# AZIRIDINES: RETHINKING THEIR APPLICATION AND MANIPULATION IN SYNTHESIS

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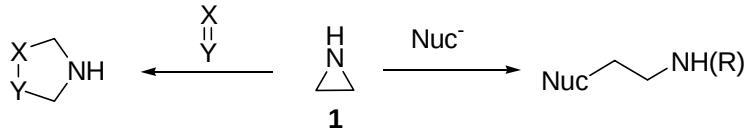
## INTRODUCTION

Aziridines (**1**) have been synthetic targets as well as useful building blocks in synthesis since Gabriel's 1888 discovery of the smallest nitrogen containing heterocycle.[1,2] Attracted by the increased strain and unique reactivity of the three-membered ring, synthetic chemists have extensively explored the various manipulations of aziridine-containing compounds.[3] Many of these advances have been overlooked in organic chemistry textbooks, as discussion of aziridines is often limited to heterocyclic nomenclature. Nonetheless, aziridines exhibit a wide range of useful reactivities including nucleophilic ring opening, which harnesses the release of ring strain (Scheme 1). In recent years, many other transformations have been described, such as cycloadditions,[4] but the limited application of aziridines in organic synthesis is due in large measure to the paucity of general methods for their preparation.

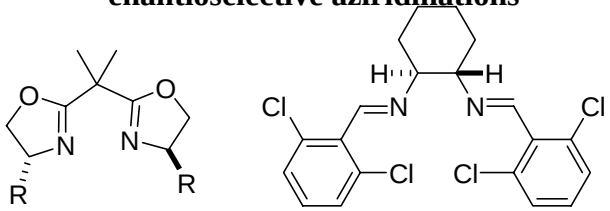
**Scheme 1. General transformations of aziridines**




**1**

Because aziridines are closely related in structure to oxiranes and cyclopropanes, the approaches to their synthesis are very similar. The majority of methods for the preparation of aziridines mimic the highly developed syntheses of epoxides[5] or cyclopropanes.[6] This connection is illustrated in the catalytic asymmetric aziridination of olefins developed in the early 1990's, in which complexes based on Evans' bis-oxazoline (**2**) and Jacobsen's SALEN (**3**) ligands have been applied[7,8] using copper-nitrenoid equivalents. Although the enantioselectivity is generally not high, these studies serve to illustrate the limitiation in aziridination methods, and stimulate a revitalization of aziridine synthesis.[9]

**Chart 1. Representative ligands used in enantioselective aziridinations**




**2** **3**

The recent development of aziridine chemistry has followed two main paths: first, the development of reliable preparations and second, control over the subsequent ring-opening transformations of aziridines. The current state of the art features catalytic, highly enantioselective aziridinations, reliable ring-opening transformations, and stereoselective cycloadditions, all of which illustrate the unique reactivity of aziridines.



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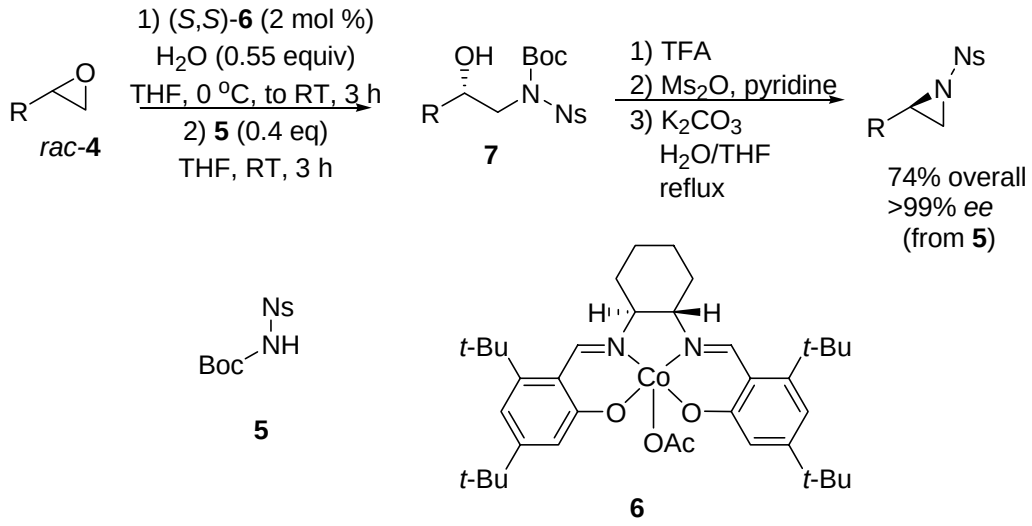
## SYNTHESIS OF AZIRIDINES

### From Epoxides

The simplest (and oldest) preparation of aziridines is the ring closure of a β-functional ethylamine. Although ring closure itself is quite facile, the synthesis of the required precursors can be problematic. However, an efficient and stereoselective approach has been developed by an extension of Jacobsen's hydrolytic kinetic resolution (HKR) (Scheme 2).[10] Doubly protected amine **5** reacts with racemic epoxides in the presence of catalyst **6**, to provide an excellent yield of amino alcohol **7,** albeit with limited enantioselection. Noting the propensity for epoxide opening, it was proposed that an initial HKR, followed by introduction of amine **5,** would allow ring opening of the "mismatched" (initially unopened) epoxide.[11] In practice, this nucleophilic ring opening affords highly enantioenriched 1,2-amino alcohols in excellent yields, *via* a one-pot process from racemic terminal epoxides. The protected amino alcohol is then converted to the corresponding aziridine. Excellent enantioselectivities and high yields are observed regardless of substrate. Unfortunately, this method requires the loss of the "matched" enantiomer (50% of the starting material).

**Scheme 2. Modified HKR synthesis of enantiopure aziridines**

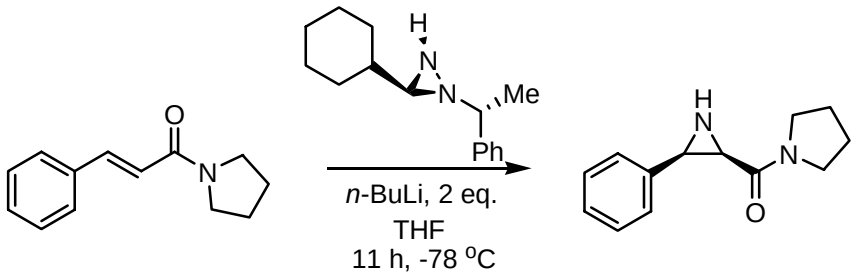



### Nitrogen Transfer to Olefins

Unlike stepwise ring closure, the strategy of nitrogen transfer to olefins does not require highly functionalized precurors. The use of a diaziridine provides an alternative, diastereoselective aziridination of α,β-unsaturated amides, as reported by Itoh (Scheme 3).[12] Diaziridine-based nitrogen transfer allows for reagent-controlled diastereoselective synthesis of either cis- or trans-aziridines in good to excellent yields (73-99%) from a single alkene. Aldehyde-derived diaziridines provide the trans-aziridines,

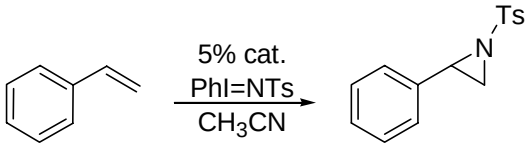
whereas bulky, ketone-derived diaziridines allow access to cis-aziridines. Furthermore, excellent enantioselectivities for the production of trans-aziridines are obtained with chiral diaziridine **6**, albeit in moderate yield. Unfortunately, this reagent requires the use of an α,β-unsaturated amide, thus severely limiting its scope, and it also suffers further from the requisite preparation of the diaziridines.

**Scheme 3. Aziridination using chiral diaziridines.**

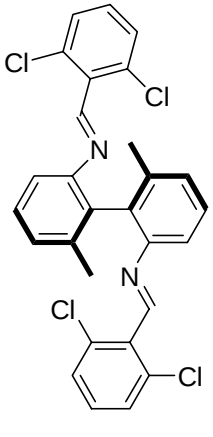



Although the preparation of diaziridines is not completely impractical, a catalytic enantioselective nitrogen transfer method would be fundamentally more efficient, eliminating the need for stoichiometric chiral reagents. Transition metal catalysis, which allows for enantioselection using chiral ligands, was first introduced in aziridination by Evans, who demonstrated that a catalytic amount of copper(II) triflate could facilitate nitrene transfer to a variety of olefins in high yields (55-95%) (Scheme 4).

**Scheme 4. Copper-catalyzed aziridination**




| Catalyst | Yield |
|---|---|
| $Cu(MeCN)_4ClO_4$ | 89 |
| $Cu(acac)_2$ | 95 |



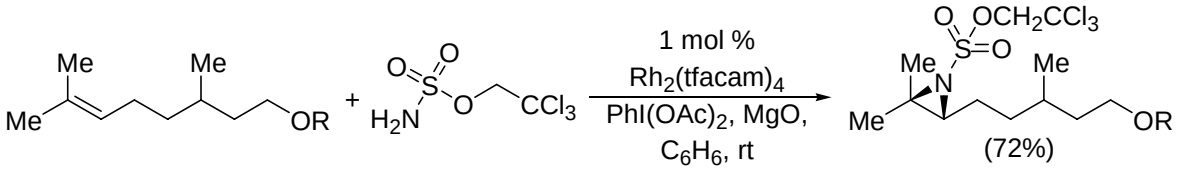

**8**

Evans[7] and Jacobsen[8] have simultaneously developed asymmetric copper-catalyzed aziridination by application of their respective bisoxazoline (**2**) and SALEN (**3**) ligands, respectively. More recently, a new series of Schiff base ligands has been applied to catalytic, enantioselective copper-nitrenoid additions.[13] This 2,2'-diarylimino-6,6'-dimethylbiphenyl-derived ligand **7** facilitates highly stereoselective aziridination of chromenes (100:1 er) and *trans*-cinnamate esters (17-65:1 er). However, poor selectivity is observed with other olefins, emphasizing the

lack of substrate scope in copper-catalyzed asymmetric aziridination.

A newly-developed alternative to copper-based aziridinations uses a dimeric rhodium catalyst to catalyze nitrene-transfer to olefins, as reported by Du Bois (Scheme 6).[14] Although rhodium-based aziridination is known,[15] this method provides a wider range of aziridine structures in higher yields (57-84%). The iminoiodananes required for copper-nitrene transfer are generated *in situ* with sulfamate esters and diacetoxyiodosobenzene. Rhodium trifluoroacetamide exhibits the greatest activity among rhodium sources screened, allowing for reactions at low catalyst loadings (1-2 mol %). The sulfamate

**Scheme 6: Rhodium catalyzed nitrene transfer**

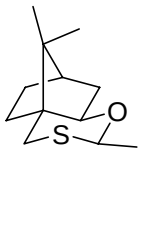



ester protecting group can then be easily cleaved by zinc amalgam following aziridination. Although only a few examples of enantioselective aziridination have been demonstrated by the use of chiral ligands on rhodium, the potential for development of stereoselective methods is certainly evident.

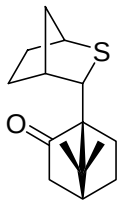
**Carbene Transfer to Imines**

In contrast to the nitrogen transfer strategy, in which successful catalytic aziridination required the development of nitrene-transfer systems, progress in aziridination by transfer of carbenes to imines has been more easily developed, due, in part, to the existence of established carbene-transfer systems. The potential for highly enantioselective aziridination has been realized in two particular systems.

**Chart 2. Chiral Sulfides**



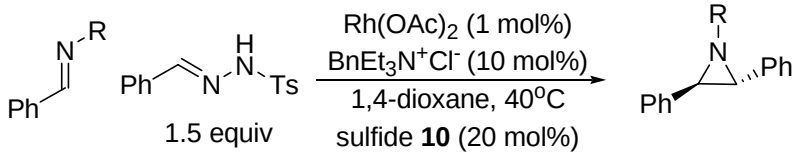

**9**



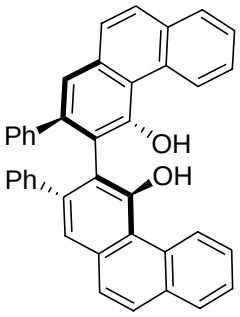

**10**

Aggarwal has reported a highly enantioselective aziridination by transferring the carbene generated from a tosylhydrazone to an imine.[16] Rhodium initially traps the generated carbene and transfers it to chiral sulfides (**9**) and (**10**), which provide a chiral environment for subsequent nucleophilic attack on the imine. This process shows wide generality and excellent enantioselectivity (24-99:1), but suffers from lower diastereoselectivities (~2:1) for most substrates.

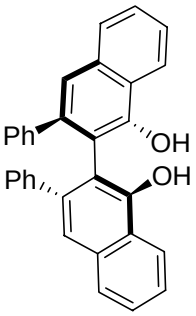
**Scheme 7. Addition of chiral carbenes to imines**



An alternative to generating a chiral carbene transfer agent (sulfonium ylide) is the activation-desymmetrization of the imine by complexation with a chiral Lewis acid (Scheme 8).[17] The use of a mixed aryl borate catalyst derived from either (*S*)-VANOL and (*S*)-VAPOL ligands represents a highly diastereo- and enantioselective method for aziridination of aryl imines with ethyl diazoacetate. In comparison to the related 1,1'-binapthyl-2,2'-diol ligands (BINOL), VANOL and VAPOL promote greater reactivity and selectivity (20-65:1 er, >50:1 dr). This method is compatible with a wide range of imines, including aromatic and aliphatic imines and also reflects the state of the art in the preparation of chiral aziridines.

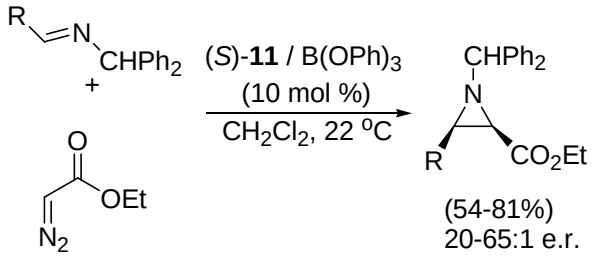



**11** (*S*)-VAPOL




**12** (*S*)-VANOL

**Scheme 8. VAPOL-catavzed preparation of aziridines**



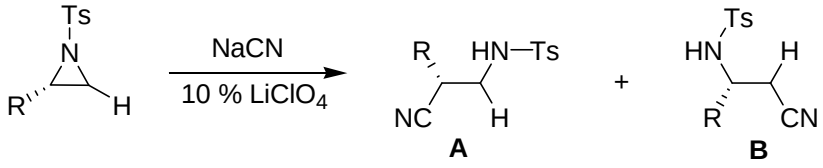

## SELECTED AZIRIDINE CHEMISTRY

### Nucleophilic Ring Opening

Aziridines are versatile intermediates which undergo a variety of synthetically useful transformations. Nucleophilic ring opening (NRO), the most thoroughly studied manipulation of aziridines,[3] is facilitated by the release of strain (25-26 kcal/mol), and attack by a variety of nucleophiles reveals a primary or secondary amine, affording a diverse range of β-substituted ethylamines. The nitrogen substituent plays a crucial role in the NRO of aziridines, as the electronic-withdrawing nature of sulfonyl and carbonyl substituents lower the pKa (from ~30 to ~16) of the ring opened nitranion, facilitating ring opening. Carbonyl substituents also present an alternate reactive site to the nucleophile, and are often avoided. Electron-donating groups suppress the rate of ring opening and require harsher conditions. Although the toluenesulfonyl (Ts) group is most widely used as an N-substituent, two alternate groups have shown increasing favor. The 4-nitrophenylsulfonyl group (Ns) and the 2-(trimethylsilyl)ethylsulfonyl (SES)[18,19] group allow for a wider range of nucleophiles and enhance the

reaction rate in the NRO of aziridines. Nosyl aziridines undergo more rapid NRO (50-60 times faster) compared to tosyl aziridines, but are incompatible with organometallic reagents. The SES group has been adapted to allow for sufficient activation while retaining ease of cleavage (TBAF) and good compatibility with a range of nucleophiles, including organometallic reagents.

**Scheme 9: Regioselectivity of aziridine ring opening**

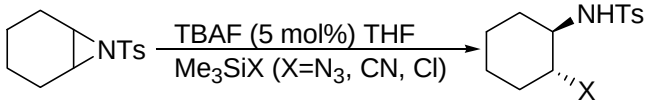



| R | Yield(%) | **A:B** |
|---|---|---|
| Ph | 90 | 92:8 |
| *n*-Bu | 87 | 15:85 |
| *n*-Oct | 83 | 10:90 |

The regioselectivity of aziridine NRO has been extensively studied[20], and depends on the structure of the aziridine. Unlike the analogous epoxide NRO, wherein the regioselectivity is determined to an extent by reaction conditions, the direction of azridine opening is mainly determined by the substrate. This is demonstrated by the addition of cyanide to terminal aziridines (Scheme 9). The ring-opening follows normal $S_N2$ behavior, where substitution at the benzyl center is favored over substitution at the primary and secondary carbons. In all cases, good yields (83-90%) are observed.

Hou and coworkers have recently developed a simple, catalytic activation procedure that allows simple nucleophiles to participate directly in NRO[21]. Catalytic amounts of TBAF, in concert with a trimethylsilyl nucleophile (chloride, cyanide, or azide) affords ring-opened products in excellent yields (86-97%). These conditions are general for aziridines with either sulfonyl- or acyl-protecting groups, but failed with unsubstituted aziridines.

**Scheme 10: TBAF-catalyzed ring-opening**

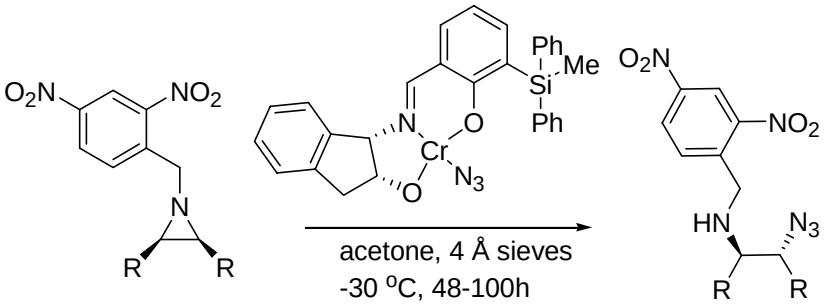



**Enantioselective Nucleophilic Ring Opening**

An important subset of NRO reactions involves the use of meso aziridines. In this class, the central issue is the enantiotopic group selectivity for the generatiion of enantiomerically enriched products from achiral starting materials. By analogy to the ring-opening of epoxides, Jacobsen has

examined the use of chromium-SALEN-complex-catalyzed desymmetrization of aziridines, which exhibited low reactivity and poor enantioselectivity.[22] To accomodate the increased steric demand from the nitrogen substituent, a new, less encumbered catalyst system was developed (Scheme 11). This new structure (**11**) chelates the chromium at only three binding sites, while the fourth site is occupied by the azide nucleophile. Application of this new ligand provides excellent enantioselectivities (11-32:1 er) and yields (73-90%) of ring-opened products.

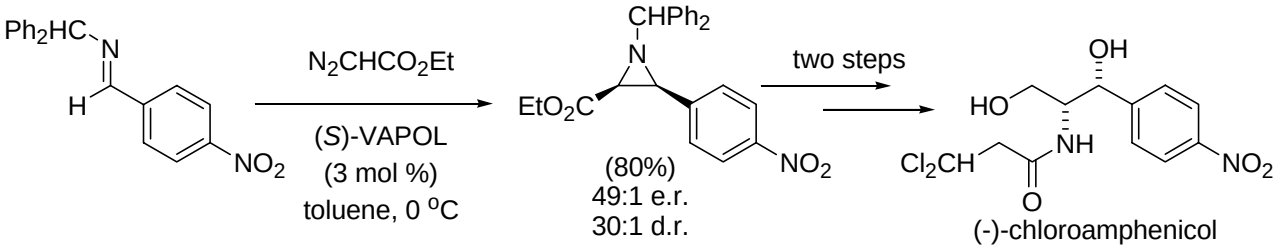
**Scheme 11: Catalytic enantioselective nucleophilic ring opening**



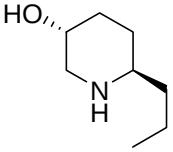

**Aziridines in Synthesis**

The renewed interest in aziridination methods has fostered increased application in synthesis, including the synthesis of natural products. (-)-Chloroamphenicol has been prepared by the asymmetric carbene addition to an imine (Scheme 12).[23] The application of the VAPOL ligand in this key step allows for a significantly shorter route to the enantiopure natural product.

**Scheme 12: Asymmetric aziridination en route to chloroamphenicol**

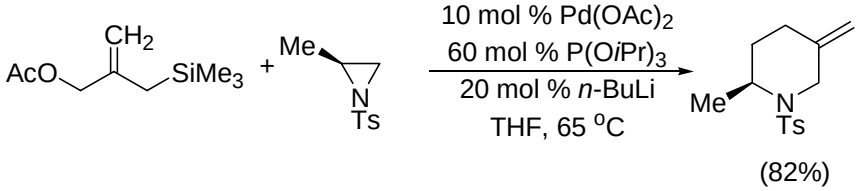



Harrity has developed a synthesis of chiral piperidines, utilizing a novel [3+3] cycloaddition strategy from chiral aziridines and trimethylenemethane (Scheme 13).[4] This palladium-catalyzed cycloaddition, which proceeds stereoselectively to give enantiopure piperidines in good yield, is highlighted in the short natural product synthesis of (-)-pseudoconhydrine (**12**).




**12**

**Scheme 13: [3+3]-cycloaddtion of aziridines**



## Conclusion

A variety of new, enantioselective methods have been developed for the reliable preparation of aziridines. The use of hydrolytic kinetic resolution to transform racemic epoxides into aziridines provides rapid access to enantiopure aziridine building blocks. The development of metal-nitrenoid additions to olefins has afforded efficient methods which may allow for late stage aziridination in a complex molecule synthesis. To date, these methods provide enantioenriched aziridines in only limited cases, such as chromenes and styrenes. The use of VANOL and VAPOL ligands, in conjunction with triphenylborate provides excellent enantio- and diastereoselectivities for a wide range of chiral aziridines. Subsequent manipulation of these aziridines has been established, and can be predicted reliably. An enantioselective ring-opening has been developed by Jacobsen, that transforms *meso*-aziridines into enantioenriched β-functional amines. Although application of asymmetric aziridnation methods to the synthesis of natural products is still in its infancy, the newfound generality of these reactions will no doubt result increase their stature in the synthetic chemist's toolbox.

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