bond to undergo cleavage using mild conditions. Thus, in the case of simple sulfonyl substituents (most frequently tosyl, **5**), strongly acidic or reductive conditions must often be employed to liberate the amine product, which is inevitably the desired target of the synthetic sequence.

In addition to the study of novel, milder methodology to allow for removal of such groups,[4] several structurally-modified sulfonamides have been devised to solve this blemish on an otherwise exemplary synthetic copybook, including the use of the β-(trimethylsilyl)ethylsulfonyl (SES) group, **6**,[15] (deprotection effected using fluoride ion), nitrobenzene sulfonamides, **7** and **8**,[16] (deprotection using thiolate ion, *via* Meisenheimer complexes) and 2,2,5,7,8-pentamethylchroman-6-sulfonamide (pmc, cleaved by aqueous acid), **9**.[17] Despite these valuable contributions to the synthetic armoury, still there remains a need for an alternative to sulfonamide activation of aziridines.

N-Sulfonyl aziridines have been widely reported to undergo a range of alkylative ring-opening reactions; where other

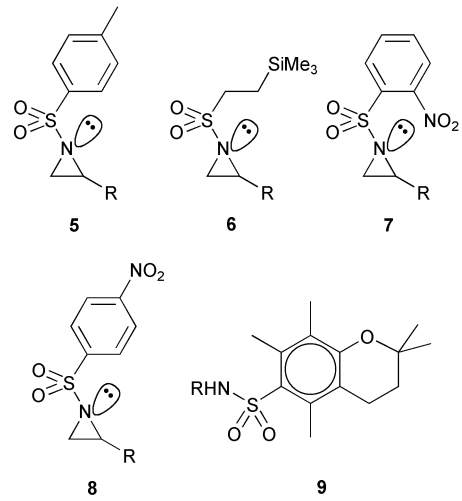
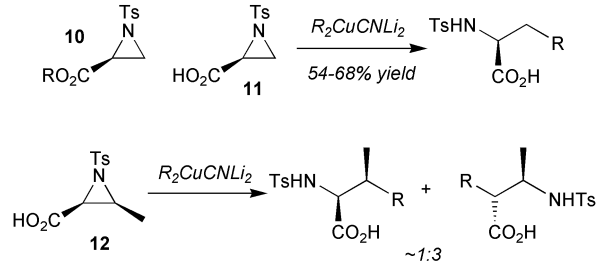


Fig. 6

electrophilic substituents are present in the aziridine (as in the reaction of carboxy aziridines) issues of regiochemistry can be overcome by judicious choice of protection.

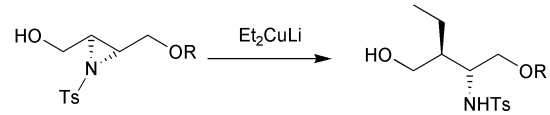
Thus, Young *et al.* overcame this type of problem (as witnessed in the reaction of chiral aziridine **10**, where a mixture of products arising both from ring-opening and attack at the carbonyl group were obtained upon reaction with nucleophiles) by hydrolysing the ester and reacting the aziridine carboxylate **11** with higher order cuprates, whereupon only ring-opened products were observed (Scheme 11). The reaction of the



Scheme 11

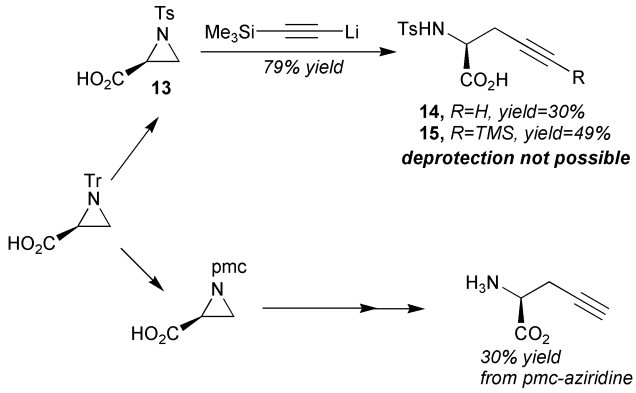
similar aziridine **12** derived from (*S*)-threonine reacted under the same conditions with lower levels of regiocontrol, as might be predicted.[18]

Where unsymmetrical aziridines of similar substitution pattern are used as electrophiles, control of regioselectivity is somewhat more problematic. Tanner and Somfai addressed such a situation by using a directing effect of an unprotected hydroxyl group in the reaction of an aziridine derived from butene-1,4-diol (Scheme 12). Nucleophilic ring-opening by organocuprates then occurred only at the aziridine carbon directly adjacent to the directing group.[19]



Scheme 12

The problems associated with desulfonylation were mentioned above: an example of the problems this can cause is shown below. Thus, chiral aziridine **13** (prepared from serine) was ring-opened efficiently by an acetylide anion to give propargyl glycine derivatives **14** and **15**, which were wanted as part of a study utilizing non-proteinogenic amino acids (Scheme 13).[20] To the disappointment of the researchers involved, no

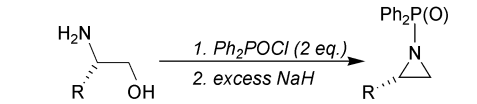


Scheme 13

conditions for desulfonylation were compatible with the triple bond and recourse had to be made to the pmc protecting/activating group (*vide infra*) devised by Ramage *et al.* as a peptide protecting group. The pmc group is readily removed using mild acid, but the need to prepare the corresponding sulfonyl chloride in a relatively laborious manner renders the method unwieldy for synthesis.[21]

3.6 *N*-Phosphoryl and *N*-phosphinyl aziridines

Several groups have investigated the use of phosphorus activating groups in the ring-opening reactions of aziridines. Thus, *N*-dialkylphosphoryl aziridines have been shown to undergo a range of ring-opening reactions with representative nucleophiles, including anions derived from 1,3-dicarbonyl compounds (*vide supra*); *N*-diphenylphosphinyl ('*N*-Dpp') aziridines have been prepared, in a 'one-pot' transformation of enantiomerically-pure 1,2-aminoalcohols by ring-closure of the corresponding N,O-diphenylphosphinylated intermediates (Scheme 14).[22] *N*-Dpp aziridines undergo ring-opening by a



R	iBu	iPr	Bn	Ph	Me	sBu	MeS(CH$_2$)$_3$
Yield	78%	67%	86%	52%	51%	87%	79%

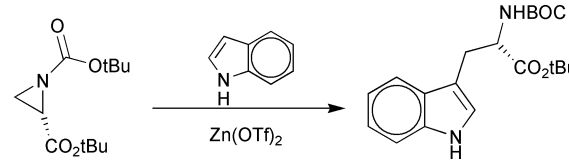
Scheme 14

range of heteroatom and carbon-centred nucleophiles.[22] Both of these classes of phosphorus-substituted aziridine have the advantage that removal of the phosphorus activator may be accomplished under reaction conditions which are significantly milder than those needed for desulfonylation.

3.7 *N*-Acylaziridines

As mentioned above, the oxidation state of the acyl activator plays a crucial effect upon the outcome of ring-opening reactions of *N*-acylaziridines. Thus, when *acyl* activation is employed, ring-opening with certain, soft nucleophiles proceeds by ring-cleavage whereas other, 'hard' nucleophiles deacylate the aziridines. The prediction of regiochemical preference in the reaction of such aziridines with nucleophiles, especially carbon nucleophiles, is not necessarily reliable, with the aforementioned reaction of anions of 1,3-dicarbonyls with *N*-acylaziridines proceeding by deacylation rather than ring-cleavage.[13] Thus, the use of *N*-acyl aziridines is perhaps to be embarked upon with some trepidation.

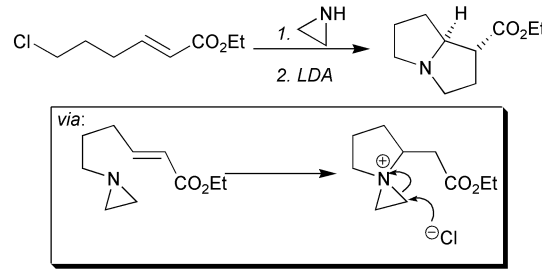
When *alkoxycarbonyl* activation of aziridines is exploited, the situation is somewhat clearer, though still far from entirely predictable. Thus, Kozikowski and co-workers showed that enamine-like nucleophiles reacted with the *N*-BOC aziridine derived from (*S*)-serine exclusively *via* alkylative ring-cleavage (Scheme 15), whereas Baldwin and coworkers found that similar aziridines reacted with organocuprates with variable regioselectivity, obtaining a mixture of products arising from both ring-opening and attack at the ester functionality.[23]



Scheme 15

3.8 Activation *via* aziridiniums

A distinctive class of activation in ring-opening in aziridine chemistry utilizes *in situ* formation of aziridinium cations. Such cations are powerfully activated due to the quaternization at N which further polarizes the C–N bonds and induces ring-opening under mild conditions. Both *inter*- and *intra* molecular (Scheme 16) variations on this theme have been reported.

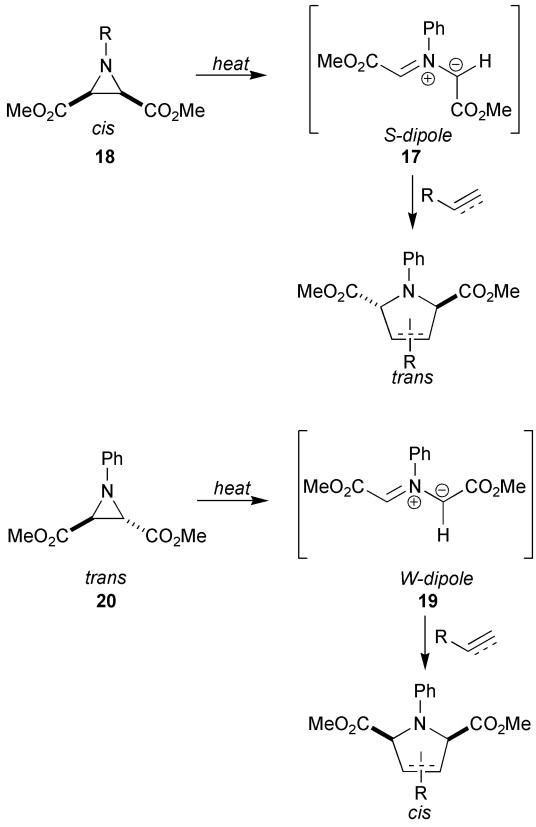


Scheme 16

3.9 Electrocyclic aziridine ring-opening

Aziridines may be considered as precursors to azomethine ylids: when heated, the three-membered ring ruptures stereospecifically (*vide infra*) to generate 1,3-dipoles efficiently and these may be trapped *in situ* with dipolarophiles to give a range of substituted pyrrolidines (Scheme 17). The aziridine stereochemistry is maintained in the stereochemistry of the dipole such that *S*-dipoles (**17**) (and thence *trans*-2,5-substituted pyrrolidines) are obtained from *cis*-aziridines (**18**) and *W*-dipoles (**19**) (leading to *cis*-2,5-substituted pyrrolidines) are obtained from *trans*-aziridines (**20**). *S*-Dipoles are more reactive, reacting efficiently with a wide range of dipolarophiles with retention of geometry whilst *W*-dipoles react cleanly only with very reactive dipolarophiles such as acetylenedicarboxylates and maleimides.

Garner *et al.* have exploited this property of aziridines to design an asymmetric protocol based on this chemistry. These workers prepared camphor sultam-substituted acylaziridines **21** and thermolyzed them in sealed tubes in the presence of maleates, maleimides, vinylidine carbonate and acrylates, obtaining cycloadducts in good yield and with variable diastereoselectivity (Scheme 18).[24] The separated diastereoisomers could be denuded of their auxiliary to give the corresponding pyrrolidines in an efficient manner, thereby providing a means for obtaining a range of chiral pyrrolidine acids.



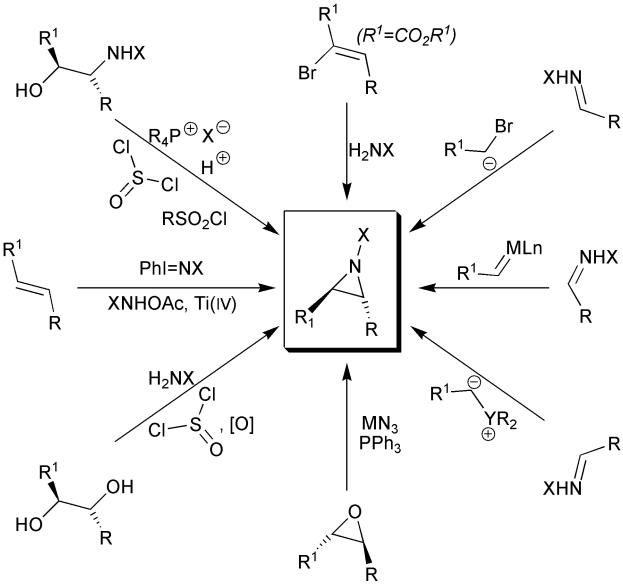
Scheme 17

4 Synthesis of aziridines

It is certain that the chemistry of aziridines has been hindered by the dearth of suitable methods available: as a synthetic class, aziridination is (as Atkinson has observed[25]) 'epoxidation's poor relation'. In other words, the range of synthetic methodology available for preparation of aziridines (summarized diagrammatically in Scheme 19) is dwarfed by that available for preparation of epoxides, especially those methods involving alkenes, such methods traditionally being the mainstay of epoxide preparation.

As summarized diagrammatically in Scheme 20, a key feature responsible for this incongruity is the comparative inertness of N–O and N–N bonds compared to the peroxide bond.

Thus, whereas alkenes react with peroxyacids and (especially in the presence of Lewis acids) alkylhydroperoxides, a parallel reactivity is not observed when alkenes are treated with the aza-analogues, *O*-acylhydroxylamines and *O*-alkylhydroxylamines, respectively. Of great synthetic interest of late (particularly in the enantioselective manifold) is the efficient reaction of



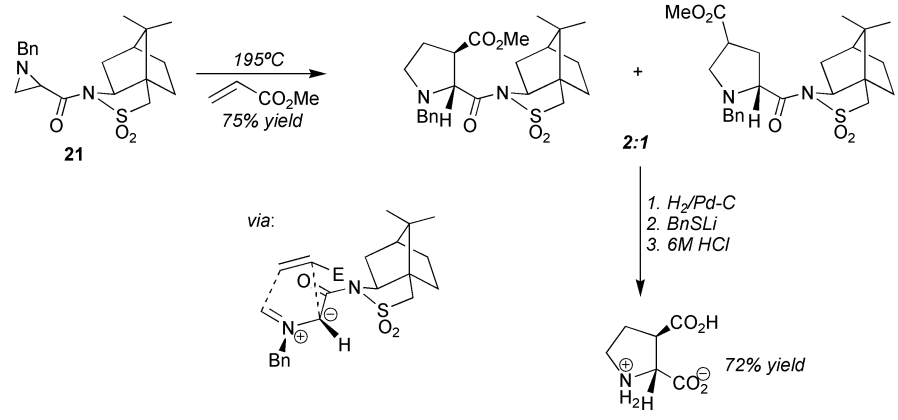
Scheme 19

dioxiranes with alkenes, a process again not mirrored in the reaction of the aza-analogues, diaziridines.[26] Thus, it has been of necessity that the synthetic methods which have been developed for preparation of aziridines have been of a type usually distinct from those apposite for epoxide synthesis; *asymmetric* aziridine-forming reactions have been slow to develop and often have relied on the presence of pre-existing stereogenic centres in the starting material, so much so that it is still fair to say that no truly general method for *direct* asymmetric aziridination exists. The categories available to the synthetic chemists are briefly adumbrated below.

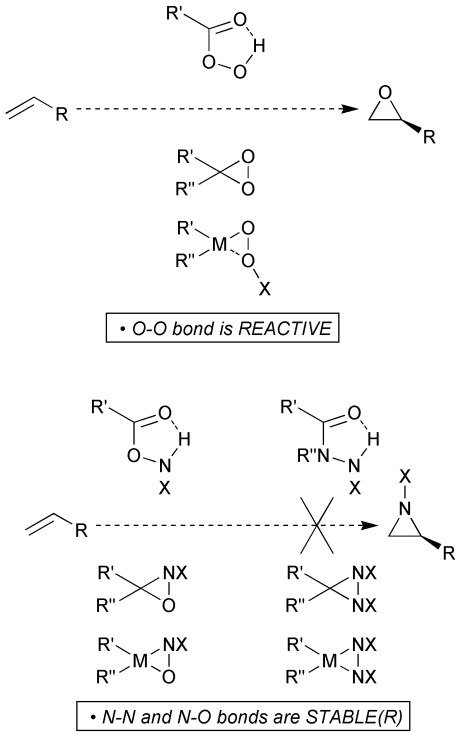
4.1 By addition to alkenes

Nitrene methods[25]. 'Classical' methods for direct aziridination of alkenes have traditionally featured addition of *nitrenes* [reactive intermediates in which nitrogen bears only one substituent, one lone pair and two other electrons (*vide infra*)] to the unsaturated partner. The limitations to the method (often involving alkoxycarbonylnitrenes) are well-documented, with the necessity for harsh reaction conditions and the lack of stereoselectivity constituting two major factors which have limited the attractiveness of this methodology.

Such nitrenes typically were generated by thermal or photochemical decomposition of the corresponding azides and these methods intrinsically lead to mixtures of (more reactive) singlet and (more stable) triplet nitrenes; only singlet nitrenes (in which nitrogen may be imagined to retain its non-bonded

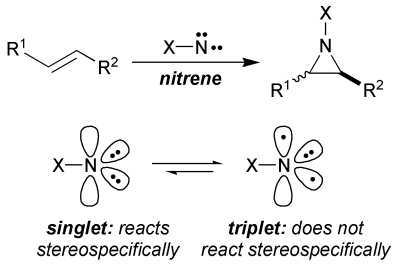


Scheme 18



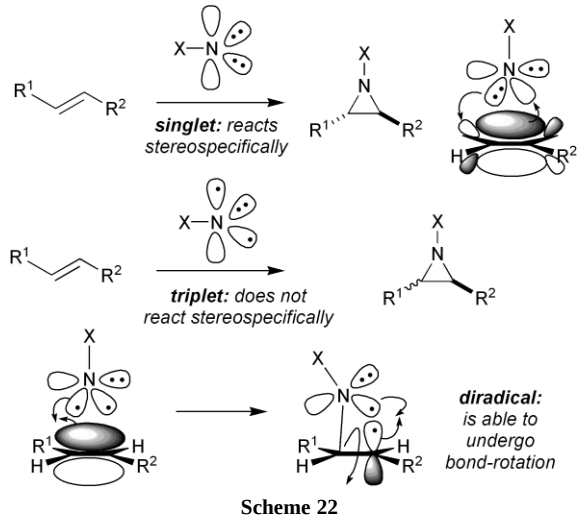
Scheme 20

electrons in *two* orbitals, each containing an anti-parallel electron pair) may be relied upon to react stereospecifically with 1,2-disubstituted alkenes (Scheme 21). Triplet nitrenes (bearing



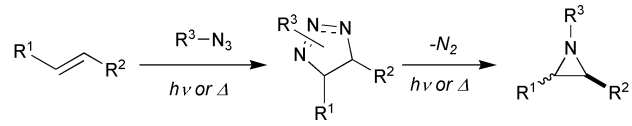
Scheme 21

non-bonded electrons in *three* orbitals, one filled with an anti-parallel electron-pair and two others being semi-filled with one electron each, of parallel spin) react in a two-step process with alkenes (Scheme 22), in which an N–C bond is formed in each step, whereas singlet nitrenes are able to form both new bonds in a concerted process.



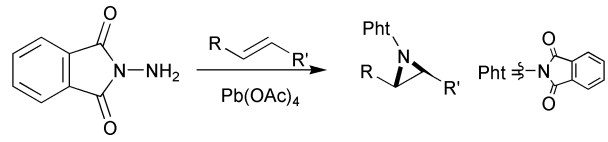
Scheme 22

The nature of the N-substituent in these reactions exerts a powerful effect upon the course of the reaction: the reaction mechanism described above prevails only when acylnitrenes are intermediates. When non-acyl azides are photo- or thermolyzed, a cycloaddition reaction occurs as the first step of the reaction, generating a 4,5-dihydro-1,2,3-triazoline which eliminates N_2 under the reaction conditions to give an aziridine product (Scheme 23). In many instances, however, the intermediate triazoline can be isolated and separately converted to the aziridine product which is not usually formed with good stereocontrol.



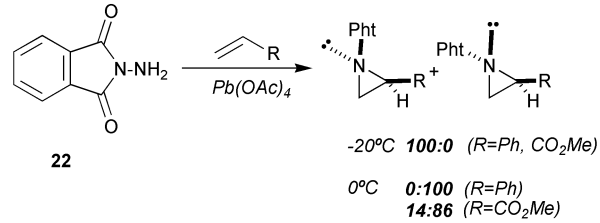
Scheme 23

A useful modification of the method involves *in situ* generation of nitrenes, by means of oxidation of hydrazine derivatives. Of particular relevance is the methodology of Rees and his collaborators by which a range of *N*-amino aziridine derivatives were prepared by reaction of the corresponding hydrazine derivatives with alkenes in the presence of lead tetraacetate (Scheme 24).



Scheme 24

These reactions proved considerably more stereoselective than those of nitrenes generated by the methods mentioned previously, necessarily implying that the nitrene intermediate was formed in the singlet state. Bearing in mind that the nitrogen atoms in N-substituted aziridines are stereogenic (*vide supra*), there is (at least theoretically) an issue of diastereoselectivity in such reactions. Atkinson *et al.* demonstrated that these reactions are highly diastereoselective even when the alkenic component is monosubstituted: thus styrene and methyl acrylate react with *N*-aminophthalamide (**22**) at low temperature (−20 °C) to give exclusively *cis*- (or, perhaps more correctly, *endo*-) configured *N*-phthalamidoaziridines (Scheme 25).



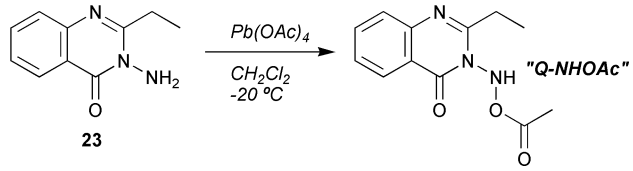
22

Scheme 25

This pronounced stereoselectivity is due to two mutually-reinforcing factors, the inherently high barrier to inversion (*vide supra*) of nitrogen in aziridines and the presence of the electron-withdrawing phthalimido group. That these *endo*-products are formed according to kinetic control is demonstrated when the reactions described above are allowed to warm to temperatures near or above 0 °C, whereupon a partial or complete (*vide infra*) inversion of configuration at nitrogen is observed (as evinced by NMR spectroscopy); in the case of the 2-phenylaziridine, only *exo*-2-phenylaziridine can be detected, but the methoxycarbo-

nylaziridine is obtained as a 5:1 mixture of *invertomers*, this ratio favouring the *exo*-isomer. If the solutions of these aziridines are recooled to −20 °C, no change is observed in the NMR spectra, suggesting that the conversion is an irreversible process. These diastereoisomers can, in certain cases, be separated by crystallization: the solid samples slowly undergo inversion over the course of several weeks upon standing.

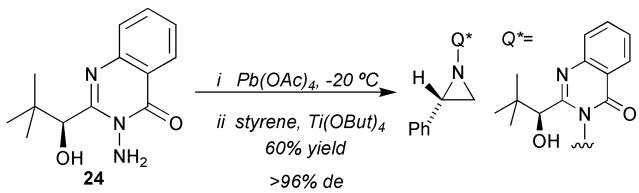
The Atkinson group have shown that the active aziridinating species in reactions involving *N*-aminoquinazolinones (often termed 'Q-NH_2') is very likely to be the corresponding *N*-acetoxylated hydrazine derivatives, rather than the corresponding nitrenes. Thus, reaction of ethylquinazolinone **23** ('Q^1-NH_2') with lead tetraacetate at low temperature generates the corresponding *N*-(acetoxyamino)quinazolinone ('Q^1-NHOAc') as a relatively stable intermediate. This compound, and its analogues, are active aziridinators, reacting with alkenes in good yield to give the corresponding *N*-quinazolinonylaziridines (Scheme 26). *O*-Sulfonyl and *O*-alkylhydroxylamines also act as aziridinating reagents, but the scope of such reactions is limited.[3a]



23

Scheme 26

Upon reflection, these reagents may be considered to be one of the elusive aza-analogues of peroxyacids and these workers have described the mechanistic similarities between the present reaction and that of the Bartlett epoxidation mechanism. Atkinson has since extrapolated these observations and he and his co-workers have developed the chiral Q-reagent **24**, which effects highly stereoselective aziridination of alkenes (Scheme 27).

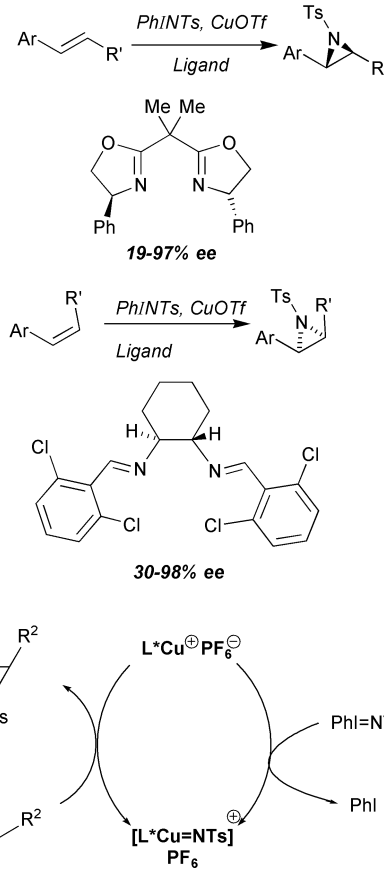


24

Scheme 27

Since the mid-1990s, synthetic attention has been directed more towards the use of metal-stabilized nitrenes as synthetic effectors of alkene aziridination. Thus, porphyrin and salen catalysts, known for their ability to aziridinate alkenes in the presence of the nitrene precursor *N*-tosyliminophenyliodinane, provided the inspiration for a new generation of copper-based catalytic processes. In particular, Evans, Jacobsen and Katsuki have described the utility of chiral bis-oxazolines and 1,2-diamines in *enantioselective* aziridination of a range of alkenes.[27] Jacobsen *et al.* have accrued data which suggest that the process proceeds *via* a discrete copper–nitrene complex, rather than a radical mechanism (Scheme 28).[27c]

These reactions, though representing a major achievement in the synthesis of enantiopure aziridines, still retain some drawbacks, not least of which is the frequent requirement for the reactions to be conducted using a large excess (often 5 equivalents) of alkene. A further limitation to the methodology is the variable enantiocontrol exerted during the processes. Subsequent efforts inspired by the seminal work of these groups

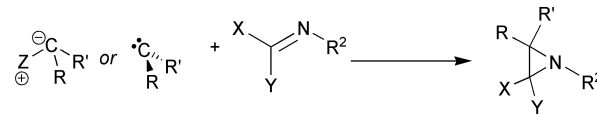


Scheme 28

have ameliorated some, though by no means all, of the blemishes which impair the elegance of the method.

4.2 By addition to imines

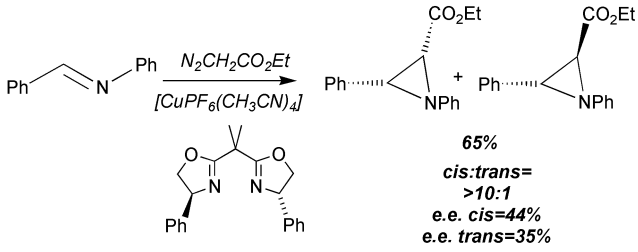
Carbene and ylid methods. The synthesis of aziridines by reaction of nitrenes and nitrene equivalents with alkenes involves the roughly simultaneous (*vide supra*) formation of two new C–N bonds. If one performed an alternative synthetic analysis, one can immediately identify a method which is centred around the simultaneous formation of *one* C–N bond and *one* C–C bond. Thus, if a *carbene* or equivalent thereof (such as an *ylid*) were to react efficiently with an imine, a useful aziridination protocol would result (Scheme 29). This area of research has only recently attracted the attention of synthetic organic chemists.



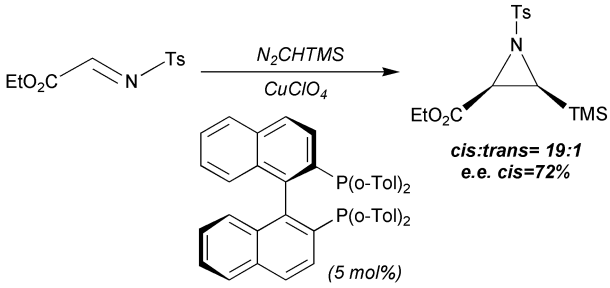
Scheme 29

Thus, Jacobsen and Finney reported that the metallocarbene derived from ethyl diazoacetate and copper(I)hexafluorophosphate adds with mediocre stereoselectivity to *N*-arylaldimines. At best, diasteroeselectivities were acceptable (often > 10:1, in favour of the *cis*-isomers) but enantioselectivity was low (= 44% ee) (Scheme 30).[28]

The similar copper(I)-catalyzed reaction of trimethylsilyldiazomethane with *N*-tosylimines in the presence of (*R*)-Tol-BINAP proceeded with better levels of enantiocontrol, but still falls short of the standards expected of modern asymmetric transformations (Scheme 31).[29]

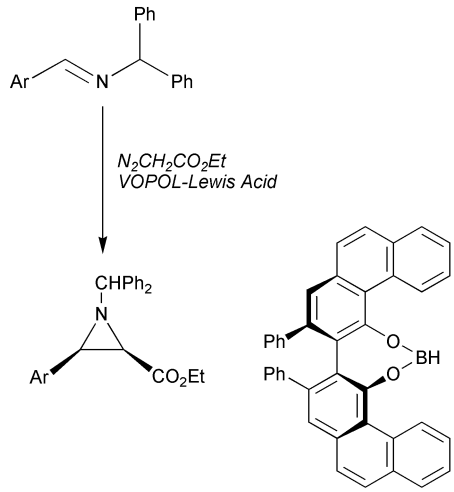


Scheme 30



Scheme 31

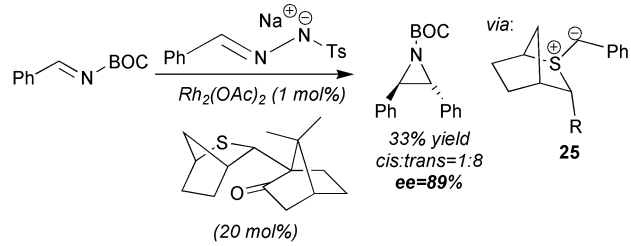
Wulff *et al.* have approached this reaction class from a different perspective, utilizing so-called 'vaulted', axially-chiral boron Lewis acids to catalyze the asymmetric addition of ethyl diazoacetate to imines (Scheme 32).[30] Although impressive in terms of the enantiocontrol shown during the reaction, the elegance of the procedure is slightly tarnished by the requirement that a benzhydryl substituent be present on the imine nitrogen atom, since this group is not an aziridine activator and there is, therefore, a need for deprotection and attachment of a suitable activating group.



Ar	cis:trans	*Yield/%*	*ee/%*
Ph	*>50:1*	*77*	*97*
2-Naphthyl	*30:1*	*70*	*97*
p-$AcOC_6H_4$	*40:1*	*67*	*96*
p-$NO_2C_6H_4$	*11:1*	*68*	*91*
p-BrC_6H_4	*16:1*	*64*	*97*
o-MeC_6H_4	*3:1*	*51*	*98*
2-furyl	*16:1*	*55*	*95*
n-propyl	*>50:1*	*54*	*91*
cyclohexyl	*35:1*	*72*	*96*

Scheme 32

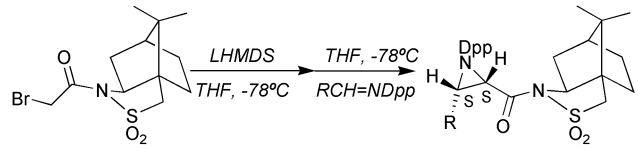
The reaction of sulfur and iodine ylids[31] with imines to generate aziridines is a process analogous to the carbene methods described above. Thus, these ylids react to give β-sulfonium or β-iodonium amide anions which are not isolated, instead preferring to react *via* ring-closure to give aziridines directly. Aggarwal *et al.* have made great contributions to the sulfonium area of late, with the results of their investigations into the catalytic asymmetric synthesis of a range of aziridines using chiral sulfides to catalyze the addition of metal carbenoids to imines (Scheme 33).



Scheme 33

Thus, this group has tackled the problems incurred by the need to use diazoesters (with the associated safety issues) by devising a cunning method for *in situ* generation of these intermediates from the considerably stabler tosylhydrazones, and has used a range of imine N-substitution (tosyl, SES, Dpp and carbamoyl, amongst others) [32] to allow for preparation of a range of usefully-activated aziridines in high ee. The reaction proceeds *via* nucleophilic attack of chiral sulfonium species **25** upon the imine component.

The aza-Darzens reaction also falls into this category of aziridine-forming reaction. Several groups have investigated this route to aziridines, especially in the asymmetric manifold, in recent years. Thus, reactions of *N*-Dpp imines with (*R*)- and (*S*)-camphorsultam-derived α-bromoenolates[33] (Scheme 34)

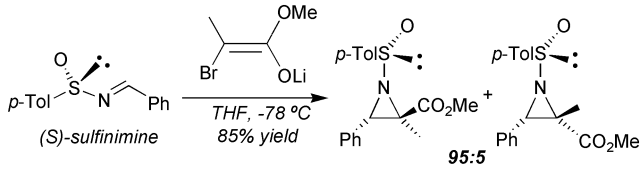


R	*Yield Aziridinylsultam/%*
Ph	*71*
p-$MeOC_6H_4$	*60*
o-$NO_2C_6H_4$	*72*
p-FC_6H_4	*57*
m-BrC_6H_4	*60*
p-BrC_6H_4	*65*
2-pyridyl	*71*
ethenyl	*47*
2,2-diMe ethenyl	*40*
tBu	*40*

Scheme 34

and of *S*-chiral sulfinylimines with achiral bromoenolates[34] (Scheme 35) have been studied; in both cases, high levels of enantio- and diastereocontrol are observed.

The products of the former reaction, *N*-Dpp aziridines, have previously been demonstrated to be useful reagents for ring-



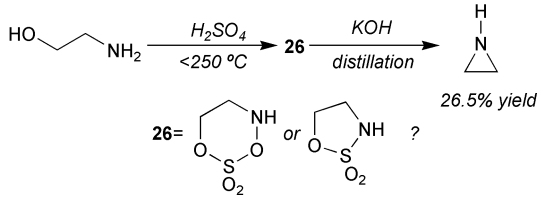
Scheme 35

opening (*vide supra*), whilst the products of the latter reaction are themselves activated aziridines. Thus, sulfinyl aziridines undergo hydrolytic and hydrogenolytic ring-cleavage in good yields, but the aziridines must be oxidized to the sulfonyl state to undergo ring-opening reactions with carbon nucleophiles.

Other reactions adapted from asymmetric aldol reactions suffer in comparison from the fact that (probably due to the strength of the boron–nitrogen bond) boron-mediated processes generally yield the intermediate 2-halo-3-aminoester products, rather than aziridine products directly.[35]

4.3 From 1,2-aminoalcohols and 1,2-aminohalides[3]

This particular class of aziridine-forming reaction is the oldest (and perhaps conceptually-simplest) class of reaction leading to these heterocycles. In 1888 Gabriel demonstrated that aziridines could be prepared in a two-step process, by chlorination of ethanolamines with thionyl chloride followed by alkali-mediated cyclization. In 1935, Wenker showed that heating 600 g of ethanolamine in the presence of more than 1 kg of 96% sulfuric acid to high temperature produced a compound **26**, at that time termed 'β-aminoethyl sulfuric acid'; 282 g of this compound was distilled from aqueous base to give 23 g of aziridine itself, representing the first preparation of the parent compound in a pure condition. It is perhaps more likely that the intermediate in these reactions is a cyclic sulfamidate (*vide infra*) rather than a simple sulfate ester or 'β-aminoethyl sulfuric acid' (Scheme 36).

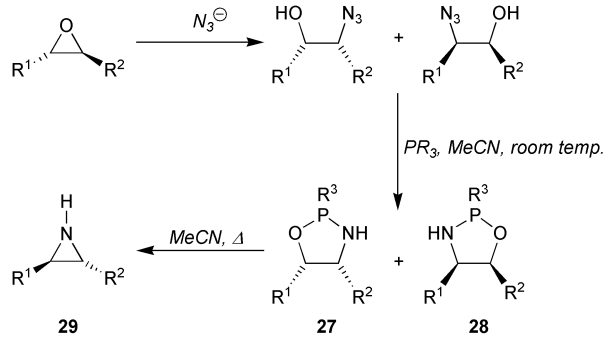


Scheme 36

These conditions were not generally applicable to a wide range of aminoalcohols, leading to mixtures of cyclized and elimination product when any substitution α-to the hydroxy moiety was present. From this relatively primitive reaction (about the first stage of the preparation, Wenker commented that 'at about 250 °C charring begins, necessitating the end of the operation'), a wide range of conditions for activation of the hydroxy group has evolved, enabling the preparation of a wide range of achiral and enantiomerically-pure aziridines for use in synthesis and the reader is directed to review sources for fuller details of this type of aziridine-forming process.[2,3] In particular, Mitsunobu-like oxyphosphonium activation has been used extensively to execute the transformation.

4.4 From 1,2-azidoalcohols[2,3]

Given the ready availability of enantiomerically-pure epoxides by a range of asymmetric processes, much use has been made of the multi-step preparation of aziridines from these precursors. In particular, the phosphine-mediated ring-closure of azidoalcohols (a Staudinger reaction), themselves obtained from chiral epoxides by ring-opening reaction using a range of azide sources, has attracted much interest. The pivotal reaction of this particular sequence revolves around the reaction of the hydroxyazide with trialkyl- or triarylphosphine, leading to oxazaphospholidines **27** and **28**, which is rapidly formed and may be slowly converted to N-unsubstituted aziridine product **29** upon heating in acetonitrile (Scheme 37). The reaction is reliable for a wide range of chiral and achiral epoxides and there is no issue of regiochemistry: both asymmetric centres are cleanly and predictably inverted during the process.

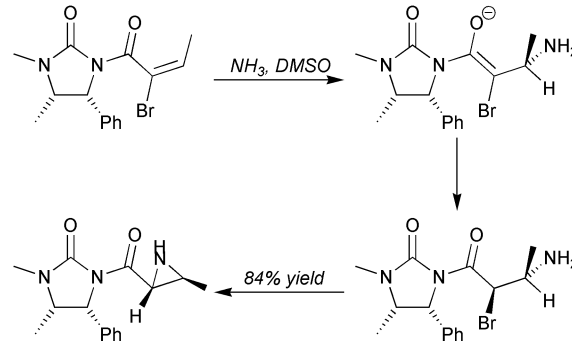


Scheme 37

4.5 From α-bromoacrylates: Gabriel–Cromwell reaction

A range of chiral derivatives of α-bromoacrylates undergo reaction with amines to yield chiral aziridines (the Gabriel–Cromwell reaction) (Scheme 38).[2] Ammonia itself may be used as the nitrogen source, providing a useful entry to chiral N-unsubstituted aziridines (Scheme 39).[2]

Scheme 38



Scheme 39

5 Concluding remarks

This article has sought to delineate the key properties, reactions and preparations of a range of aziridines. The author hopes that the comments made here have convinced the reader that these versatile heterocycles are no longer the 'ugly cousin' of the three-membered ring class. In particular, the recent develop-

ments in asymmetric aziridine synthesis indicate to the synthetic community that, whilst significant challenges remain (particularly with regard to the 'sulfonamide problem') there is a bright future for aziridine research.

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