Heterocycles

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A Scalable Rhodium-Catalyzed Intermolecular Aziridination Reaction

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Aziridines are strained three-membered rings composed of one nitrogen atom and two carbon atoms. Over the last several decades aziridines have been shown to be incredibly useful and versatile synthetic intermediates.[1] The diversity of reactions which employ aziridines is such that with the proper selection of precursors having an appropriate nitrogen substitutent (X), this strained motif can be employed in a variety of downstream processes (Figure 1). Although aziridines are not common as naturally occurring motifs,[2] mitomycin C is an example of an important natural product containing an aziridine and is an approved chemotherapeutic agent (Mutamycin) for treating several types of cancer.[3]

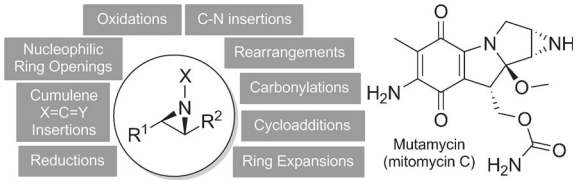

Figure 1. Aziridines are important synthetic building blocks.

The main obstacle holding back aziridine chemistry from expanding faster and being employed more frequently in industrial settings is the lack of useful methods for making aziridines. Of the approaches that have been developed to access aziridines the two shown in Figure 2 represent the most promising disconnections. Ideally, such methods should provide stereospecific access to aziridine enantiomers by addition of appropriate reagents to either olefins (approach 1) or imines (approach 2). In trying to achieve these important goals one has to consider what would be the synthetically most attractive nitrogen substituent (X). This group should not impede the approach, for example, by making imine formation difficult or opening the door for unwanted reaction pathways. Furthermore, the nitrogen substituent should be easily removable to provide maximum synthetic flexibility. Current approaches of type 1 are limited

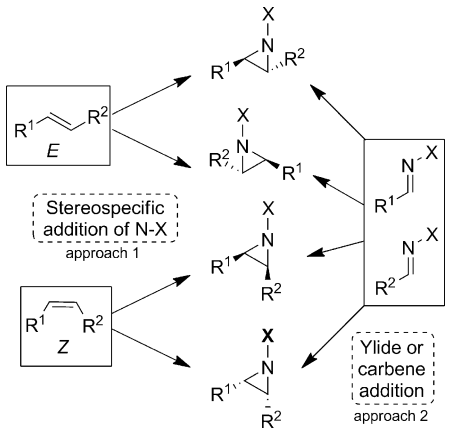

Figure 2. Complete stereocontrol: 21st century aziridination goals.

in scope, employ unattractive nitrogen sources (PhI=NTs), and had little success in asymmetric reactions, forming in most cases aziridines with non-ideal nitrogen substituents such as sulfonamides.[4] Approaches of type 2 are currently more attractive for natural product and pharmaceutical applications, as more success has been had in asymmetric syntheses.[5] The main drawback of this strategy is that it is restricted to certain classes of stable imines, and the ylides or carbenes employed invariably need a stabilizing substituent to succeed. Furthermore, stereochemical control is more challenging for approach 2 as selective addition to one face of the imine π system is not sufficient to guarantee access to a single aziridine stereoisomer.

In focusing the discussion on intermolecular aziridinations of olefins it is important to present and briefly discuss the three most commonly investigated classes of olefins (Figure 3). Styrenes have historically been the favorite olefin testing group for new aziridination reactions, but in recent years conjugated olefins have received more attention. The

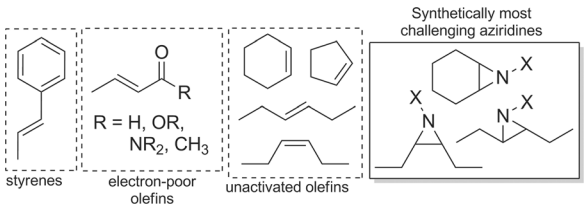

Figure 3. Intermolecular aziridination of olefins is still a challenge.

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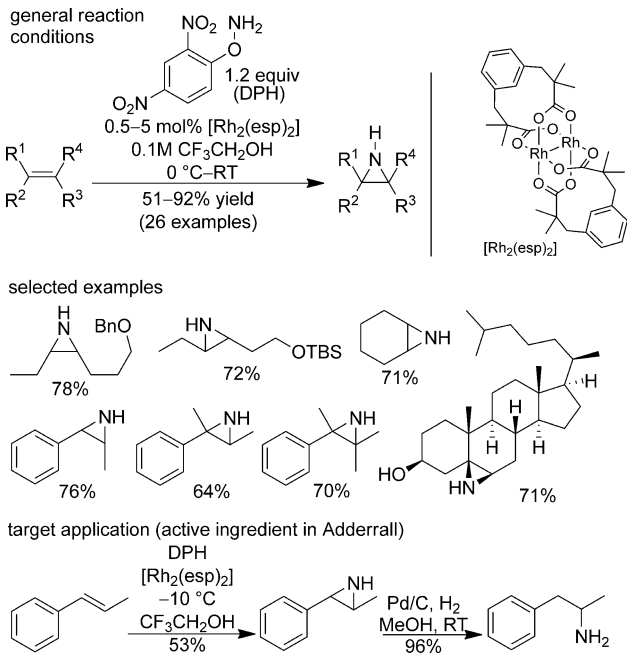
most challenging class of olefins, with few available solutions, still remains unactivated olefins. The majority of metal-catalyzed aziridinations are limited to styrenes while most organocatalyzed routes are uniquely suited for conjugated olefins (enals, enones, etc.). The Sharpless aziridination,[6] which relies on halonium ions, is one of the more successful intermolecular aziridination reactions. Despite limitations, it is one of few reactions that can convert members of all three olefin classes (Figure 3) into aziridines.

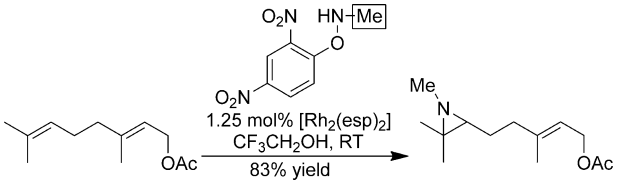
The most challenging class of olefins to convert into aziridines intermolecularly are unactivated olefins (Figure 3). Some successes have been had in this area, but most are not amenable to scale up and also deliver synthetic baggage in the form of nitrogen substituents (X). Furthermore, imine addition strategies (approach 2, Figure 2) are generally unable to access such aziridine products as these rely on adjacent functional groups to succeed. From the standpoint of broad reactivity and stoichiometry (equimolar amounts of reagents), *N*-aminophthalimides[7] and trichloroethylsulfamate esters[8] are particularly noteworthy successes. Clearly, the state of the art for aziridination chemistry at the start of 2014 is in need of continued development.

In the first issue of *Science* for 2014, a useful new catalytic method to convert unactivated olefins into aziridines is reported by Kürti, Falck, and Ess et al. (Scheme 1).[9] Following their recent success in converting aryl boronic acids into anilines using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) as the aminating agent,[10] their attention turned to employing this reagent in the aziridination of olefins. They have now demonstrated that DPH can be used in direct aziridination of olefins in the presence of a rhodium catalyst, $[Rh_2(esp)_2]$, which was first reported by Du Bois and co-workers.[11] This remarkable new reaction affords NH aziridines[12] using low catalyst loadings and only a slight excess of DPH while operating at ambient temperature in trifluoroethanol. Not only are the reaction conditions mild and catalytic, but equally important is the observation that this new aziridination reaction is stereospecific, with *E* olefins being cleanly converted into *trans*-NH aziridines and *Z* olefins into *cis*-NH aziridines. Unactivated and styrene-type olefins alike undergo aziridination in high yields using this method. Reaction conditions are compatible with amides, esters, ethers, aryl groups, and even free alcohols. In addition to the high yielding and selective aziridination of cholesterol serving as a good example for the practical application of their new reaction, the researchers chose to showcase its utility with a two-step synthesis of the active ingredient in the pharmaceutical agent Adderall. The protecting-group-free synthesis was accomplished by aziridination of *trans*-β-methyl styrene and subsequent hydrogenolysis of the benzylic C–N bond.



Scheme 1. New rhodium-catalyzed aziridination protocol. TBS = *tert*-butyldimethylsilyl.

A particularly attractive feature of this new catalytic method is the formation of NH aziridines instead of aziridines substituted with a protecting group, which in majority of cases are not desired. The free NH group provides the flexibility to protect the aziridine with the group of choice, to leave it as is, or to decorate it directly with the functional group needed for a particular synthetic goal. For those interested in accessing N-methylated aziridines directly from olefins, the research team has shown (6 examples) that N-methylated (*N*-Me) aziridines can be obtained stereospecifically using the same reaction conditions (Scheme 2) simply by replacing DPH with the methylated form, N-Me-DPH.



Scheme 2. Direct N-methyl aziridinations are possible.

In summary, this novel catalytic aziridination now represents the state-of-the-art for styrenes and unactivated olefins. The DFT calculations performed by the group provide support for the occurrence of a rhodium nitrene intermediate, which suggests that the next phase for this important new reaction will be to identify suitable chiral rhodium catalysts to enable synthesis of chiral NH aziridines. In addition to the NH organocatalyzed aziridination reactions recently developed for enones and enals,[12c–f] synthetic chemists are now able to convert olefins of most structural classes into NH aziridines.

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