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Advances in Nitrogen Transfer Reactions Involving Aziridines

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ABSTRACT

In recent years, our search for new nitrogen transfer reactions has concentrated on aziridine chemistry. This Account highlights our efforts toward the synthesis and functionalization of aziridines. In the course of our research, we have investigated the electrochemical aziridination of olefins, the acid-catalyzed ring opening of aziridines, and the development of transition metal mediated nitrogen allylation, arylation, and alkenylation of unprotected aziridines. Our studies have also involved the synthesis of aziridine-based enamine intermediates and their stereoselective transformations into heterocyclic compounds.

Introduction

The vast majority of biologically important molecules such as drugs and natural products contain nitrogen in their frameworks. The elaborate biosynthetic pathways for the construction of numerous natural products have been identified. Curiously, none of them involve direct metal-based nitrogen transfer. The position of the C−N bond is determined by its progenitor, a C−O bond, which is installed by oxygen transfer enzymes such as p450s. This apparent lack of Nature-inspired oxidative nitrogen transfer continues to fuel interest in synthetic reactions of this type. In the past four years, our search for new oxidative nitrogen transfer reactions has been concentrated on aziridine chemistry.[1] Despite the well-known advantages of aziridines, they have received limited application in synthesis due to perceived difficulties in their preparation and handling. Our goal has been to create a family of processes that provide straightforward links between aziridines and larger, more complex heterocycles in regio-, chemo-, and stereoselective ways. In this Account, we summarize our recent findings.[2]

The aziridine functionality is present in a small number of naturally occurring molecules.[1] The biological properties of aziridine-containing compounds such as azinomycins, mitomycins, FR-900482, ficellomycin, miraziridine, maduropeptin, and azicemicins are of significant interest (Figure 1). The antibiotic and antitumor properties of several of these compounds are well-known. Mitomycin C has a broad activity against a range of tumors and has been used in the clinic since the 1960s. Many analogues have been synthesized and evaluated for anticancer activity. Antitumor antibiotics FR900482 and FR66979 are structurally related to the mitomycins. Semisyntheic derivatives have been prepared and are being investigated in clinical trials as anticancer drugs. Azinomycins possess in vitro cytotoxic activity against the L5178Y tumor cell line, as well as antibiotic activity against both Gram-positive and Gram-negative bacteria.

In addition to their utility as synthetic endpoints, aziridines are also important intermediates in organic chemistry.[1] In terms of synthetic transformations, their utility comes from selective ring-opening reactions.[3] The transformations of these strain-loaded three-membered rings allow for regio- and stereoselective installation of a wide range of functional groups in a 1,2 relationship to nitrogen. Aziridines are also useful intermediates in natural product synthesis as in the case of the kainoids, (−)-mesembrine, (−)-platynesine, sphingosines, actinomycin D, L-epicapreomycidine, and feldamycin.[1] Over the past several years, our studies resulted in a number of useful connections between aziridines and value-added products of their ring-opening (Scheme 1).[2g,h,k,m]

Novel Methods for Aziridine Synthesis by Formal Nitrene Transfer to Olefins

Synthetic methodologies for the preparation of aziridines[1] include nitrene addition to olefins, carbene and ylid addition to imines, and cyclization of 1,2-amino alcohols, 1,2-aminohalides, and 1,2-azido alcohols (Scheme 2). Olefin aziridination reactions are typically accomplished via metal-mediated transfer of nitrene fragments or by 1,4-addition of nitrogen transfer reagents to electron-deficient olefins followed by elimination.[4,5]

Our entry into aziridine chemistry commenced with efforts in developing new electrochemical processes for oxidative nitrene transfer.[6] The approach we opted to explore had to overcome significant challenges (path A in Scheme 3). The goal of the selective oxidation of an amine in the presence of an olefin is not trivial because the oxidation potential regions of olefins and amines overlap (Scheme 3).[2b] Traditional homogeneous reagents

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Lily Yu was born in Ottawa, Canada. She received her B.Sc. in biopharmaceutical science (medicinal chemistry-coop) from the University of Ottawa in 2004 where she worked under the supervision of Dr. John Pezacki in the field of chemical biology. She joined the research group of Professor Andrei K. Yudin in 2004 and is currently pursuing her M.Sc.

Andrei K. Yudin completed his undergraduate studies at Moscow State University. He received his Ph.D. in Chemistry in 1996 from the University of Southern California where he worked with Professors G. K. S. Prakash and George A. Olah. After postdoctoral studies in the laboratory of Professor K. Barry Sharpless at the Scripps Research Institute, he accepted an Assistant Professor position at the Department of Chemistry, University of Toronto, and was granted tenure in 2002. His research interests are in the development of new chemo- and stereoselective transformations with particular emphasis on nitrogen transfer methodologies, target-oriented synthesis, and asymmetric synthesis.

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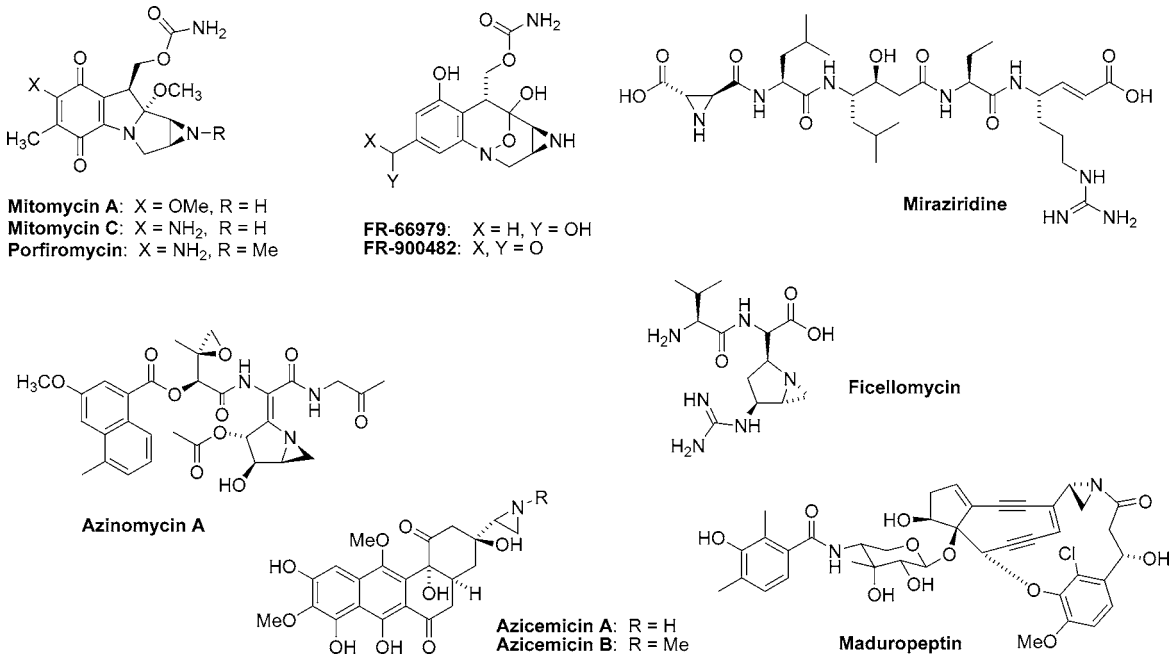
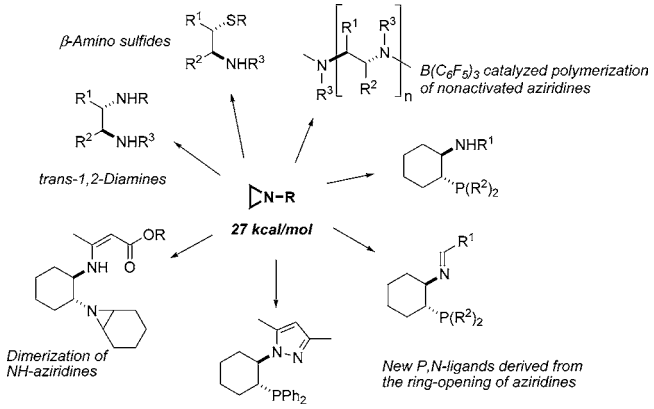
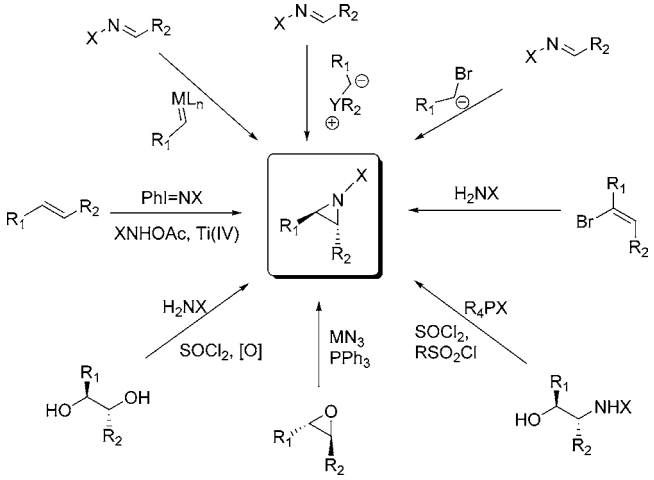


FIGURE 1. Aziridine-containing natural products.

Scheme 1. Ring Opening of Aziridines

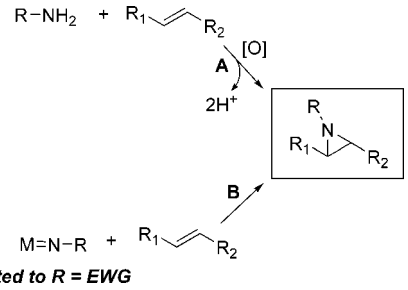


Scheme 2. Methods for the Synthesis of Aziridines



or catalysts rely on premade nitrogen sources such as chloramine-T to circumvent this problem. Thereby, reactive metal-imido complexes are generated in situ in the presence of olefins (Scheme 3, path B). However, the

Scheme 3. The Challenge of Selective Oxidation of Amines in the Presence of Olefins

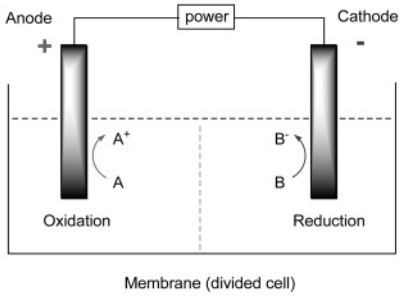


resulting aziridines contain substituents that are difficult to remove without destroying the sensitive three-membered ring.

In our studies, cyclic voltammetry on platinum revealed that selective transformation of *N*-aminophthalimide into the active nitrogen transfer species is taking place directly at the anode at around +1.80 V in the presence of olefins. After that, a simple combination of platinum electrodes, triethylamine, and acetic acid has led to a highly efficient, room-temperature nitrene transfer from *N*-aminophthalimide to cyclohexene (Scheme 4).[2n] The reaction employs a small excess of *N*-aminophthalimide relative to the olefin and can be performed in a divided cell using silver wire as a pseudo-reference electrode. Monitoring the reaction progress is easy: the aziridination is typically stopped when the cell current drops below 5% of its original value. The success of the reaction is attributed to *overpotential*. This phenomenon is best known in electrolytic hydrogen production. According to its classical definition, hydrogen overpotential is the additional potential (beyond the thermodynamic requirement) needed to drive hydrogen production at a certain rate. This effect is kinetic in origin and manifests itself in dependence of proton *reduction* on the nature of the electrode surface (Figure 2). It follows from our studies that overpotential can be used as a

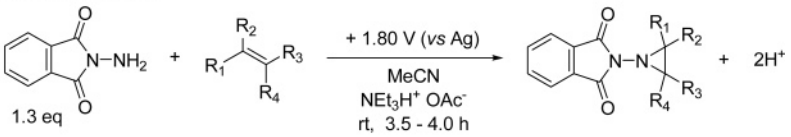
Scheme 4. Electrochemical Aziridination of Olefins

(a) schematic representation of an electochemical cell

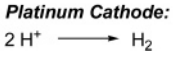


(b) electrochemical aziridination of olefins

Platinum Anode:



Platinum Cathode:



guiding principle to selectively *oxidize* a given species in the presence of a thermodynamically similar acceptor molecule without detrimental background reactions. In the case of oxidation, this finding solves an important problem that is normally difficult to tackle under homogeneous conditions with soluble reagents and catalysts.

In contrast to literature-based metal nitrogen transfer reactions, both electron-rich (Table 1) and electron-poor olefins (Table 2) are converted to aziridines with high efficiency under anodic oxidation conditions.[4b] For certain olefins such as allyl bromide, methyl acrylate, 1-hexene, dimethyl maleate, and succinic anhydride, the electrochemical aziridination (see Figure 3) was not successful although redox behavior of these olefins is not significantly different from others (Figure 4). Surprisingly, dimethyl maleate, a *cis*-olefin, was found to be inert toward electrochemical aziridination, while the trans isomer, dimethyl fumarate, gave excellent yield of the aziridine (Table 2, entry 9). In all cases with inert olefins, *N*-aminophthalimide was completely converted to phthalimide, which precipitated from the reaction mixture, and the olefins were recovered quantitatively. This observation indicates that the anodic amine oxidation process does take place, but the active nitrogen transfer species is not intercepted by the olefin. This lack of reactivity is a relative rate phenomenon: an experiment with a 1:1 mixture of 1-hexene and chalcone gave an 83% yield of the chalcone-derived aziridine while 1-hexene remained unreacted.

The electrochemical aziridination protocol allows access to a wide variety of aziridines in excellent yields. The requirement for acetate anion in aziridine synthesis implies the involvement of an *N*-acetoxyamino intermediate in our reaction (Scheme 5). In a background reaction, the electrochemically generated *N*-nitrene intermediate inserts into the N−H σ-bond of *N*-aminophthalimide to afford the tetrazane product (Scheme 6). The tetrazane is further oxidized to give tetrazene and, subsequently, phthalimide. The crucial role of acetate anion is to prevent the unwanted nitrene dimerization pathway. This is also evidenced by the correlation between aziridine yields and

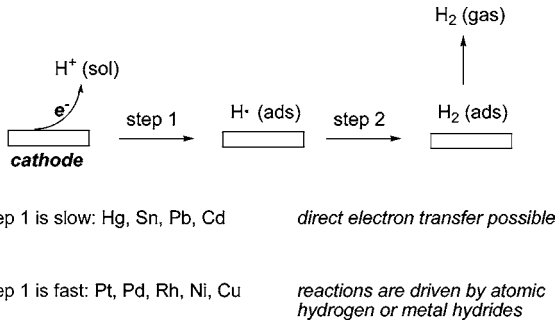


FIGURE 2. Hydrogen overpotential.

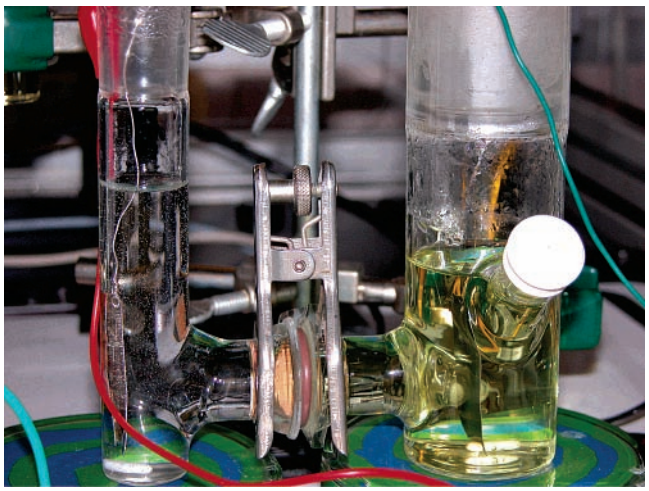


FIGURE 3. Apparatus for electrochemical aziridination (5 mmol scale).

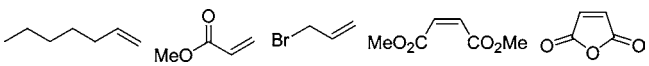
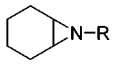
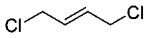
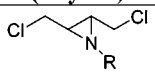
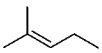
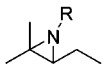
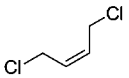
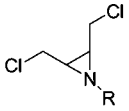
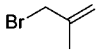
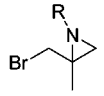
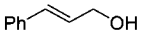
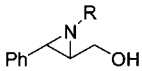
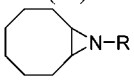
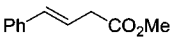
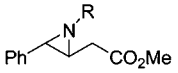
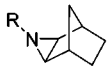
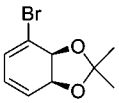
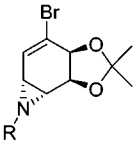
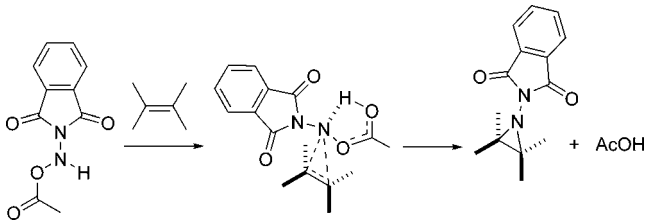


FIGURE 4. Olefins that are inert to electrochemical aziridination.

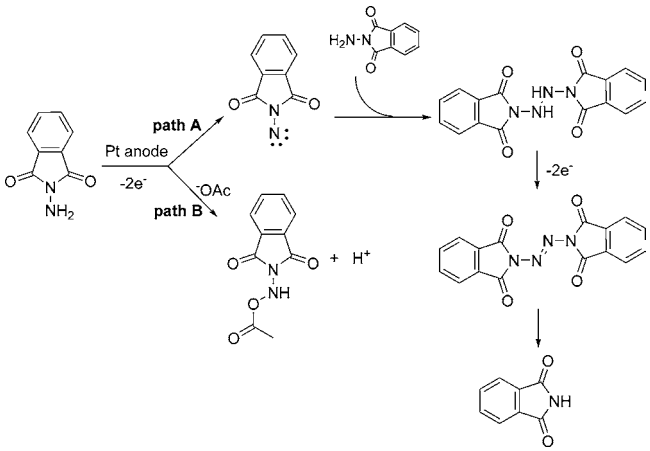
Table 1. Electrochemical Aziridination of Electron-Rich Olefins

Entry	Substrate	Product (% yield)	Entry	Substrate	Product (% yield)
1		 (85)	7		 (76)
2		 (91)	8		 (73)
3		 (42)	9		 (81)
4		 (85)	10		 (83)
5		 (51)	11		 (80)
6		 (88)	12		 (40)

Scheme 5. Mechanism of Nitrene Transfer to Olefins Involving an *N*-Acetoxyamino Intermediate

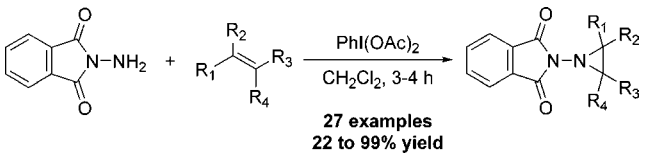


Scheme 6. Electrochemical Oxidation of *N*-Aminophthalimide



acetate concentration. In the case of "inert" olefins, the nitrene transfer is slow and an alternate path A depicted in Scheme 6 predominates to give phthalimide as the reaction product, leaving the olefin intact. The key role of the acetate anion is to intercept the product of initial oxidation, leading to the *N*-acetoxy species.

Scheme 7. Aziridination of Olefins with PIDA

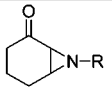
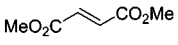
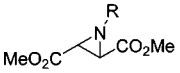
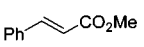
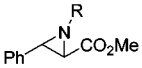
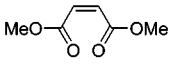
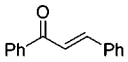
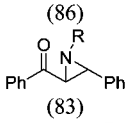
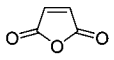
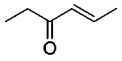
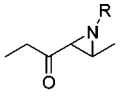
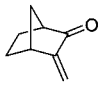
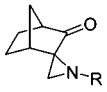
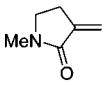
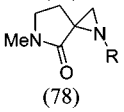
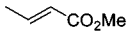
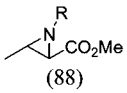
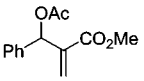
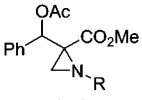
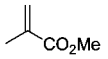
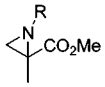
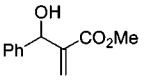
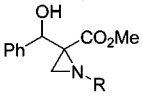
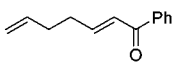
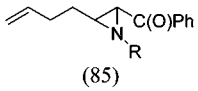
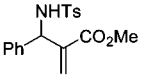
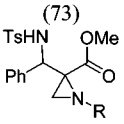
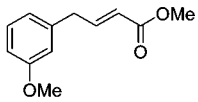


The mechanistic understanding of aziridination prompted us to investigate the utility of chemical oxidants that may offer a nonelectrochemical version of the process. As a result, we developed a synthetic protocol for the aziridination of olefins and sulfoximination of sulfoxides with *N*-aminophthalimide and phenyliodine(III) diacetate (PIDA) as an oxidant (Scheme 7).[2f,5,7]

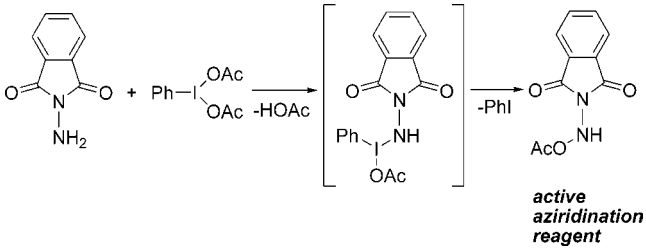
The reaction tolerates a variety of functional groups such as carbonyl, nitrile, hydroxyl, and amide. The reaction can be scaled (up to 5 mol of olefin) without any substantial changes in yield. Under similar conditions, sulfoxides were shown to undergo smooth transformation into sulfoximines.

The chemical method possesses several advantages over the electrochemical one. The availability of PIDA, its safe storage attributes, and its mildness make this procedure more accessible in a setting lacking electrochemical equipment. The only byproduct of the reaction, iodobenzene, is easily separated and poses no problems for other functional groups. It is also instructive to remark that the combination of *N*-aminophthalimide and PIDA delivers an active aziridinating agent capable of nitrogen transfer in the absence of any metal additives (Scheme

Table 2. Electrochemical Aziridination of Electron-Poor Olefins

Entry	Substrate	Product (% yield)	Entry	Substrate	Product (% yield)
1		 (78)	9		 (92)
2		 (86)	10		-
3		 (83)	11		-
4		 (93)	12		 (82)
5		 (78)	13		 (88)
6		 (79)	14		 (90)
7		 (73)	15		 (85)
8		 (81)	16		-

Scheme 8. Mechanism for the Formation of the Active Aziridination Reagent



8). The nature of the amine is critical in this instance. For instance, carbamates in combination with PIDA lead to aziridination but require the presence of a rhodium catalyst.[8]

New Catalysts for Selective Aziridine Ring Opening

Aziridines can be divided into two classes depending on the nature of the *N*-substituent (Figure 5).[9] Activated aziridines, such as *N*-tosyl and *N*-acyl aziridines, contain a strongly electronegative group that facilitates their ring-opening transformations. Nonactivated aziridines, such as *N*-alkyl aziridines, do not have a substituent that is capable of stabilizing the anion resulting from the ring opening.

There have been relatively few reports on the chemistry of simple *N*-alkyl aziridines compared to *N*-activated aziridines such as *N*-tosyl or *N*-acetyl aziridines. This is despite the fact that useful heterocycles, derived from aziridine intermediates, do not contain activating groups on nitrogen. The use of an activated aziridine as a synthetic intermediate would always require a difficult deprotection of an amide or sulfonamide product as an additional step.

We have found that a range of alkyl aziridines undergo ring-opening reactions catalyzed by *tris*-(pentafluorophenyl)borane.[2h] The reaction proceeds with a variety of amines and thiols resulting in functionalized *trans*-diamines and β-aminosulfides in high yields (Scheme 9). The reaction with alcohol nucleophiles under similar conditions failed to give *trans*-1,2-aminoethers. Furthermore, activation in the absence of nucleophile leads to polymerization of *N*-alkyl aziridines.[10]

Concurrently, an interesting mechanistic picture has developed (Figure 6). NMR evidence indicates that in situ formed $[(C_6F_5)_3B(OH_2)]\cdot H_2O$ (Figure 6, **B**) is the catalyst promoting the reaction through a Brønsted acid manifold.

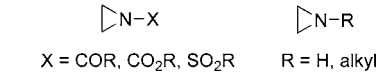


FIGURE 5. Activated and nonactivated aziridines.

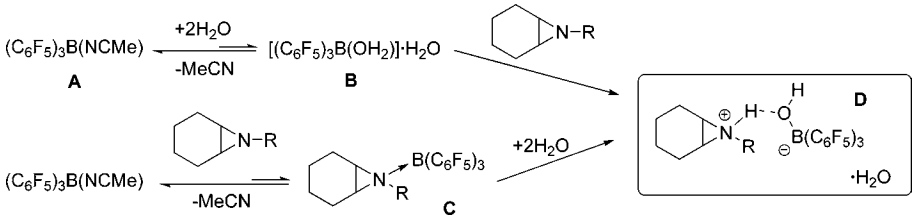


FIGURE 6. Proposed structure of the catalyst–substrate complex.

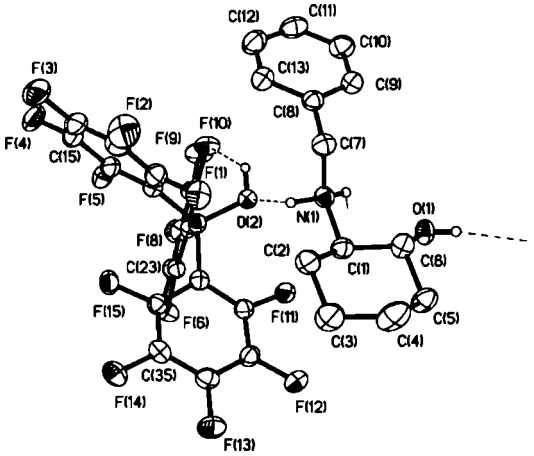
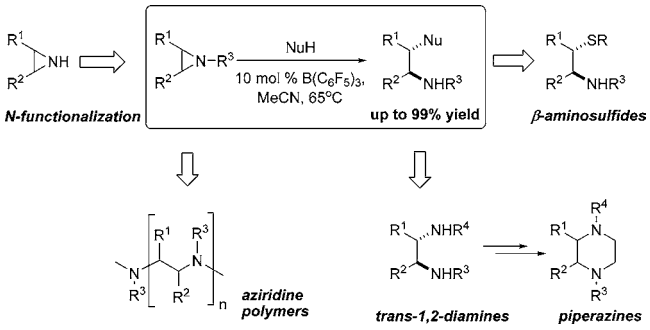


FIGURE 7. X-ray structure of the cyclohexane-derived amino alcohol–$(C_6F_5)_3B(OH_2)$ complex.

Scheme 9. Ring Opening of Unactivated Aziridines Catalyzed by $B(C_6F_5)_3$

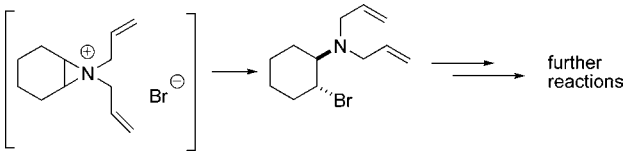


The aziridine is activated toward ring opening by formation of an aziridinium adduct (Figure 6, **D**), which is subsequently opened by the nucleophile. NMR analysis provides support for the formation of **D**. Further evidence for the involvement of the protic activation is provided by the X-ray structure of an amino alcohol–$(C_6F_5)_3B(OH_2)$ adduct prepared by mixing stoichiometric quantities of *N*-benzyl cyclohexene imine, $B(C_6F_5)_3$, and H_2O in toluene/pentane. The product is a *trans*-1,2-amino alcohol, formed upon ring opening of the aziridine by water, which is bound to the borane part of the complex via hydrogen bond (Figure 7).

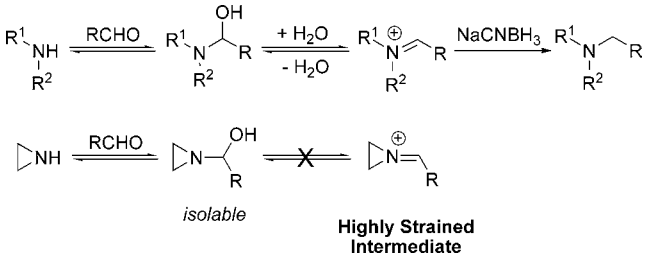
Palladium-Catalyzed Allylation of NH Aziridines

The aziridine ring does not benefit from a straightforward, one-step protocol similar to the abundant examples of oxygen atom transfer in epoxidation chemistry. Enantiomerically enriched aziridines are available via transition metal catalysis, but only in their *N*-protected forms.

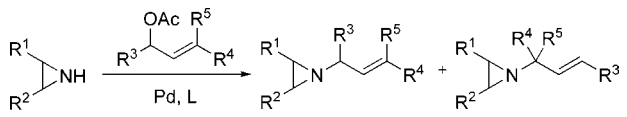
Scheme 10. Attempted Synthesis of *N*-Allyl Cyclohexene Imine by Alkylation



Scheme 11. Reaction of Unprotected Aziridines with Aldehydes



Scheme 12. Palladium-Catalyzed Allylation of NH Aziridines



R^1,R^2 = -$(CH_2)_4$-
R^1 = CH_3, R^2 = H
R^1 = CO_2Me, R^2 = H
R^1 = COPh, R^2 = -$(CH_2)_2CH{=}CH_2$
R^1 = Ph, R^2 = H
R^1 = Ph, R^2 = CH_3
R^1 = Ph, R^2 = COPh

Conventional methods of making aziridines[2l] pose functional group compatibility issues. Therefore, *modification* of aziridine-containing starting materials can be viewed as a viable route if the ring installation is desired at a later stage of synthesis. Only a few reactions fall into this category.[1] We opted to explore routes from unprotected aziridines to their allylated derivatives. Allylamines are valuable synthetic intermediates for the preparation of α- and *β*-amino acids, alkaloids, and aza-carbohydrate derivatives.

N-Allylation of aziridines may be complicated by side reactions (Scheme 10). The classical solution to this problem, reductive amination, is also problematic due to the increased strain energy of the aziridinium intermediate. We observed this effect when a number of aldehydes were reacted with unprotected aziridines. Even under forcing conditions, we were only able to isolate 1,1-aziridine-ol intermediates and have been unable to detect any evidence of iminium ion formation (Scheme 11).[11]

This challenge led us to consider the palladium-catalyzed allylic amination reaction using unprotected aziridines (Scheme 12). This protocol delivers a possibility for the introduction of aziridine moieties into function-

Table 3. Synthesis of Allyl Aziridines by Palladium-Catalyzed Allylic Amination

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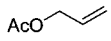
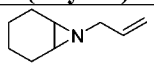
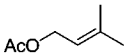
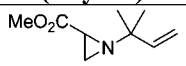
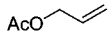
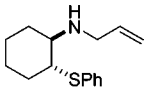
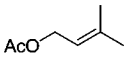
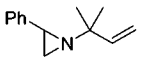
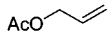
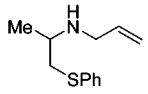
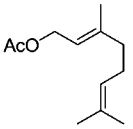
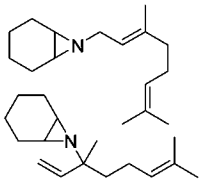
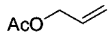
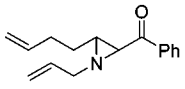
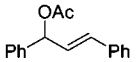
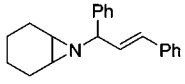
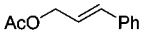
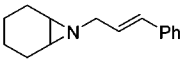
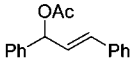
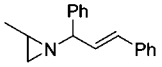
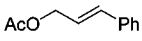
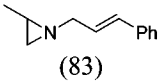
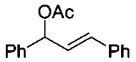
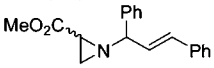
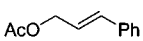
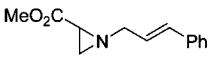
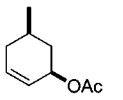
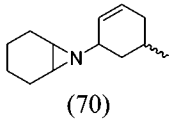
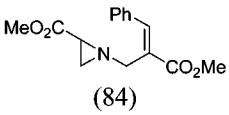
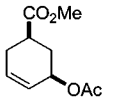
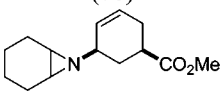
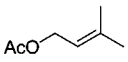
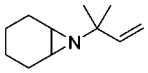
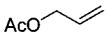
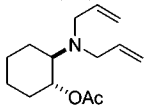
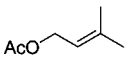
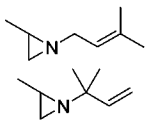
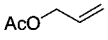
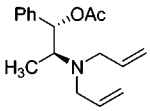
1		 (45)	10		 (43)
2		 (99)	11		 (72)
3		 (64)	12		 12:88 (80)
4		 (79)	13		 (97) 97% ee
5		 (99)	14		 (97) 98% ee
6		 (83)	15		 (79)
7		 (83)	16		 (70)
8		 (84)	17		 (80)
9		 (89)	18		 (84)
10		 29:71 (90)	19		 (65)

alized environments with high levels of regioselectivity and high isolated yields (Table 3).[2a,d]

A byproduct can sometimes be observed, caused by acetic acid ring-opening of the allyl aziridine (Table 3, entries 18 and 19). Formation of the byproduct can be suppressed by basic conditions or by the use of allyl carbonates. The use of *(R)*-BINAP as a ligand can afford allyl aziridines in high enantioselectivities (Table 3, entries 13 and 14). These values are the highest achieved with BINAP in allylic amination, a ligand that usually gives low enantioselectivities.[12]

In the case of 1,1-dialkyl allyl acetates, two regioisomeric outcomes are possible. Nitrogen nucleophiles, including primary and secondary alkylamines, azide, and amides, all favor the linear allylamine under palladium-catalyzed conditions. We unexpectedly found that the reaction of prenyl acetate with cyclohexene imine produced the branched isomer as the only detectable product, isolated in 89% yield (Table 3, entry 9). When we performed the same reaction between piperidine and prenyl acetate, only the linear isomer was detected (Scheme 13).

Scheme 13. Dependence of the Regiochemistry of Products in Allylic Amination as a Function of Amine

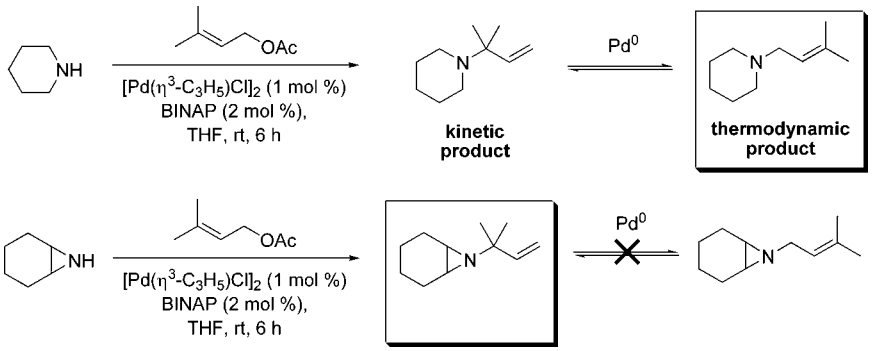


FIGURE 8. Differences in experimentally observed products in the course of allylic amination chemistry.

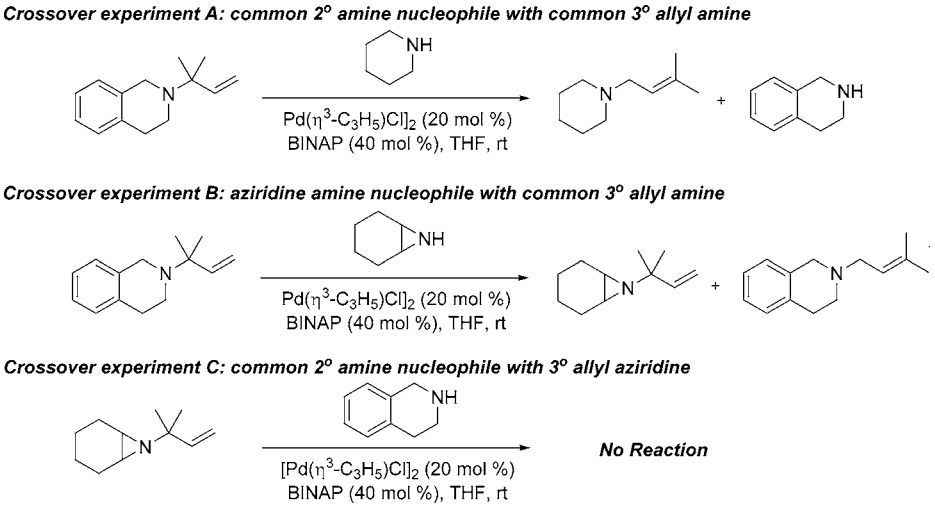


FIGURE 9. Crossover experiments in amine allylation chemistry.

Likewise, in agreement with the literature reports, the use of a number of other amines under identical palladium-catalyzed conditions, produced only the linear isomers. Palladium catalysis is significantly different from the iridium, rhodium, molybdenum, and ruthenium catalysis in that all of the latter favor the branched product.[13] There are only a few other examples of palladium-catalyzed allylic aminations of terminal allyl esters or carbonates resulting in predominant formation of the branched isomers.[14] In these examples, special ligands are employed to switch the regioselectivity. In our case, the same catalyst−ligand system produces different regioisomers depending on whether a common secondary amine or aziridine nucleophile is used. The steric environment around palladium appears to have no effect on the regiochemical outcome of the reactions with unsubstituted aziridines. A number of bidentate phosphines incorporating a range of bite angles had little effect on the branched-to-linear ratio.

Once the allyl aziridine product is produced, it appears to be stable toward isomerization. When the linear aziridine, synthesized by a separate method, was subjected to the typical reaction conditions, no branched product was observed. We observed that the initially produced branched product in the reaction between piperidine and prenyl acetate disappears. Meanwhile, the amount of linear isomer increases, indicating that the allylamine isomers are able to equilibrate (Figure 8). Therefore, in the case of aziridines and other secondary amines. the kinetic product is the branched isomer. In the case of other amines, the branched product converts to the linear isomer, the thermodynamic product, while in the case of aziridines this equilibration does not occur (Figure 8).

A series of crossover experiments were carried out (Figure 9). The fact that crossover of the prenyl moiety is observed from a branched amine to other amines such as piperidine indicates that the mechanism of isomerization is bimolecular. The crossover experiments also clearly demonstrate the different abilities of branched allylamines and allyl aziridines to act as electrophile precursors under the reaction conditions.

The experimental evidence is consistent with the following mechanistic scenario (Figure 10). In THF, the reaction produces protonated branched amine as the kinetic product, by an S_N2' reaction with an allyl palladium σ-complex. Recomplexation of Pd^0 to the product alkene (complex **D**) enables ionization to the π-complex **B**, which is in equilibrium with the σ-complex **A**. It is the generation of these electrophilic components that enables crossover reactions to take place. Attack of an amine on the more prevalent σ-complex **A** simply regenerates branched allylamine. However, the reaction at the π-complex **B** should favor attack at the less substituted carbon resulting in formation of the linear product. The strength of the palladium/olefin interaction in complex **D** is higher than that in complex **E** due to the higher degree of substitution

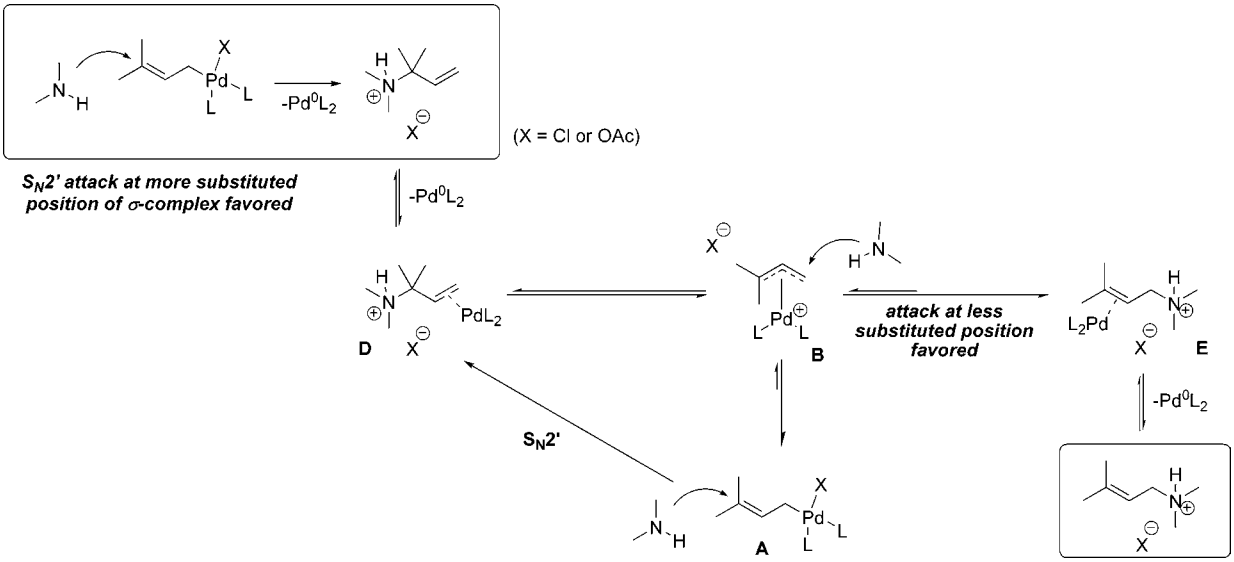
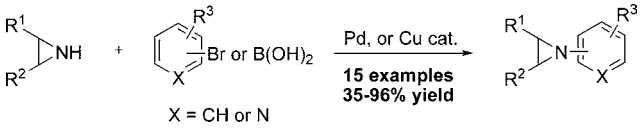


FIGURE 10. Rationale behind allylamine isomerization.

Scheme 14. Palladium-Catalyzed Arylation of Unprotected Aziridines



in **E**.[15] As a consequence, ionization of complex **D** should be more facile than that of complex **E**. Therefore, the dynamic process outlined in Figure 10 steadily increases the amount of the linear product. With aziridine, the formation of either **A** or **B** does not take place, which accounts for the observed lack of branched-to-linear isomerization in the case of allyl aziridines. The significant deviation in the behavior of aziridine nucleophiles in palladium-catalyzed allylic amination allows for the facile synthesis of useful branched amines that are difficult to obtain using other methods.

Aziridine Nucleophiles in Cross-Coupling Reactions

A range of *N*-arylaziridines can be prepared by the palladium- or copper-catalyzed reaction between unsubstituted aziridines and aryl bromides or arylboronic acids without premature aziridine ring opening (Scheme 14).[2j] The $Pd_2(dba)_3$/BINAP combination in toluene at 70 °C with NaO^{t}Bu as base serves as an effective catalyst for the amination of unsubstituted aziridines. Using this methodology, one can synthesize *N*-arylated products in 35−96% yield. The insertion of palladium into the nitrogen−carbon bond was not observed in any of these cases, although oxidative addition of Ni to *N*-tosylaziridines has been reported[16] and oxidative addition of transition metals to aziridines has been invoked in catalytic carbonylation of aziridines to give β-lactams.[17]

We extended this protocol to aziridinyl enamine synthesis. Enamines are among the most versatile intermediates for introducing a nitrogen-containing fragment in a synthetic sequence. However, typical protocols for the synthesis of imines and enamines based on carbonyl condensation chemistry have low functional group tolerance. Reported methods for the synthesis of *N*-alkenyl aziridines are scarce and have many limitations including the requirement for activated alkenyl halides and acetylenes. We have found that aziridinyl enamines can be prepared in a fashion similar to *N*-aryl aziridines. Moreover, since aziridines are not effective nucleophiles in carbonyl condensation reactions, the metal-catalyzed

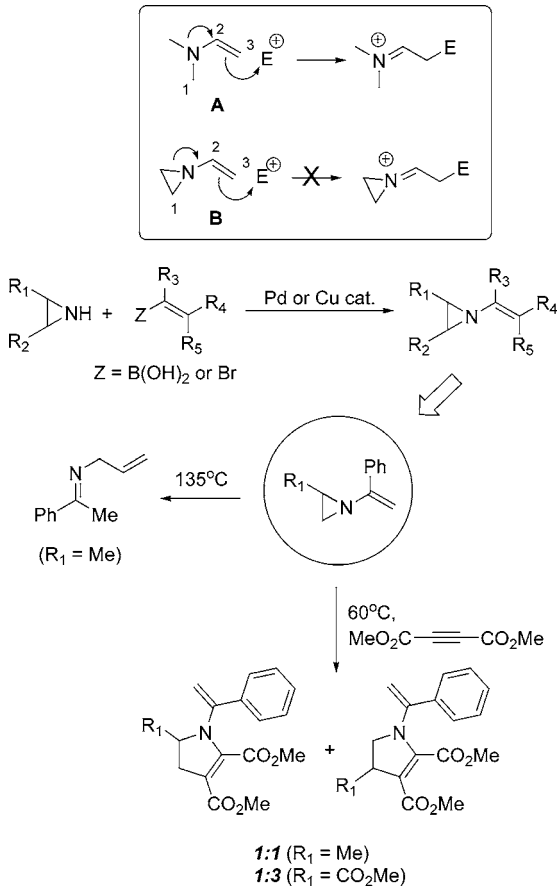
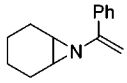
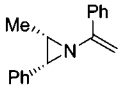
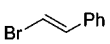
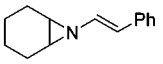
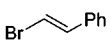
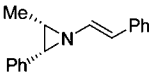
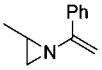
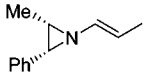
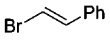
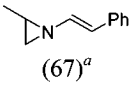
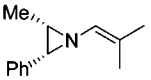
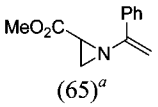
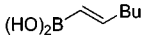
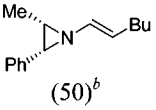
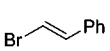
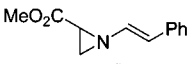
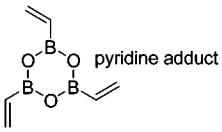
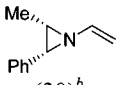


FIGURE 11. Synthesis and chemical reactivity of *N*-alkenyl aziridines.

Table 4. Scope of Palladium- and Copper-Catalyzed *N*-Alkenylation of Aziridines

Entry	Substrate	Product (% yield)	Entry	Substrate	Product (% yield)
1		 (69)[a]	7		 (64)[a]
2		 (65)[a]	8		 (68)[a]
3		 (75)[a]	9		 (65)[a]
4		 (67)[a]	10		 (70)[a]
5		 (65)[a]	11		 (50)[b]
6		 (60)[a]	12	 pyridine adduct	 (30)[b]

[a] Palladium-catalyzed. [b] Copper-catalyzed.

route is the only reliable procedure to access this interesting and unusual class of compounds. The corresponding enamines deviate significantly from conventional systems. A conventional enamine such as **A** would enlist its C-2 center during nucleophilic attack. In contrast, the aziridinyl enamine **B** has no such option due to significant increase in strain in the ensuing iminium ion. This interesting difference in behavior should make aziridinyl enamines attractive intermediates with the locus of nucleophilicity at nitrogen (Figure 11, **A** and **B**).

Using $Pd_2(dba)_3$, BINAP, and NaO^{t}Bu as base at 90 °C, a number of *N*-alkenyl aziridines were synthesized with yields ranging from 60% to 85% (Figure 11, Table 4). Analogous to the previously described copper-catalyzed *N*-arylation of aziridines, the copper route to *N*-alkenyl aziridines takes place at ambient temperature and is advantageous for volatile starting materials. The yields were lower using this method compared to the palladium-catalyzed procedure. However, *N*-alkenyl aziridines can be synthesized when the boronic acid equivalent of alkenyl bromide, 2,4,6-trialkenylcyclotriboroxane-pyridine adduct, is employed.[2c]

With the *N*-alkenyl aziridines in hand, their reactivity was explored. Formally, these molecules have the appearance of an enamine. However, the chemical shift of the α-proton in the enamines derived from common amines is significantly upfield accounting for their zwitterionic character in the ground state. The ethylene imine-derived enamine α-proton is downfield compared to conventional enamines (Figure 12). One can therefore expect a deviation in reactivity of the aziridine-containing enamines compared to conventional systems.

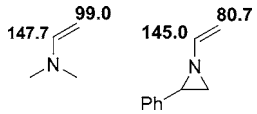


FIGURE 12. ^{13}C-chemical shifts of the *N*-vinyl group in enamines.

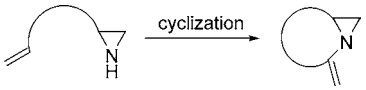
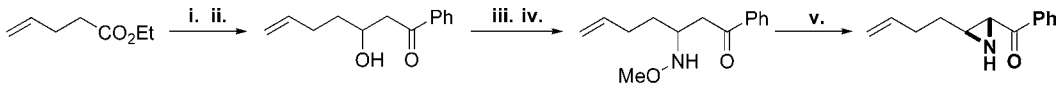


FIGURE 13. Intramolecular oxidative cycloamination of olefins with aziridines.

When sterically unhindered *N*-alkenyl aziridines were heated in the presence of dimethyl acetylene dicarboxylate (DMAD), formal [3 + 2] cycloaddition products were observed in yields ranging from 65% to 80%. The products were obtained as mixtures of two regioisomers depending on which carbon center of the aziridine ring participated in the cyclization (Figure 11). When 2-methyl-1-(1-phenylvinyl)-aziridine was heated to 135 °C, a thermal [1,5] hydrogen shift was observed (Figure 11).

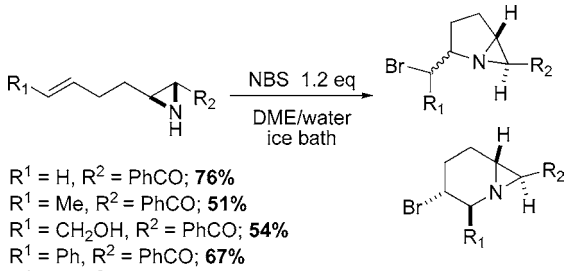
Aziridines in Oxidative Cycloamination

Known for the difficulties in controlling their reactivity, aziridines are rarely used in complex molecule synthesis.[18] Nitrogen protection/deprotection sequences in the presence of aziridine moieties are unlikely to be successful due to aziridines' susceptibility toward acidic reagents. However, aziridines are generally resistant toward oxida-



i) 1.1 equiv DIBAL-H, PhMe, -78°C ii) $PhC(OTMS)=CH_2$, $BF_3{\bullet}OEt_2$, THF, -78 to 0°C iii) 1.0 equiv TsOH, PhMe, 40°C iv) 1.2 equiv NH_2OMe, EtOH, reflux v) NaOMe, DMF, rt

FIGURE 14. Synthesis of aziridine-containing building blocks.



R^1 = H, R^2 = PhCO; **76%**
R^1 = Me, R^2 = PhCO; **51%**
R^1 = CH_2OH, R^2 = PhCO; **54%**
R^1 = Ph, R^2 = PhCO; **67%**
R^1 = H, R^2 = PhCH(OH); **55%**

FIGURE 15. Aziridine cycloamination reactions.

tive degradation. They have a significant (0.8 V) difference in oxidation potential compared to typical secondary amines such as piperidine, which is known for its low stability toward oxidation. We reasoned that an oxidative intramolecular cyclization process could be used to create new aziridine heterocycles with potential as advanced intermediates for synthesis (Figure 13). Compared to the aziridinyl enamines described in the previous section, these bicyclic systems benefit from a higher degree of strain and ease of opening.

Building blocks containing aziridines, separated by a $(CH_2)_2$ linker from the olefin, were prepared from commercially available starting materials (Figure 14).[2i] These molecules were designed toward cyclization to give pyrrolidine- and piperidine-containing heterocycles, an important class of targets for stereoselective synthesis.[19] We observed that treating these aziridines with *N*-bromosuccinimide (NBS) in DME/water allowed for conversion into 1-azabicyclo[3.1.0]hexane derivatives in good yields (Figure 15). Monitoring the reaction by TLC analysis indicated complete conversion of the NH aziridine to the corresponding N−Br species within the first 2 min of the reaction. We were able to isolate and characterize the N−Cl containing intermediates when the aziridines were treated with NCS. The haloamine thus formed is the active haloaminating agent attacking the double bond of the molecule to give the cycloamination product. The products are [5,3] bicyclic rings in the case of the terminal double bond-containing substrates, whereas aryl-substituted double bonds preferentially give [6,3] bicyclic rings.

The resulting bicycles can be readily converted into *exo*-methylene aziridines via dehydrobromination. These molecules possess considerable synthetic potential since the enamine-like aziridine ring can be transformed into an imine/enamine system upon ring opening. The perpendicular orientation of the nitrogen electron pair in relation to the double bond is evident from the single-crystal X-ray analysis. Interestingly, the bond length between C1 and C2 is 1.32 Å, which is typical of an olefin system.

The ring-opening reactions of the bicyclic aziridines proceed with high yields and excellent diastereoselectivities. The reactions are regioselective and afford the corresponding pyrrolidine and piperidine derivatives (Figure 16). The resulting enamines, obtained via strain-release protocol, tautomerize in situ into cyclic imines. The reductive ring opening of bicyclic aziridines by

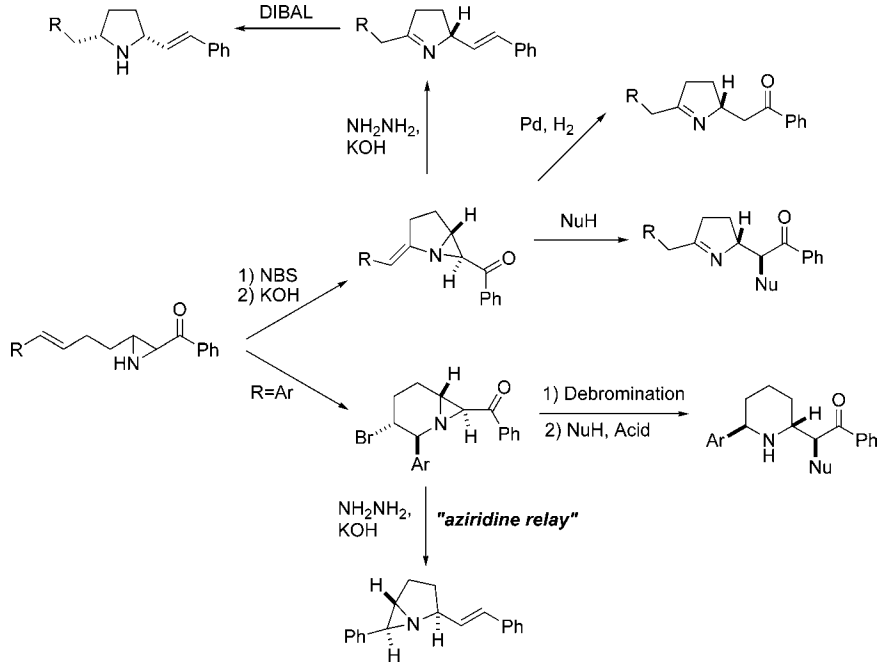


FIGURE 16. Synthetic utility of the cycloamination process.

hydrogen on Pd/C gives five-membered cyclic imines in excellent yields. Aziridine ring opening can also be triggered by hydrazinolysis. Upon treatment with hydrazine, valuable 2-allylamine derivatives are obtained in good yields. If an appropriate leaving group is present, *aziridine relay* can also be established. The resulting cyclic imines can be readily reduced to pyrrolidines using DIBAL. This strategy is a valuable addition to existing methods for assembling substituted pyrrolidines and piperidines.[20]

Conclusion

Our studies over the past several years resulted in new approaches to oxidative nitrogen transfer. We have shown that it is possible to perform metal-free nitrene transfer in the presence of olefins. Overpotential has led to the development of this process, and its mechanistic understanding resulted in a convenient chemical variant of the reaction. We have also found that as a nucleophile, aziridine deviates significantly from other secondary amines, evident from selectivity observed in palladium-catalyzed allylation. The aziridines obtained via allylic amination enable control over the quaternary carbon center next to nitrogen. Meanwhile, metal catalysts do not trigger premature aziridine ring opening. The five- and six-membered rings can be produced with high levels of control over relative stereochemistry. As a result, it is possible to maintain the aziridine-containing moiety intact far into synthetic sequence. The resulting enamine systems are versatile synthetic intermediates and should find utility on target-oriented synthesis.

We are most grateful to the many talented students who contributed to this research over the years. Without their ideas, enthusiasm, and hard work, the advances outlined in this Account would not have been possible. We thank NSERC, CFI, ORDCF, ACS-PRF, Amgen, Affinium Pharmaceuticals, and the University of Toronto for financial support.

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