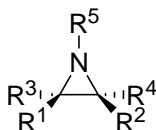


Stereoselective Routes to Aziridines

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Aziridines are three-membered nitrogen-containing heterocycles. The inherent reactivity of aziridines is due, in large part, to ring strain energy (SE) of 26.7 kcal/mol for

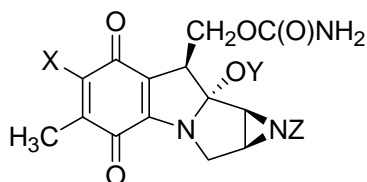


the parent, unsubstituted aziridine.¹ It is this reactivity that makes aziridines such an important component in synthetic processes and natural product modes of action. Thus, obtaining aziridines, especially optically active aziridines, has become of great importance in organic chemistry.

Despite high ring strain energy, unactivated aziridines are generally not extremely susceptible to ring opening via nucleophilic attack. Activation by protonation, quaternization, formation of a Lewis acid adduct, or replacement of the N-hydrogen with an electron-withdrawing substituent increases susceptibility to ring opening through nucleophilic attack.²

Aziridines can be found in natural products such as mitomycin, porfiromycin, and mitiromycin, which are potent antitumor and antibiotic agents (Figure 1).^{3,4}

Figure 1.



Mitomycin A: X=OMe, Y=Me, Z=H

Mitomycin B: X=OMe, Y=H, Z=Me

Mitomycin C: X = NH₂, Y=Me, Z=H

Porfiromycin: X=NH₂, Y=Me, Z=Me

Figure 1. Mitomycins are a class of potent, aziridine containing, antitumor and antibiotic agents.

More than being just an important functionality in itself, the aziridine class of compounds offers potential synthetic pathways to products which may otherwise be less accessible. Two prime examples include pathways to novel amino acids (Figure 3) and

synthetic routes to β -lactams, the latter being an important functionality in the syntheses of potent antibiotic drugs, such as (+)-thienamycin and (+)-PS-5 (Figure 2).⁵⁻⁸

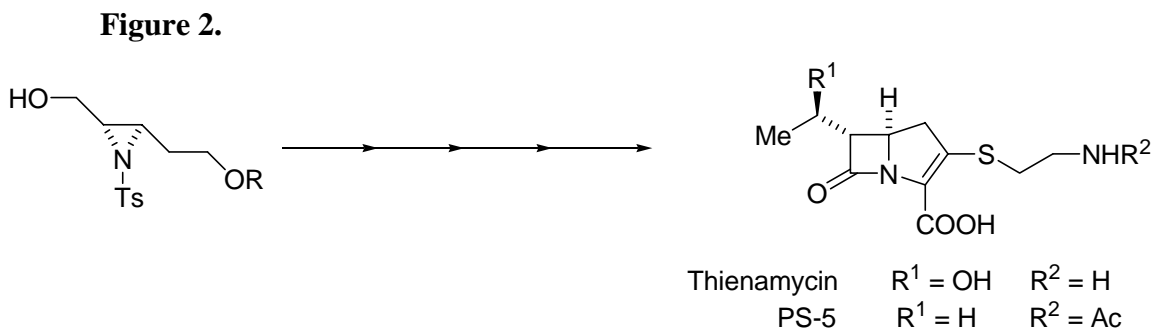


Figure 2. Carbapenem antibiotics, such as (+)-thienamycin and (+)-PS-5, can be derived from aziridines.

Figure 3.

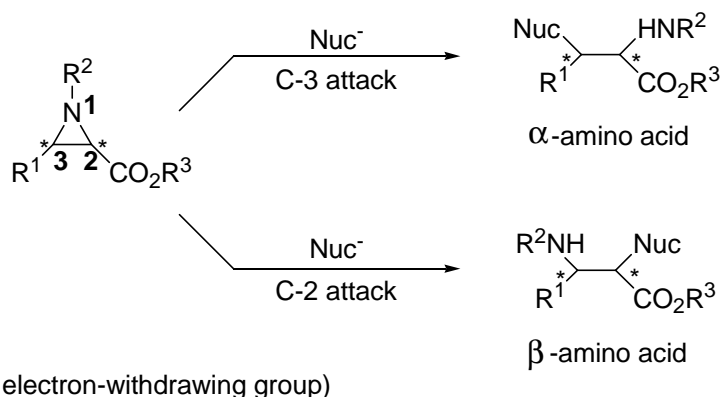
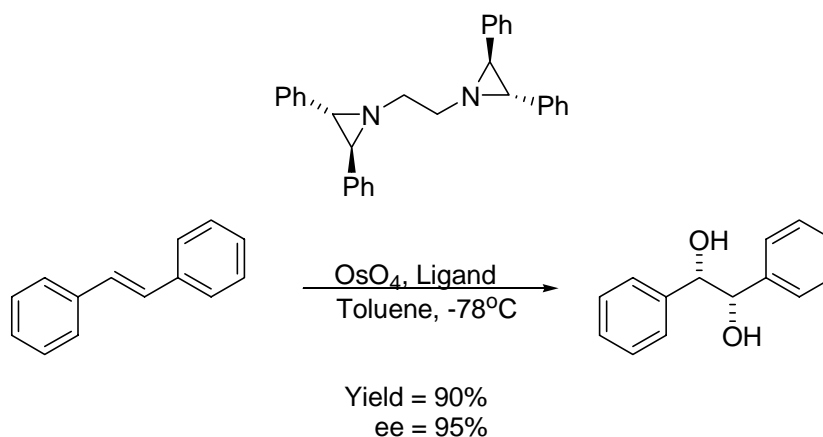


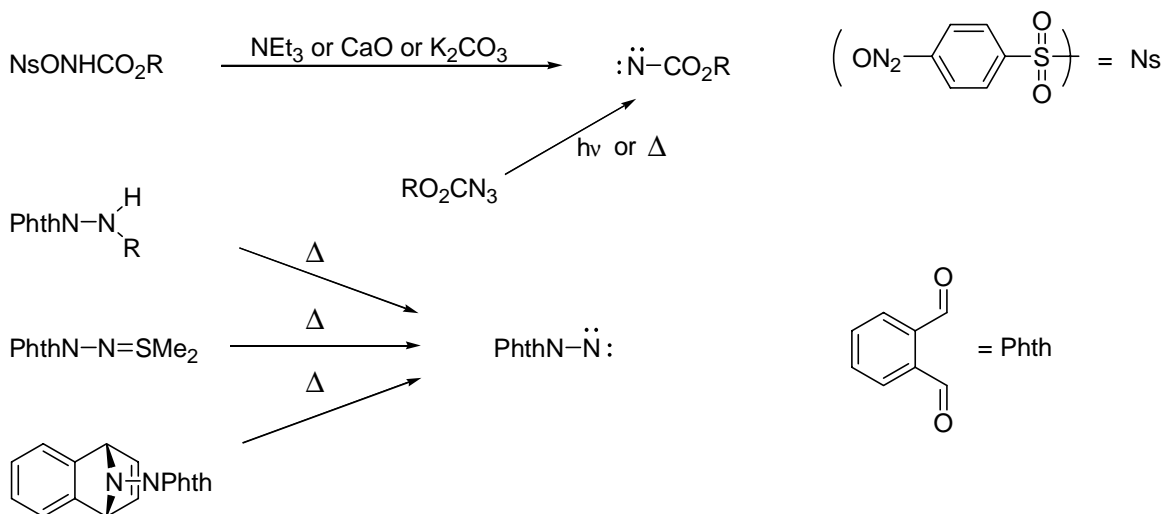
Figure 3. Regioselective nucleophilic attack at the C-2 or C-3 positions in an aziridine can provide novel amino acids.

Optically active aziridines are not only useful as synthetic precursors, but also can be utilized as ligands in asymmetric catalysis.⁹ Tanner and co-workers have designed an aziridine containing ligand, which among other things, can be used in asymmetric dihydroxylation using OsO₄ (Figure 4).

Probably, the most fundamental pathway to aziridines is addition of a nitrene to an alkene. Singlet nitrenes, much like singlet carbenes, add stereospecifically to alkenes, while triplet nitrenes, add in a non-stereospecific fashion.¹⁰ The difference in reactivities can be attributed to two differing mechanistic pathways. The singlet is thought to react in a concerted mechanism, while the accepted triplet mechanism involves a diradical intermediate, which allows for rotation before ring closing of the diradical.¹¹

Figure 4.**Figure 4.** Asymmetric dihydroxylation using an aziridine containing ligand provides very good ee's.

There are a number of ways to create nitrenes. Three of the most common involve α -elimination of a carbamate and the photolysis or thermolysis of azide or N-amino species (Figure 5).¹⁰⁻¹⁶

Figure 5.**Figure 5.** Thermolysis and photolysis of azides, along with α -elimination, represent common routes to nitrenes.

Rees and co-workers developed several N-amino species, which upon oxidation with $\text{Pb}(\text{OAc})_4$, turn into efficient aziridinating agents.^{17,18} Atkinson and co-workers have significantly extended the understanding and applicability of this class of compounds (Figure 6).

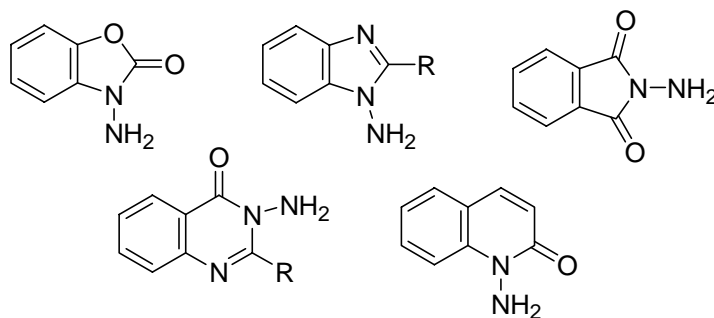
Figure 6.

Figure 6. Upon oxidation with $\text{Pb}(\text{OAc})_4$, these compounds, developed by Rees and co-workers and further investigated by Atkinson and co-workers, become efficient aziridinating agents.

Aziridines have a significantly larger barrier to nitrogen inversion than other amines (18.9 kcal/mol for the parent, unsubstituted aziridine, compared to 5-6 kcal/mol for most amines).¹⁹ This gives rise to two distinguishable invertomers: one with the nitrogen substituent *cis* to the carbon substituent and another with a *trans* relationship between the two substituents (Figure 7).²⁰

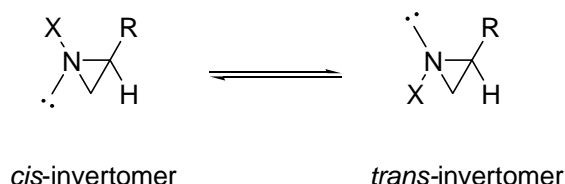
Figure 7.

Figure 7. Due to the high nitrogen inversion barrier of aziridines, the *cis* and *trans* invertomers are two distinct species at low temperatures.

In aziridinations of phenyl-substituted alkenes and alkene esters such as styrene and methyl acrylate, the *cis*-invertomer was found to be the sole kinetically formed species, which could be converted to the thermodynamically more stable *trans*-invertomer upon heating.²¹ It is proposed that the preference for the *cis*-conformer is a result of π -stacking and dipole interactions between the aziridinating agent and phenyl or carbonyl functionalities of the alkene, respectively.²²

It was later proposed that the Atkinson-type aziridinating agents were not reacting through nitrenes, as previously proposed, but were converted to acetoxyamino species (QNHOAc instead of QN) upon oxidation with $\text{Pb}(\text{OAc})_4$.²² This led to a new proposed mode of reaction in which the electron pair of nitrogen is directed toward the more

electron-deficient side of the alkene, while the acetate group lies anti to the more electron-rich site, in an S_N2 backside attack fashion (Figure 8).²³

Figure 8.

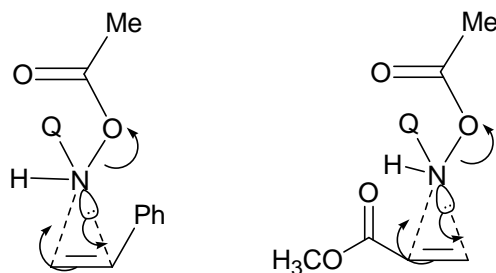


Figure 8. Acetoxyamino aziridinating agents are thought to arrange in such a fashion that the nitrogen electron pair aligns with the more electron-deficient site of the alkene, while the acetate lies anti to the more electron-rich alkene site.

Evidence for this mechanism was provided in experiments designed to exploit hydrogen bonding to facilitate departure of acetate.²³ Taking advantage of this mechanism of aziridination, respectable to excellent diastereomeric excesses can be obtained through facial selectivity in the presence of chirality on either the aziridinating agent or the alkene.^{24,25}

While Atkinson's work is important and abundant, there are a number of other methods for stereoselective aziridinations. For example, asymmetric aziridination catalysts can be utilized to obtain reasonable to high enantiomeric excesses via a metal-nitrenoid intermediate (Figure 9).^{26,27}

Figure 9.

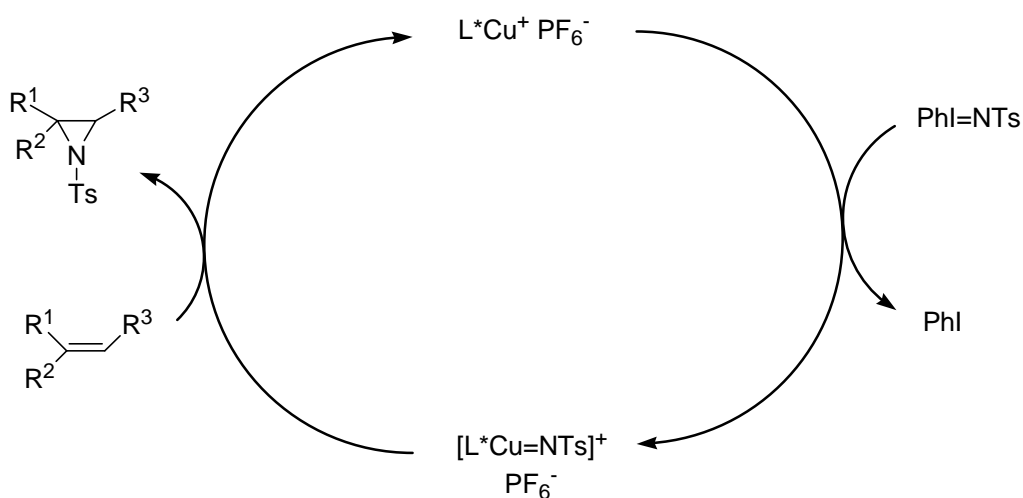


Figure 9. Jacobsen proposes a catalytic cycle going through a nitrenoid intermediate.

Another protocol for creating optically active aziridines uses Sharpless asymmetric epoxidation.² Among other possibilities, optically active epoxides can be converted to the corresponding aziridines via a Staudinger or aza-Payne reaction.²⁸⁻³¹

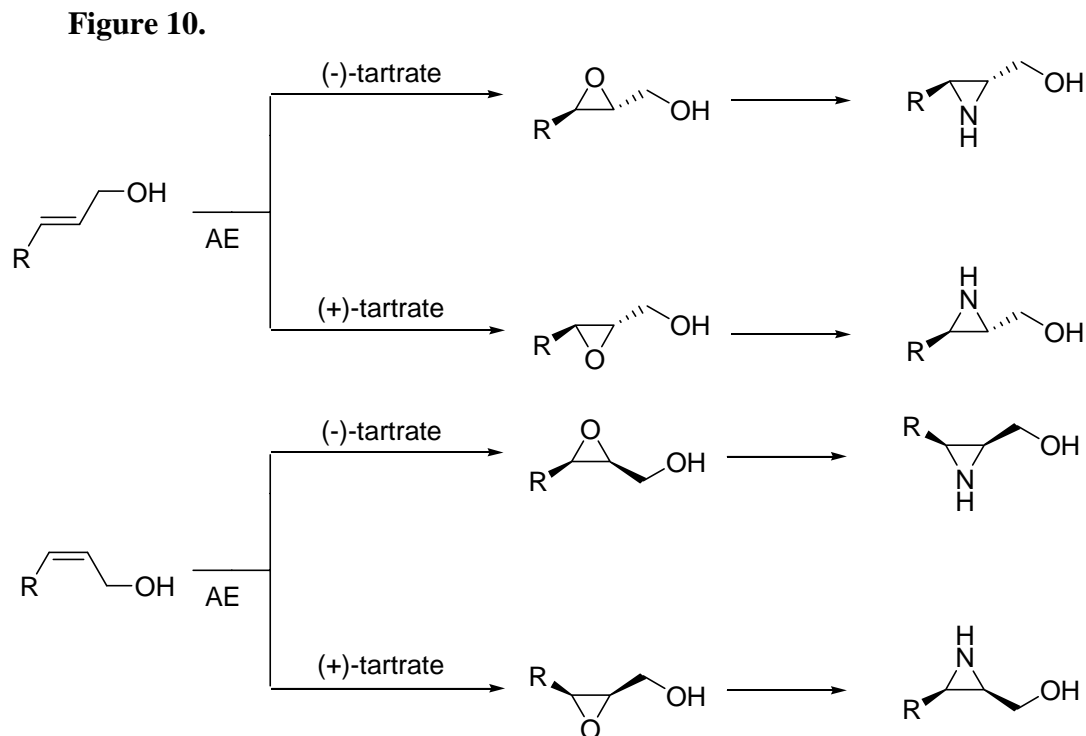
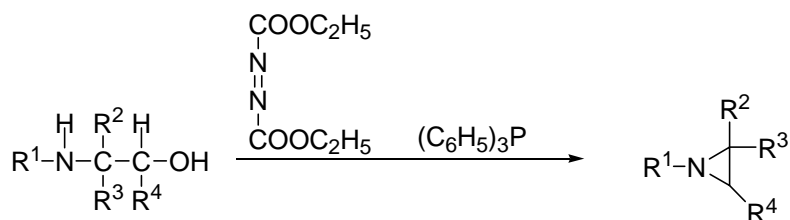


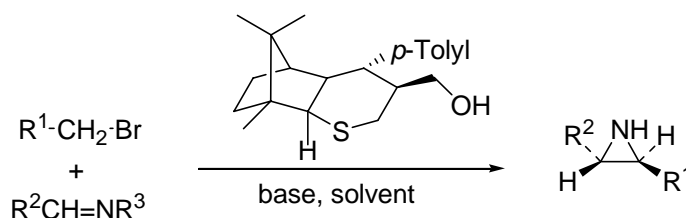
Figure 10. Conversion of Sharpless AE derived epoxides to aziridines gives absolute inversion at both ring carbons.

In a very similar fashion, Sharpless asymmetric dihydroxylation provides aziridines in excellent enantiomeric excess, usually utilizing a cyclic sulfate intermediate.^{2,32}

Several routes to aziridines exist utilizing amino alcohols.³³ One of the more common of these routes is the Mitsunobu reaction.^{34,35} With an optically pure amino alcohol, the Mitsunobu reaction can give aziridines with complete inversion at the alcoholic center.

Figure 11.**Figure 11.** With a chiral alcohol, the Mitsunobu reaction can give optically pure aziridines.

Imines also represent an important precursor in aziridine synthesis. An azadarsens reaction between a chiral sulfinimine and a metal enolate can give aziridines with high diastereoselectivity.³⁶ The imino Corey-Chaykovsky reaction of an imine with a sulfonium-ylide auxiliary can also yield aziridines in very good enantiomeric excess.³⁷ Finally, reaction of an imine with a diazo compound can preferentially give the *cis* diastereomer in large excess over the *trans*-diastereomer.³⁸

Figure 12.**Figure 12.** Very good enantiomeric excess can be obtained in a Corey-Chaykovsky reaction of an imine with a sulfonium-ylide.

Michael addition also represents an efficient pathway to optically active aziridines. For example, Michael addition of an amine to an α -bromo- α,β -unsaturated ketone can yield aziridines via Gabriel-Cromwell reaction.³⁹

Azirines represent yet another precursor to optically active aziridines. With facially selective deprotonation using a base such as quinidine, a Neber reaction can be utilized to give optically active azirines.⁴⁰ Reduction of these azirines with NaBH_4 gives exclusive formation of *cis*-aziridines.

A final process for obtaining optically active aziridines involves optical resolution. The utilization of either an optically active host, used for complexation, or an enzymatic catalyst with a preference for a specific substrate stereochemistry can result in optically pure aziridines through resolution.^{41,42}

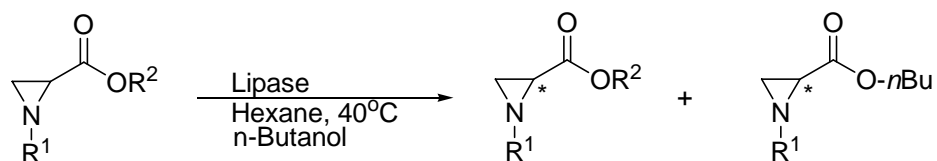
Figure 13.

Figure 13. Lipase catalyzed alcoholysis of an aziridine-ester with a reaction preference for a specific stereochemical configuration can lead to optically active aziridines through resolution.

Obtaining optically active aziridines becomes ever more important as more aziridine-containing natural products and uses for these natural products are discovered. Beyond that, optically active aziridines represent an extremely important building block in organic synthesis. For these reasons, and numerous others, optically active aziridines represent an important target for organic chemists. The routes described above represent an overview of individual tactics and strategies often employed by modern day organic chemists for obtaining aziridines.

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