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# PREPARATION AND SYNTHETIC APPLICATIONS OF AZETIDINES†

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**Abstract** – Azetidines (four-membered saturated nitrogen heterocycles) are found in a diverse range of natural products, and also serve as valuable building blocks for other structural classes. The ring-strain inherent in these compounds poses challenges in their preparation, and a number of creative methods for the synthesis of substituted azetidines are presented. The application of azetidines in the construction of acyclic products or other heterocyclic systems is also described. Finally, recent examples of the use of chiral, enantiomerically pure azetidines in asymmetric catalysis are detailed.

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† Dedicated with respect and affection to Professor Albert Padwa on the occasion of his 75th birthday, in recognition of his countless inspiring contributions to the field of heterocyclic chemistry.

## INTRODUCTION

Azetidine (**2**) is the parent molecule of a class of small, nitrogen-containing heterocycles, which have been gaining attention for their versatility in many areas of chemistry.[1] The increased exploration into the chemistry of these molecules stems from the interesting behaviours they exhibit in synthetic and biochemical settings as well as the development of new methods to synthesize them. It has been found that these strained four-membered rings can display properties of their smaller or larger-ring counterparts, aziridines (**1**) or pyrrolidines (**3**), depending on the nature of their substitution pattern and their chemical environment (or the reaction conditions applied).

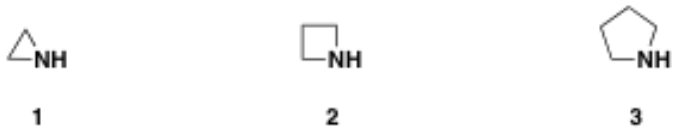
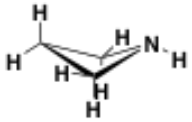



Figure 1. Small nitrogen heterocycles

The physical properties of many different azetidines have been reported in the literature. In general, azetidines are conformationally puckered, ridgid, molecules with bond angles bent 10-20 degrees out of planarity depending on their substitution pattern.[2] The diffraction data of azetidine has been used to calculate the bond lengths and bond angles present in the molecule, which are shown in Table 1. The lone pair on nitrogen is favored to be in the pseudoaxial position; however, with an inversion barrier of ~10 kcal/mol, inversion at room temperature does occur.[3]

Table 1. Geometric parameters of azetidine



| | Bond Length (Å) |
|---|---|
| N-C | 1.48 |
| C-C | 1.55 |
| C-H | 1.11 |
| N-H | 1.02 |
| | Bond Angle (degrees) |
| CNC | 92 |
| CCC | 87 |
| CCN | 86 |
| HCH | 110 |

The ring strain energy associated with the azetidine ring has been experimentally determined to be 25.2 kcal/mol.[4] This number is very close to that observed for aziridine at 26.7 kcal/mol. In contrast, the ring strain energies for pyrrolidine and piperidine are 5.8 and 0 kcal/mol respectively. Interestingly, although strained, azetidines are more similar to pyrrolidines than aziridines when it comes to several of

their physical properties. For example, the $pK_a$ of azetidine (11.29)[2] is much closer to that of pyrrolidine (11.31)[2] than to aziridine (7.98).[5] In terms of basicity, this means that azetidine can behave like a typical secondary amine in most reactions.

A comparison of the $^1H$ NMR chemical shift data of these three heterocycles also shows a much closer resemblance of azetidine (2) to pyrrolidine (3) rather than aziridine (1), as the bond angles are not deformed enough to induce an upfield chemical shift as seen in aziridine (Figure 2).[6] On examination of the coupling constants (*J*), however, the addition of substituents on either carbon or nitrogen can significantly affect the observed *J*-values between geminal protons, as commonly observed with aziridines, whereas this effect is not as prominent in pyrrolidines.

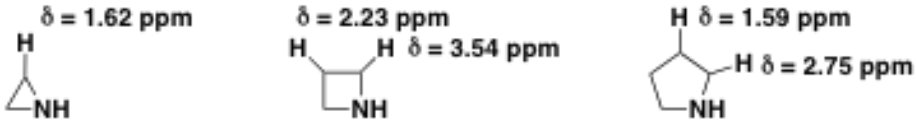



Figure 2. $^1H$ NMR chemical shifts of aziridine, azetidine and pyrrolidine

Figure 3 shows some examples of the effect changing the substituent on nitrogen (**4**, **5** and **6**) as well as the addition of a substituent on C-4 (**7** and **8**) can have on the observed $J_{2,2'}$-values.[1a,7] This is most likely due to changes in the puckering angle of the ring, which affects the hybridization on the carbon atoms, and can be explained by application of the geminal Karplus curve.[6] These data are especially notable because they give insight into the conformational changes that can occur in these molecules when different substituents are present. This will be an important factor later on in this review when there are significant changes in the reactivity of one azetidine *vs*. another based on differences in their substitution pattern around the ring.

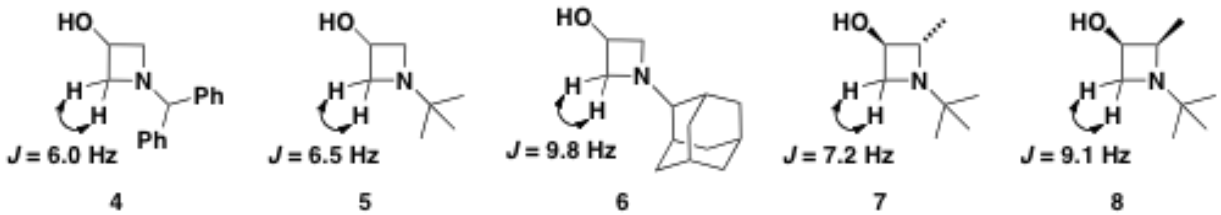



Figure 3. Effect of substituents on the observed geminal coupling of azetidines

## AZETIDINE-CONTAINING NATURAL PRODUCTS

Although azetidine itself has not been found in nature there are several analogues that have been isolated. L-Azetidine-2-carboxylic acid (**9**), the first azetidine natural product to be discovered, was isolated form *Convallaria majalis* (lily of the valley) in 1955.[8] Research into the role of this molecule suggests it is a proline receptor antagonist affecting the structure of proteins in its natural predators.[9] It has

subsequently been found in several other plants and is the parent molecule for a number of other natural products found in both plants and animals (Figure 4).[1b]

Mugineic acid (**10**), 2'-deoxymugineic acid (**11**) and nicotianamine (**12**) are structurally related phytosidophores which are produced in plants to aid in the uptake of iron for chlorophyll biosynthesis. Due to this interesting biological activitity, there have been a number of synthetic efforts towards their production.[10] Penaresidin A and B (**13** and **14**) have also been the targets of several syntheses as they have been found to exhibit biological activity in the activation of ATPase in actomycin.[11] Several members of the polyoxin family of compounds (**15**) have proven valuable as fungicides in an agricultural setting.[12] The most recently reported natural product containing the azetidine moiety, calydaphninone (**16**), was isolated from the leaves and twigs of *Daphniphyllum calycillum* in 2007.[13] This molecule, containg a 4-azatricyclo[5.2.2.0]undecane core, represents one of the most complex azetidine-containing natural products seen to date.

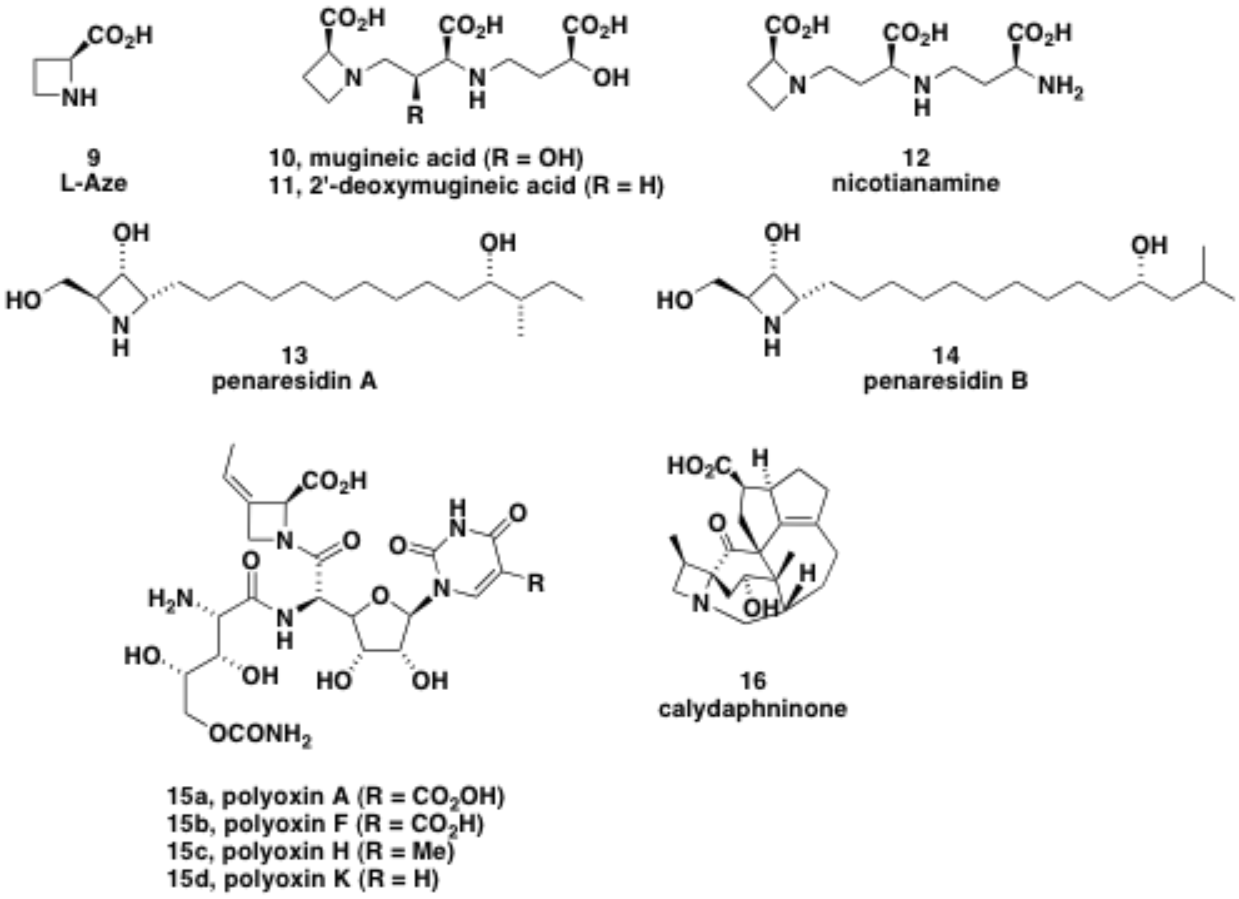



Figure 4. Azetidine-containing natural products

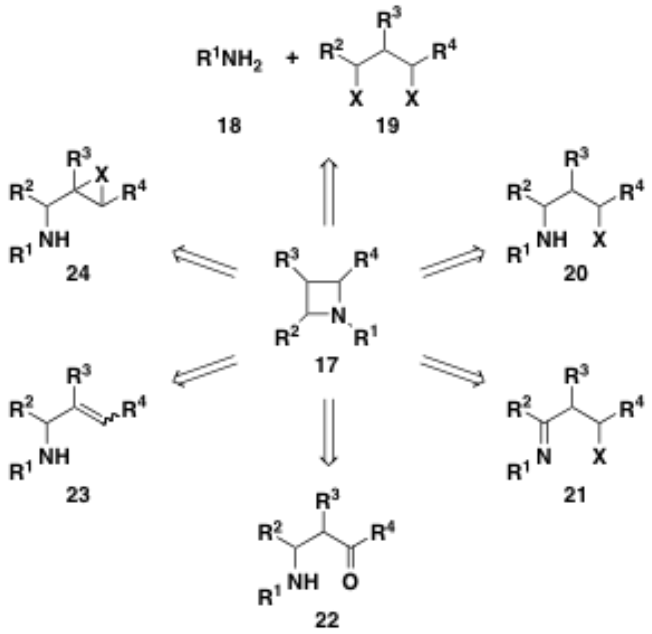
The natural products in Figure 4 all possess at least one stereogenic center on the azetidine ring. The presence of up to three contiguous stereogenic centers, seen in **13** and **14**, as well as an α-quaternary center, seen in **16**, illustrate the challenges that can arise in the preparation of such compounds. The

need to synthesize the azetidine core with complete control over the stereochemistry is important, as it is well known that the biological activity of a molecule is often directly related to the relative and absolute configuration of its substituents.

## SYNTHESIS OF AZETIDINES

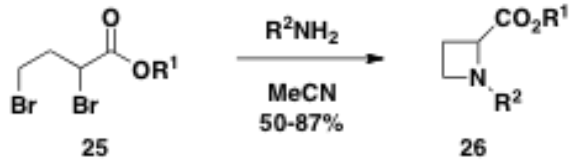
Increased activity in the area of azetidine synthesis over the last few decades has been driven by growth in their application in both synthetic and medicinal chemistry. The azetidine ring system, however, is one of the most challenging ring systems to form of the common azaheterocycles (5>3>6>7≈4). The difficulty in its formation lies in the increased ring strain of the target molecule once it is formed. This makes the ring closure significantly uphill in energy. Although there are multiple reported methods for the synthesis of azetidines in the literature, only a few are generally applicable to form a diverse range of products with the ability to place substituents at different positions around the ring.[1a-c] This section will focus on summarizing the most versatile methods for azetidine synthesis with a highlight of some promising new methodology.

**Ring Closure by C–N Bond Formation.** The displacement of a leaving group by nitrogen is the oldest and most commonly used route for the formation of the azetidine ring system. This method, which allows for the incorporation of multiple substituents on various positions around the ring, has taken on several variations over the past few decades. Scheme 1 shows some general methods for azetidine formation that are present in the literature. These methods include, but are not limited to: addition of amines (**18**) to 1,3-dielectrophiles (**19**), ring closure of γ-haloamines or activated γ-aminoalcohols (**20**), reductive cyclization of γ-haloimines (**21**) or α-amino aldehydes/ketones (**22**), activation of allylamines (**23**) and ring-opening of epoxides or aziridines (**24**).



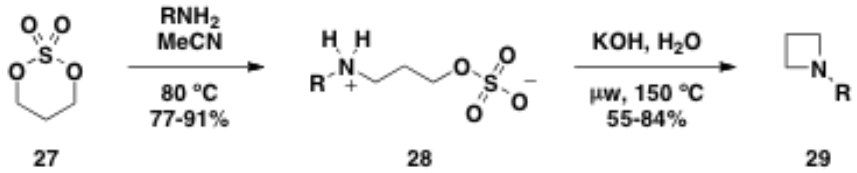

Scheme 1. Retrosynthetic pathways to azetidines

The double $S_N2$ cyclization of 1,3-electrophiles with primary amines is well established in the literature. A classic example is the synthesis of azetidine-2-carboxylic esters **26** from the reaction of primary amines with 2,4-dibromobutyrates **25** (Scheme 2).[14] This approach generally allows for a number of different alkyl or aryl substituents on both $R^1$ and $R^2$ to accommodate for subsequent functionalization. A wide variety of other leaving groups have also been utilized, including chlorides, iodides, triflates, mesylates, tosylates and sulfonic esters depending on the nature of the reaction media. Unfortunately, a drawback of this methodology is the tendency for polymerization and/or elimination side reactions to occur during prolonged heating, which contributes to low yields.



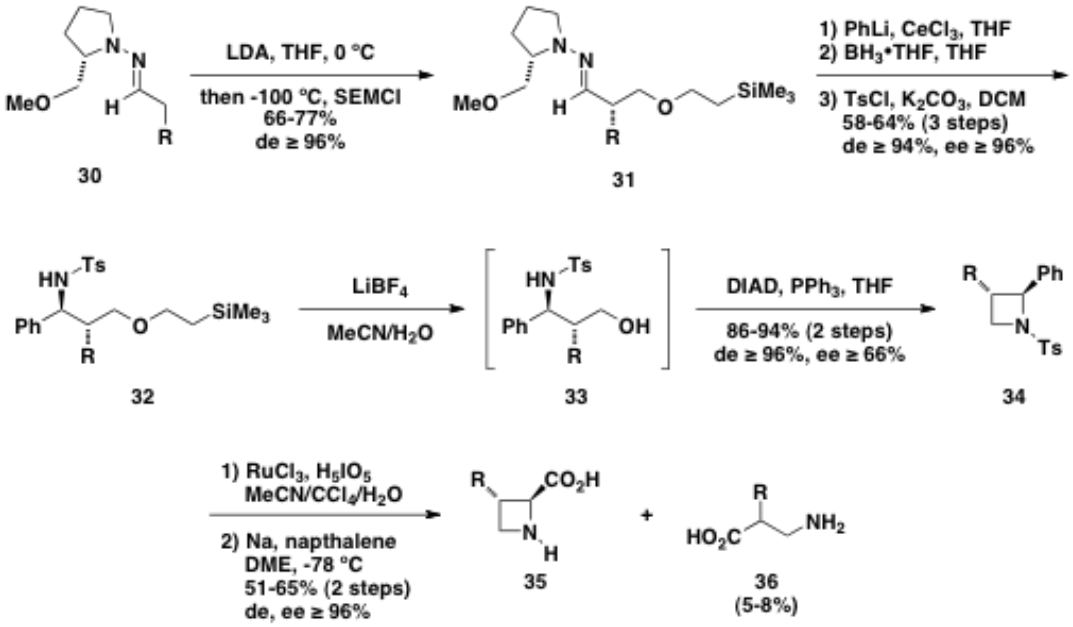

Scheme 2. Synthesis of azetidines *via* double $S_N2$ displacement of halides

The advancement of microwave technology has been fortuitous for the preparation of azetidines by this type of displacement. Burkett and coworkers have reported the synthesis of a variety of different *N*-substituted azetidines in good yields by reaction of primary amines with the cyclic sulfate of propanediol (**27**) (Scheme 3).[15] Initial formation of 3-(amonio)propyl sulfates (**28**) followed by 15 minutes of microwave irradiation in basic aqueous media gave rise to analytically pure azetidines (**29**) in moderate to good yields.



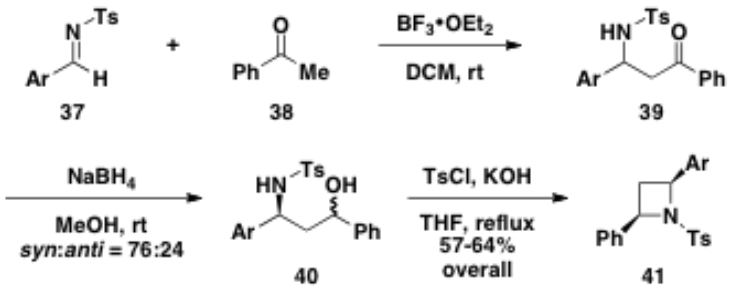

Scheme 3. Expedient synthesis of azetidines using microwave heating

The ability to access enantiopure 1,3-aminoalcohols has been key to the successful construction of enantiopure azetidines. In 2005, the Enders group reported the synthesis of *N*-tosyl-2,3-disubstituted azetidines (**34**) with excellent diastereo- and enantioselectivities from the cyclization of 1,3-aminoalcohols derived from SAMP/RAMP-hydrazone methodology (Scheme 4).[16] Most notably, the authors were subsequently able to transform the 2-phenyl substituent on **34** to the acid (**35**) by oxidation with ruthenium tetroxide followed by deprotection of the amine. The small amounts of acyclic products (**36**) obtained were most likely the result of ring opening followed by oxidation at the benzylic position.




Scheme 4. Cyclization of chiral 1,3-aminoalcohols for azetidine-2-carboxylic acid synthesis

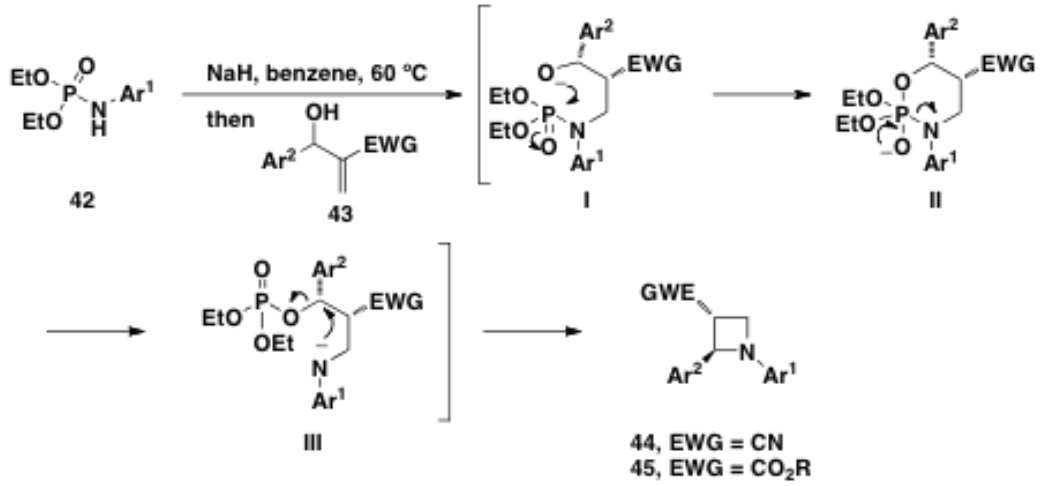
On a similar note, Das and coworkers have recently reported the synthesis of *N*-tosyl-2,4-disubstituted azetidines (**41**) from *N*-tosylaldimines (**37**) and acetophenone (**38**, Scheme 5).[17] The authors treated a mixture of **37** and **38** with $BF_3{\cdot}OEt_2$ in dichloromethane to generate β-amino ketone **39**, which was subsequently reduced to a mixture of *syn* and *anti* 1,3-aminoalcohols (**40**) in the presence of sodium borohydride. After separation, the *anti*-isomer of **40** was refluxed with potassium hydroxide and tosyl chloride to give the *cis*-azetidine product **41** in 57-64% yield over three steps with only one purification step.




Scheme 5. Synthesis of 2,4-*trans*-disubstituted azetidines from aldimines and acetophenone

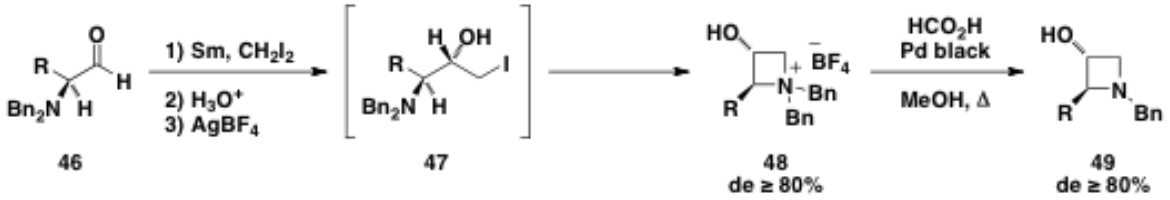
The Yadav group has reported a clever way to access activated 1,3-aminoalcohols derivatives *in situ* for the synthesis of azetidine-3-carbonitriles **44** and azetidine-3-carboxylates **45** by the addition of phosphoramidates (**42**) to Morita-Baylis-Hillman adducts (**43**, Scheme 6).[18] This one pot protocol involves treatment of diethyl *N*-arylphosphoramidates (**42**) with sodium hydride followed by addition of Morita-Baylis-Hillman adduct **43** to form aza-Michael intermediate **I**. Intramolecular attack of the alkoxide ion on phosphorus generates intermediate **II**, which opens to **III** before displacement of the phosphate ester with the amide nitrogen. The resulting azetidine (**44**/**45**) is isolated in 94-96% yield

with exclusively the *trans* stereoisomer.



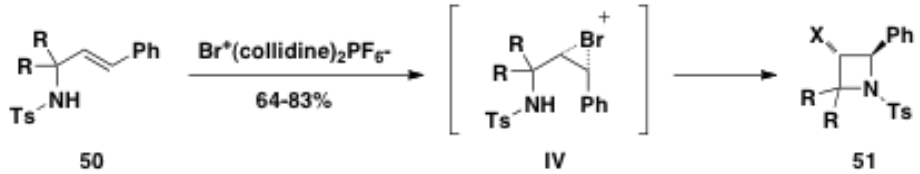

Scheme 6. Azetidines from Morita-Baylis-Hillman adducts

The conversion of α-amino aldehydes **46** to aminoiodohydrins **47** with $Sm/CH_2I_2$ followed by treatment with silver tetrafluoroborate has resulted in the formation of stable enantiopure 3-hydroxy-azetidinium salts **48** in good yields which could be almost quantitatively monodebenzylated to the azetidine (**49**) by hydrogenolysis (Scheme 7).[19]




Scheme 7. $SmI_2$-mediated cyclization of of α-aminoaldehydes

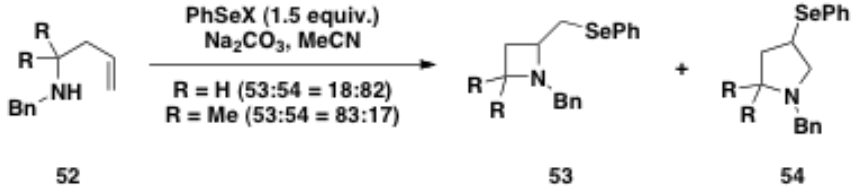
The activation of allylic and homoallylic amines for the regioslective synthesis of azetidines has been accomplished with several alkene-activating agents. The most commonly employed reagents are electrophilic halogen sources, which give rise to halonium ion intermediates that are displaced by the pendant amine to form the desired azetidine. In an example of this approach by the Rousseau (Scheme 8), activation of allylic amines (**50)** with an electrophilic bromine source, results in the construction of azetidines (**51**) in moderate to good yields by a 4-*endo* cyclization.[20]




Scheme 8. Activation of allylamines for the synthesis of azetidines

The Outurquin group has described the activation of homoallylic amines (**52**) with phenylselenyl halides resulting in the generation of both azetidines (**53**) and pyrrolidines (**54**).[21] The ratio of the observed

products was initially found to be dependent on the number of equivalents of the activating agent used as well as the substitution alpha to the nitrogen (Scheme 9).

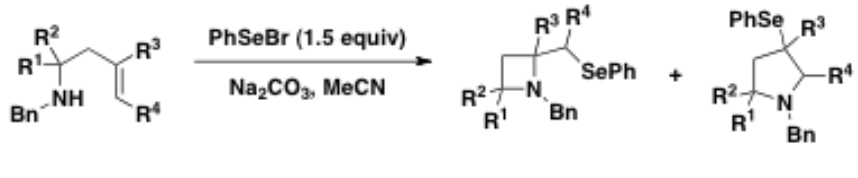



52 53 54

Scheme 9. Azetidine and pyrrolidine formation *via* selenium activation of homoallylic amines

More recently, however, the group has been able to fine-tune this methodology to allow for preferential azetidine formation without being constrained by substitution at the α-position. The authors can instead change the substitution on the alkene portion of allylamine **55** to preferentially form either the azetidine (**56**) or the pyrrolidine (**57**) without having to rely exclusively on the Thorpe-Ingold effect to induce cyclization to the desired product (Table 2).

Table 2. Substituent effects on the formation of either azetidines or pyrrolidines

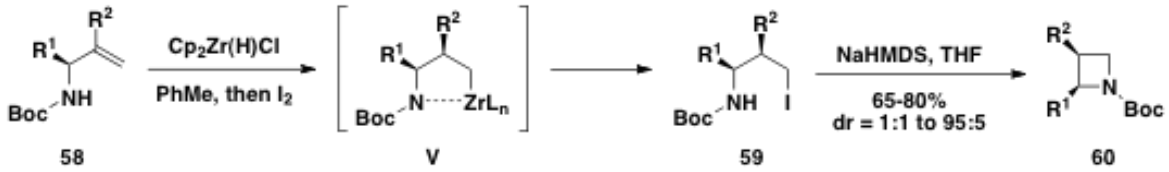



55 56 57

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield **56** (%) | Yield **57** (%) |
|---|---|---|---|---|---|---|
| 1 | H | H | H | Ph | - | 55 |
| 2 | Et | H | H | Ph | - | 73 |
| 3 | *i*Pr | H | H | Ph | - | 80 |
| 4 | Ph | H | H | Ph | - | 72 |
| 5 | Me | Me | H | Ph | - | 88 |
| 6 | H | H | Me | H | 35 | - |
| 7 | Me | H | Me | H | 45 | - |
| 8 | Et | H | Me | H | 58 | - |
| 9 | *t*Bu | H | Me | H | 68 | - |
| 10 | Ph | H | Me | H | 67 | - |
| 11 | Me | Me | Me | H | 72 | - |

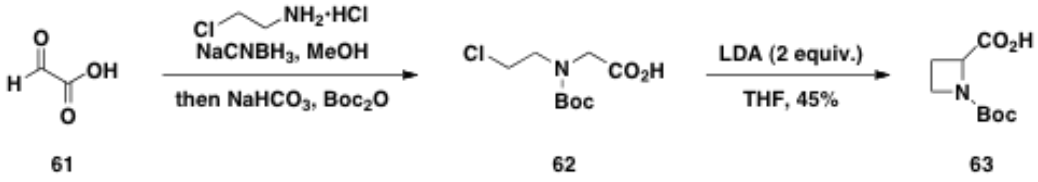
In 2011, Szymoniak and coworker published an interesting synthesis of *N*-Boc-protected azetidines through a diastereoselective hydrozirconation of chiral allylic amines.[22] Treatment of enantiomerically pure allyl amines **58** with Schwartz' reagent allowed for *syn*-hydrozirconation of the double bond (**V**), which was then converted to iodide **59**. The addition of NaHMDS promoted cyclization to the *cis*-2,3-disubstituted azetidine **60** in moderate to good yields (Scheme 10). This reaction, which is tolerant of a wide variety of substituent types (alkyl, aryl, $CH_2OR$) and possesses an easily removable nitrogen protecting group, allows for simple access to synthetically useful, diastereometrically enriched

azetidines in a short reaction sequence.



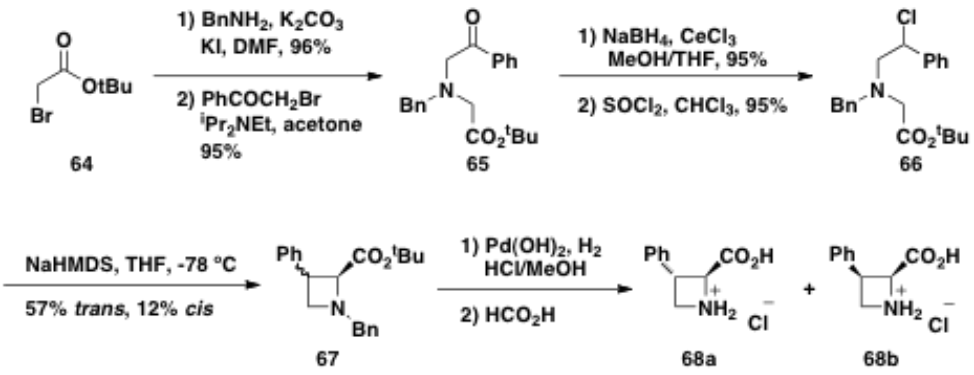

Scheme 10. *N*-Boc protected azetidines from hydrozirconation of allylamines

**Ring Closure by C–C Bond Formation.** There are significantly fewer examples of azetidine synthesis by a carbon-carbon bond formation in the literature compared to the carbon-nitrogen bond forming approaches discussed above. One advantage of this disconnection is the ability to place groups on nitrogen that are not typically amenable to nucleophilic displacement reactions. An example of this was reported by Luche and coworkers in 1994 (Scheme 11).[23] Starting from glyoxylic acid (**61**), a one-pot reductive amination/protection sequence gave *N*-(ω-chloroethyl-Boc-glycine (**62**). Cyclization of **62** in the presence of LDA led to *N*-Boc-protected azetidine-2-carboxylic acid **63**.



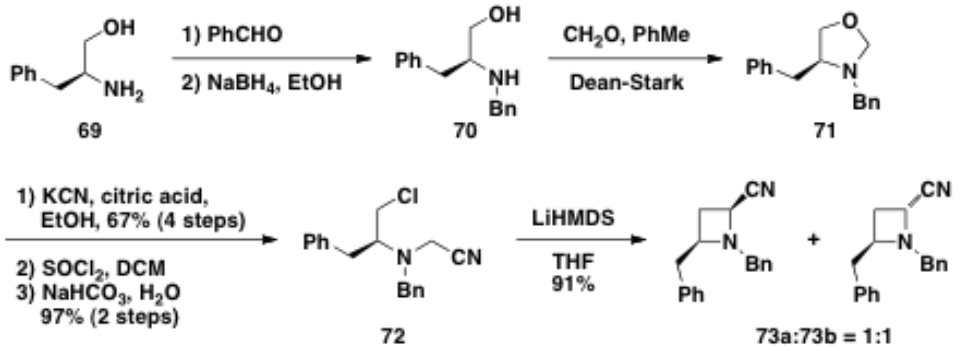

Scheme 11. Base-promoted synthesis of *N*-Boc-2-azetidine carboxylic acid

In the same year the Shue group reported the synthesis of *cis*- and *trans*-3-phenylazetidine-2-carboxylic acids using a similar ring closing strategy.[24] Conversion of *tert*-butyl bromoacetate (**64**) to the amine (**65**), followed by reduction and treatment with thionyl chloride generated chloroeth ylamine **66** in excellent yield. Cyclization of **66** upon treatment with NaHMDS resulted in formation of azetidine **67** (Scheme 12). Removal of the benzyl protecting groups provided a mixture of the *cis* and *trans* isomers **68a** and **68b** in overall yields of 35% and 6% respectively.



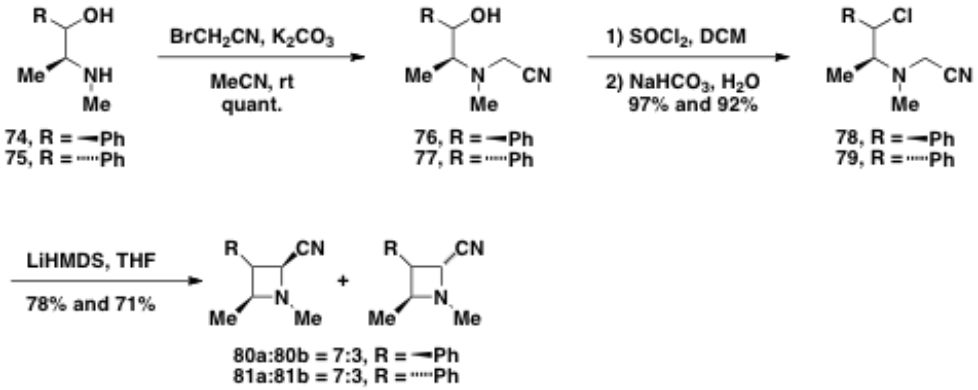

Scheme 12. Synthesis of 2,3-disubstituted azetidines through carbon-carbon bond formation

More recently, a non-racemic approach to azetidines with varied substitution was reported starting from commercially available enantiopure 1,2-amino alcohols.[25] The synthesis of 2,4-disubstituted azetidine **73** was achieved starting from (S)-phenylalaninol (**69**, Scheme 13). This procedure involved reductive amination of **69** to give *N*-benzyl (*S*)-phenylalaninol **70** followed by generation of oxazolidine **71** in the presence of formaldehyde. Subsequent ring opening with potassium cyanide in the presence of citric acid followed by chlorination gave **72**, which cyclized to a mixture of diastereomeric azetidines **73a** and **73b** when treated with LiHMDS.



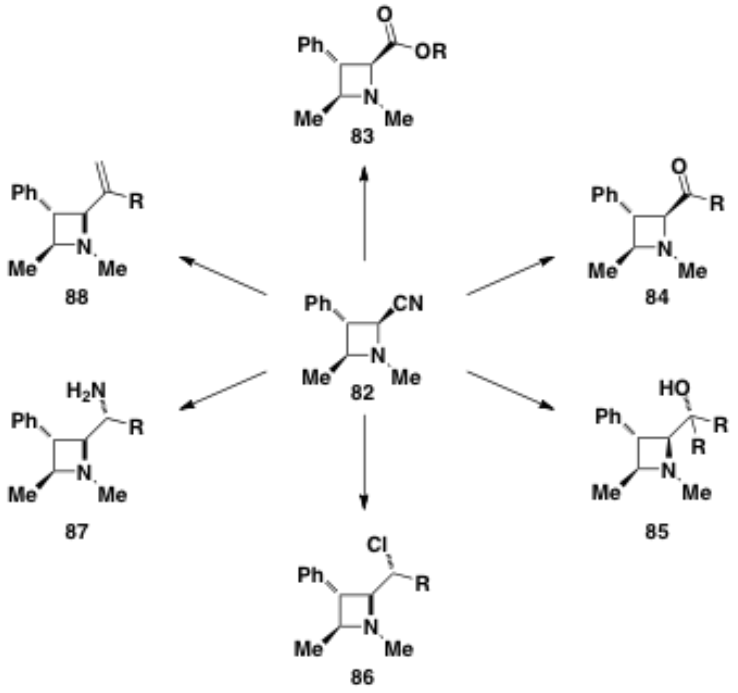

Scheme 13. Synthesis of azetidines from (*S*)-phenylalaninol

Disubstituted amino alcohols (1*R*,2*S*)-ephedrine (**74**) and (1*S*,2*S*)-pseudoephedrine (**75**) can also be utilized with this methodology to generate 2,3,4-trisubstituted azetidines (Scheme 14). Both compounds **74** and **75** were alkylated with bromoacetonitrile in the presence of base to give amines **76** and **77**. The hydroxyl groups were then converted to the chlorides before treatment with LiHMDS, which led to diastereomeric mixtures of tri-substituted azetidines **80** and **81**. The diastereomeric ratios obtained for the tri-substituted products are superior to that of disubstituted azetidine **73** (Scheme 13). The authors were also happy to report that there is no loss of enantiopurity during this process.



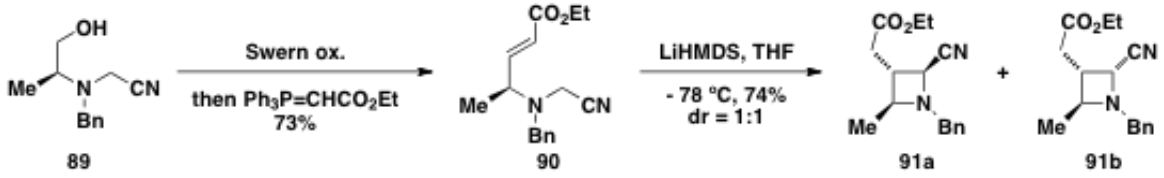

Scheme 14. Synthesis of azetidines (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine

Subsequent reports by the Couty group have shown that these 2-cyano-azetidines (**82**) are very versatile to further transformations (Scheme 15). The cyano group can be hydrolyzed to give azetidinic amino acids or esters (**83**), reacted with nucleophiles to form α-amino aldehydes and ketones (**84**) and β-amino alcohols (**85**), reduced to provide β-amino amines (**87**) and olefinated to produce 2-vinyl azetidines (**88**). [1d,26]



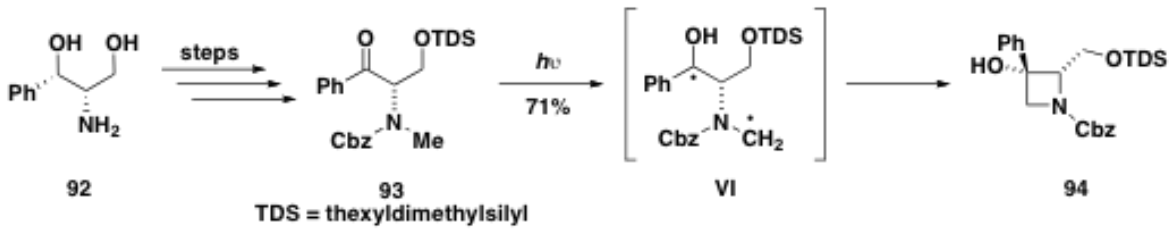

Scheme 15. Derivatives accessible from 2-cyano-azetidines

A practical extension reported by this group has been the synthesis of azetidines by intramolecular Michael addition (Scheme 16). Conversion of the hydroxyl group of **89** to α,β-unsaturated ester **90** by a one-pot oxidation/Wittig protocol, followed by treatment with LiHMDS yields a 1:1 mixture of azetidines **91a** and **91b**, epimeric at C-2. This method expands the potential of this reaction to include products with different handles on the 3-position.



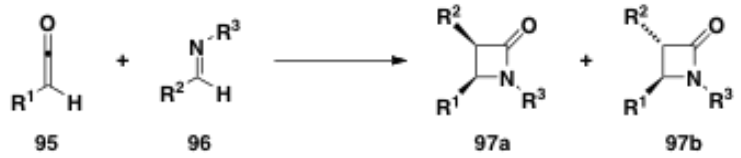

Scheme 16. The application of Michael addition towards azetidine synthesis

All of the above ring closures have been the result of selective deprotonation of an acyclic substrate with strong base followed by ring formation. An attractive contrast to this method is the use of photochemical cyclization reported by the Wessig group (Scheme 17).[27] Starting from enantiopure aminodiol **92** they were able to synthesize ketone **93**, which upon irradiation formed biradical intermediate **VI**. Recombination of the biradical gives azetidine **94**.



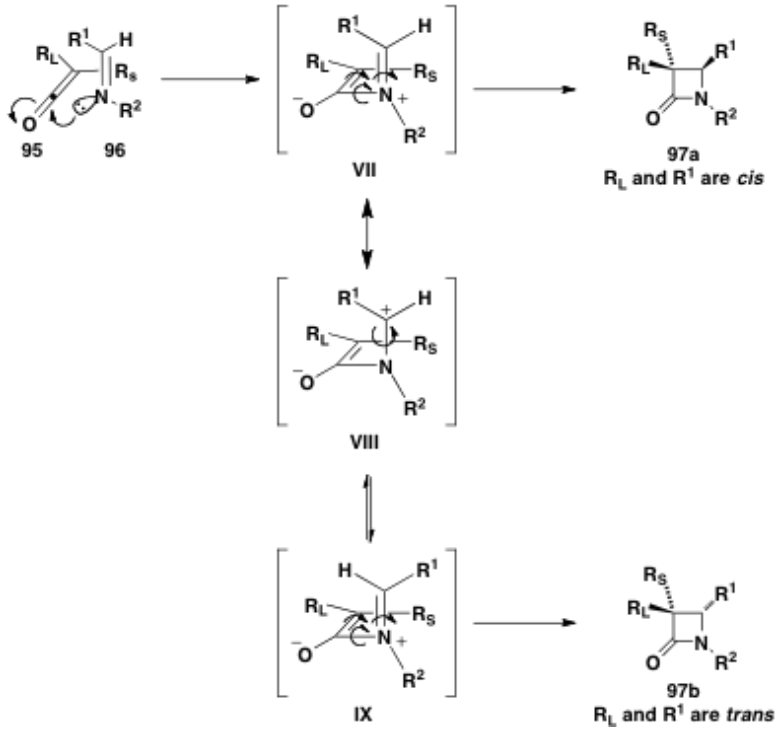

Scheme 17. Azetidines from Norrish-Yang type cyclization a-methylamino ketones

**Reduction of β-Lactams and Cycloaddition Reactions.** The construction of azetidines by cycloaddition reactions has mainly focused on the formation of β-lactams followed by subsequent reduction of the carbonyl. There are a variety of stereoselective methods available to generate the β-lactam framework. The reaction of a ketene (**95**) with an imine (**96**), known as the Staudinger reaction, is one of the most commonly used methods for the formation of β-lactams (**97**) (Scheme 18). [1b,28]



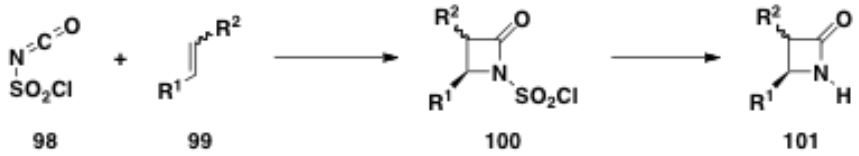

Scheme 18. The Staudinger reaction for β-lactam synthesis

This reaction proceeds through a stepwise mechanism where the imine nitrogen reacts with the ketene carbonyl, forming a zwitterionic intermediate which then cyclizes to give the desired product (Scheme 19). The nitrogen attacks from the less hindered side of the ketene in a perpendicular fashion resulting in intermediate **VII** with $R_L$(large) and $R^1$ in the same side. Concurrent rotation of the iminium into the plane of the C-C double bond and conrotatory ring closure furnishes the *cis*-substituted product **97a**. Conversely, when $R^1$ can stabilize a positive charge, isomerization of intermediate **VII** to **IX** followed by ring closure results in $R_L$ and $R^1$ being *trans* to one another in the final product (**97b**). This method can tolerate a wide range of functional groups and provides good diastereoselectivity when the substrates are appropriately substituted.




Scheme 19. Stereochemical rationale for the construction of β-lactams *via* Staudinger reaction

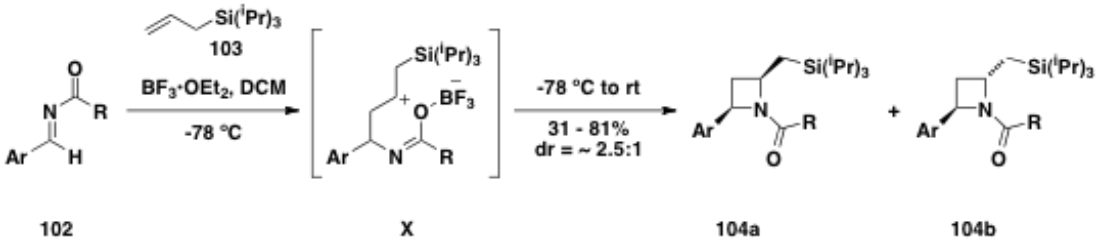
A related process for the generation of β-lactams is the [2+2]-cycloaddition of isocyanates with olefins (Scheme 20). Chlorosulfonylisocyanate (**98**) is a readily available reagent often used because of its high reactivity and the easy removal the chlorosulfonyl group on nitrogen.[29] Although related to the Staudinger reaction, the mechanism of this cycloaddition process is concerted. The geometry of the olefin (**99**) controls the relative stereochemistry of the products (**100**), with *cis* olefins leading to *syn* products and *trans* to *anti*. Diastereomeric mixtures, however, are produced if epimerization occurs during the removal of the chlorosulfonyl protecting group to give the free β-lactams (**101**).




Scheme 20. β-Lactams from the [2+2]-cycloaddition of chlorosulfonyl isocyanate and olefins

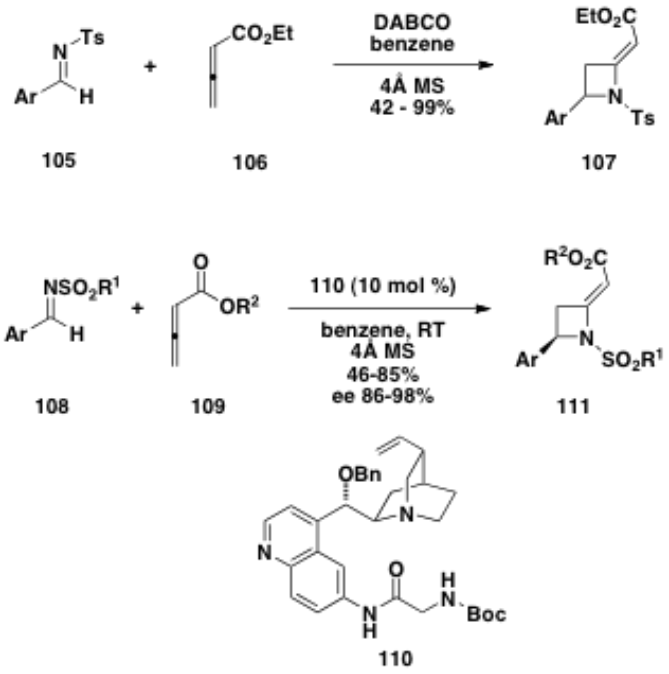
Reduction of β-lactams, such as those formed using the above-mentioned routes, can be effected with a number of different reagents. That being said, the use of DIBAL-H and chloroalanes has emerged as the most efficient method as it does not lead to reductive ring opening, a problem often observed with the use of diborane, $LiAlH_4$ and Raney nickel.[1b]

Although the reduction of β-lactams can be a fine approach to azetidines there can be problems associated with the reduction of other functional groups present in the molecule. For that reason several groups have looked into using a cycloaddition methodology to access azetidines directly. In 1995, Uyehara and coworkers reported a Lewis-acid promoted reaction of *N*-substituted aldimines (**102**) with allyltrisisopropylsilane (**103**, Scheme 21).[30] The reaction is postulated to go through an intermediate β-silyl cation (**X**), which is stable at – 78 ºC but upon warming to room temperature cyclizes to a mixture of *cis* and *trans* azetidines (**104a** and **104b**).



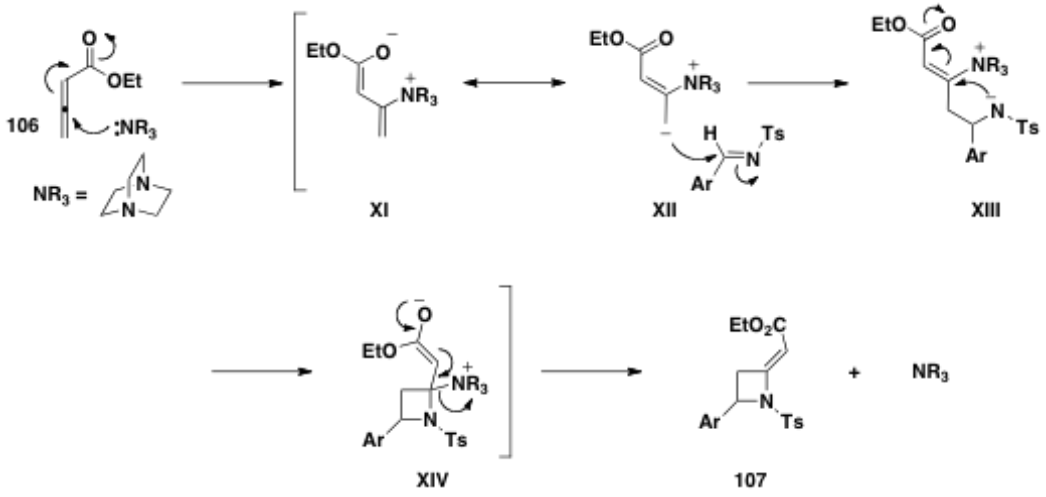

Scheme 21. Synthesis of azetidines by cyclization of aldimines with allylsilanes

In 2003, while investigating the aza-Morita-Baylis-Hillman (aza-MBH) reaction of *N*-tosylimines (**105**) with ethyl 2,3-butadienoate (**106**), Shi and coworkers came across an interesting tactic for the synthesis of azetidines (**107**) when DABCO was used as the catalyst (Scheme 22).[31] A very recent expansion of this novel transformation allows for the formation of enantiomerically enriched products (85-98% ee) when DABCO is replaced with cincona alkaloid-derived base **110**.[32]



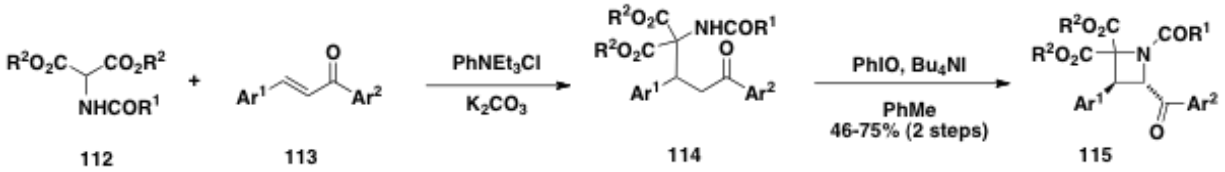

Scheme 22. Azetidine formation under Morita-Baylis-Hillman conditions

A plausible mechanism for this "abnormal" aza-MBH reaction is shown in Scheme 23. The authors suggest that the use of DABCO leads to an ambident intermediate (**XI**) which undergoes preferential attack on the imine at the γ-position of the MBH adduct **XII**, leading to amide **XIII**. Closure of the four-membered ring by an addition-elimination mechanism then affords **107**.



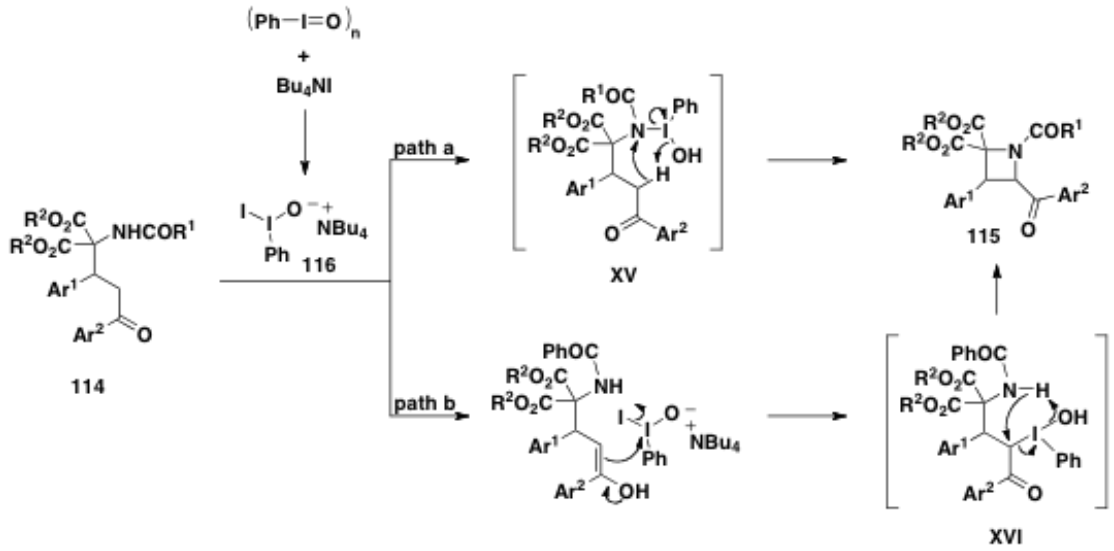

Scheme 23. Mechanism of the "abnormal" Morita-Baylis-Hillman reaction

A recent report from the Fan group allows for the stereoselective construction of azetidines using a conceptually distinct iodine-mediated oxidative cyclization (Scheme 24).[33] Addition of 2-aminomalonate **112** into chalcones **113** provided Michael adducts **114**, which upon treatment with iodosobenzene in the presence of tetrabutylammonium iodide gave azetidines **115** as single diastereomers.




Scheme 24. Azetidine formation using an iodine-mediated oxidative cylization

The mechanistic hypothesis proposed by the group was based on the results of several important control experiments. The authors believe that there are two viable pathways to generate the final products from Michael adduct **114** (Scheme 25). Pathway **a** starts with reaction of the amide nitrogen of **114** with iodine(III) species **116** generated from reaction of iodosobenzene with tetrabutylammonium iodide. Intermediate **XV** next undergoes an intramolecular reductive elimination to give azetidine **115**. The alternate mechanism, pathway **b**, involves tautomerization of the ketone followed by hyperiodination of the enol leading to intermediate **XVI**. Intramolecular attack by nitrogen with concomitant reductive elimination of PhI would also generate azetidine **115**.




Scheme 25. Possible mechanisms for oxidative cyclization

The ability to synthesize the azetidine framework in good yield from the readily available, versatile building blocks has opened the door for the use of these compounds in other synthetic applications. One possible limitation in many of these approaches is the use of phenyl or aryl groups to direct the stereochemical outcome and increase the stability of the reactants/products. Fortunately, reports in the literature for the conversion of phenyl groups to carboxylic acids on these types of strained ring systems (see Scheme 4) makes this approach more amenable for other applications.

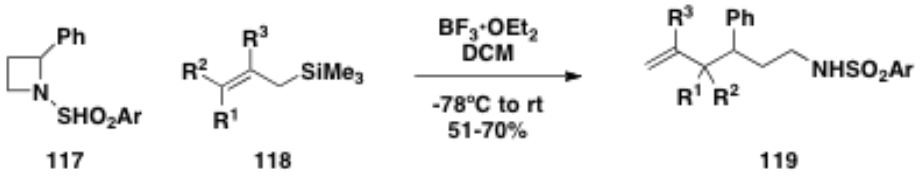
## SYNTHETIC APPLICATIONS OF AZETIDINES

As noted in the introduction, the ring strain energy associated with the azetidine system is quite high (~25 kcal/mol), which makes it a good building block for a wide variety of secondary transformations that

result in a lower energy product. This section will illustrate the versatility of this small ring system, which provides access to many different types of structures by different modes of nitrogen activation.

**Ring-Opening to Acyclic Amines.** As mentioned above, azetidines can behave similarly to either aziridines or pyrrolidines under different reaction conditions. One way that azetidines behave similarly to aziridines is in their capacity to undergo nucleophilic ring opening to give acyclic products.

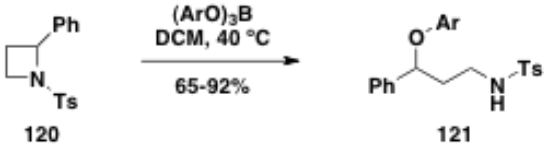
Activating the nitrogen of an azetidine with Lewis or Brønsted acid followed by addition of an external nucleophile has been found to effect ring opening of azetidines. Mann and coworkers have utilized $BF_3{\cdot}OEt_2$ to activate the nitrogen of *N*-nosyl or *N*-tosyl-2-phenylazetidines (**117**, Scheme 26).[34] After activation, the addition of an allylsilanes (**118**) provided access to amino-olefins **119**. This ring opening was regioselective, occurring at the benzylic position, and is most likely due to polarization of the benzylic C-N bond upon complexation of the Lewis acid with nitrogen.




117 118 119

Scheme 26. Lewis-acid catalyzed opening of azetidines with allylsilanes

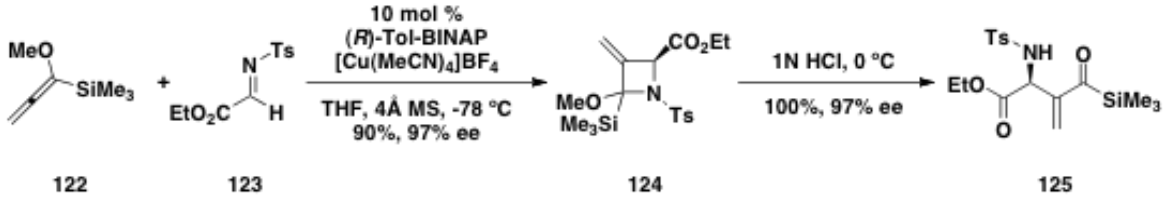
Aryl borates have also successfully been employed for the ring opening of *N*-tosyl-2-phenylazetidine (**120**, Scheme 27).[35] In this case, the Lewis acid is playing a dual role as both the activating agent and the nucleophile in the construction of amino aryl ethers (**121**). Several observations noted by the authors during this work give insight into some of the pros and cons of this methodology for the facilitation of ring opening. First, switching the protecting group on nitrogen from tosyl to methyl resulted in none of the ring-opened product being observed. This suggests that the protecting group on nitrogen must be electron withdrawing and could be a limitation for Lewis acid-promoted ring openings if its removal is difficult. The second observation was that the reaction of enantiopure *N*-tosyl-2-phenylazetidine with aryl borates gave a racemic product. This racemization, most likely due to ring opening to a carbocation intermediate, suggesting that the strength of Lewis acid complexation with nitrogen and the carbocation stabilizing ability of the group on the 2-position are crucial components that need to be fine-tuned for a successful enantioselective ring opening.




120 121

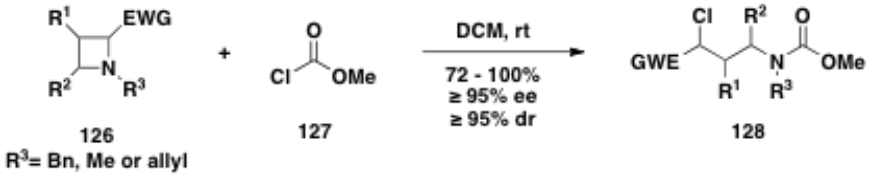
Scheme 27. Ring opening of azetidines with aryl borates

A unique synthesis of enantiomerically pure α,β-unsaturated acyl silanes was accomplished through the Brønsted acid catalyzed ring opening of properly functionalized azetidines (Scheme 28).[36] Starting from 1-methoxyallenylsilane **122** and α-imino ester **123** the authors were able to synthesize azetidine-2-carboxylate **124** in 90% yield and 97% ee in the presence of catalytic $[Cu(MeCN)_4]BF_4$ and (*R*)-Tol-BINAP. Treatment with acid then afforded the desired acyl silane **125** with no erosion of enantiopurity.




Scheme 28. Formation of acylsilanes *via* acid-mediated ring opening of azetidines

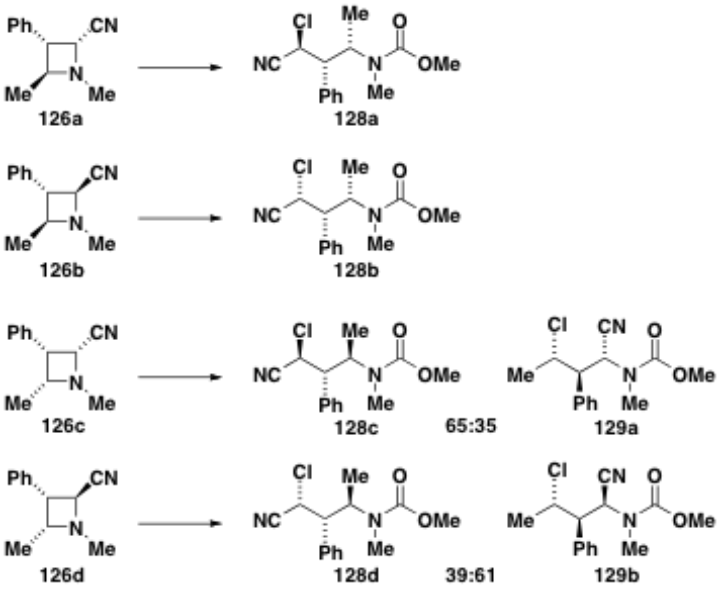
In 2006, the Couty group reported an investigation into the reaction of *N*-methyl and *N*-benzyl azetidines with chloroformates.[37] The reaction of tertiary amines with chloroformates is well established in the literature as a method for the selective removal of *N*-methyl or *N*-benzyl groups.[38] The authors, who wanted to determine whether this process was also applicable to azetidines, found instead that treating azetidines **126** with methylchloroformate **127** resulted in the formation of *N*-protected γ-chloramines (**128**) in good to excellent yields (Scheme 29).




Scheme 29. Ring opening of azetidines with methyl chloroformate

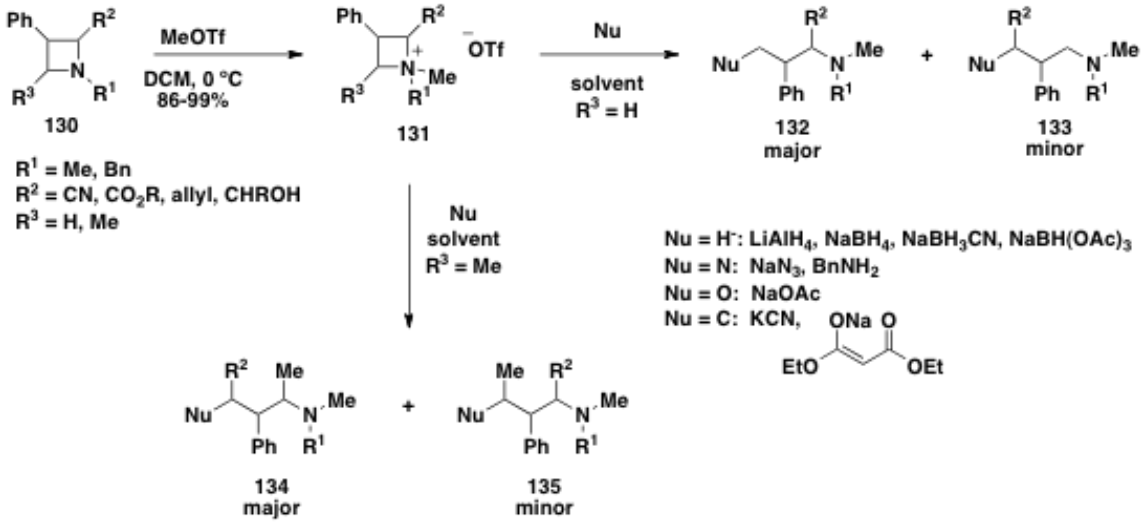
In general, the ring opening was found to be highly regioselective, with the chloride anion attacking the more electrophilic position, and stereospecific, occurring *via* a $S_N2$ displacement. No erosion of enantiopurity or change in diastereomeric ratio was detected. This ring opening, unlike those associated with Lewis acid activation as mentioned above, allowed for exocyclic alkyl groups to be present on nitrogen and resulted in an easily removable protecting group thereafter.

An interesting observation was made when the authors examined the influence of relative stereochemistry of the starting materials on the products (Scheme 30). A comparison of **126a-d** showed that the all *syn* azetidine **126c** and the *anti-syn* azetidine **126d** produced **128c** and **128d** as well as products from chloride attack at the less electrophilic center **129a** and **129b**. Although the authors did not speculate on a reason for this observation it could be possible that having substituents on the 3- and 4-position *syn* to one another may be affecting the puckering angle of the ring, which allows for competitive attack on the C-4.



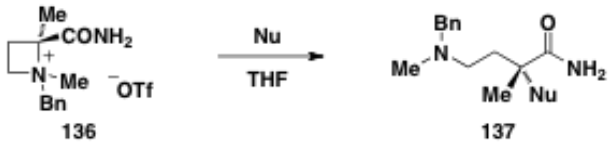

Scheme 30. Effect of relative stereochemistry on product formation

Another aspect of azetidine ring activation that has recently been explored by the Couty group deals with ring-opening reactions of azetidinium salts.[1d,39] Starting with enantiopure azetidines (**130**), alkylation with methyl triflate gives the azetidinium salts (**131**), which can then be opened with a wide range of nucleophiles to give acyclic products **132-135** (Scheme 31). Successful nucleophiles include hydride, azide, amines, acetates, alkoxides, cyanates and malonate salts. In most cases the yields are good to excellent with no observable competition by eliminative pathways. When enantiopure azetidines are used as substrates the reaction occurs in a stereospecific manner.



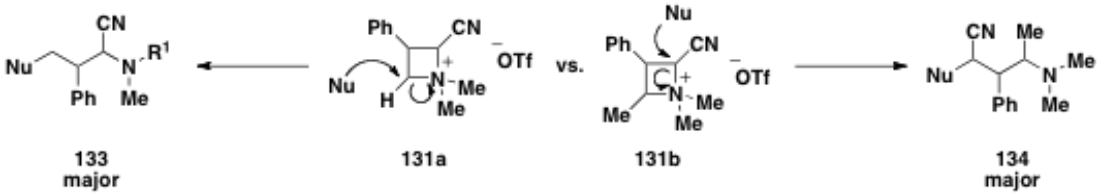

Scheme 31. Ring opening of azetidinium species with various nucleophiles

It should be noted that a complementary example recently reported by Wang and coworkers using α-amido azetidine **136** allows access to γ-amino amides (**137**) with quaternary centers alpha to the carbonyl (Scheme 32).[40]



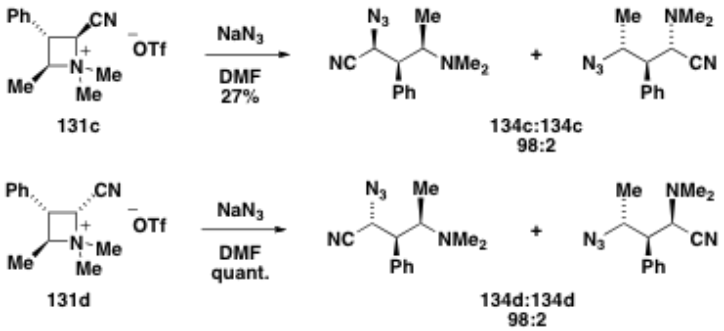

Scheme 32. Ring opening of azetidines to obtain amides with α-quaternary centers

The high regioselectivity observed in these reactions strongly depends on the substitution pattern of the starting azetidine. In general, $S_N2$ attack at an unsubstituted α-carbon will occur preferentially over that of a substituted one. If both α-carbons possess substituents, however, nucleophilic attack occurs preferentially at the most electrophilic carbon center, which in the case of compound **131b** is C-2 (Scheme 33).




Scheme 33. Rationale for observed regioselectivity of ring opening

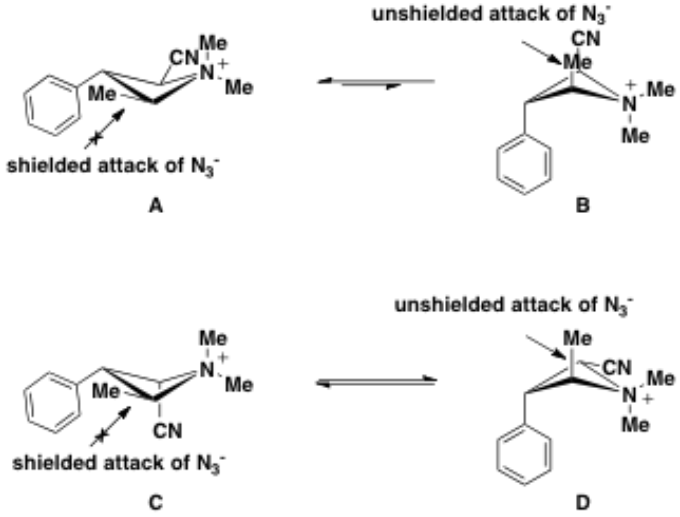
As with the observations this group made regarding the ring opening of azetidines with chloroformates (*vide supra*) the authors again found that the starting geometry of the azetidine plays a major role in the outcome of the reaction. This is exemplified by the result of nucleophilic addition of sodium azide to 2,3-*trans* azetidine salt **131c** and 2,3-*cis* azetidine salt **131d** (Scheme 34).




Scheme 34. Effect of relative stereochemistry on reaction yields

The authors attribute this drastic difference in yield to the ability of each conformer to undergo nucleophilic opening (Scheme 35). For 2,3-*trans* azetidine **131c** the equilibrium should favour conformer **A** over conformer **B**; this arranges all of the substituents in a *pseudo*-equatorial orientation. Unfortunately, due to blocking by the phenyl group, this preferred conformation (**A**) does not allow access to the electrophilic center for ring opening. Ring opening can only occur with conformer **B**, which suffers from several severe 1,3-diaxial interactions, thus rationalizing the poor yield of this

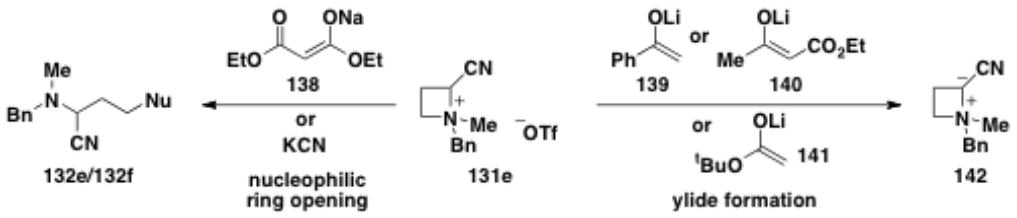
transformation. With 2,3-*cis* azetidine salt **131d**, however, the conformer that allows for unhindered attack by the azide (conformer **D**) suffers less repulsive 1,3-diaxial interactions as the cyano group is in the equatorial position. Although this conformer is still less stable than **C**, the equilibrium will not be subject to the same level of bias as in the case of conformer **A** for compound **131c**.




Scheme 35. Conformational preferences for nucleophilic attack by azide

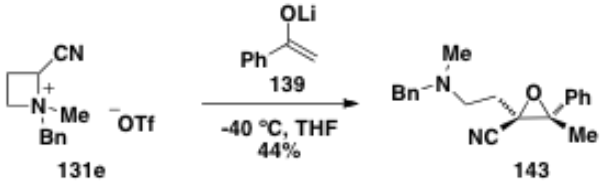
Several different hydride sources were tested as nucleophiles to compare the rate of ring opening and to determine whether the ester or cyano moieties could be preserved during the reaction.[39d] The use of $LiAlH_4$ to open the ring was moderately successful but, as expected, reduced both ester and cyano groups to the alcohol or amine respectively. Making the switch to boron-derived reagents $NaBH_4$ and $NaCNBH_3$ enabled the authors to observe reductive ring opening in much higher yields while preserving the ester or cyano groups. The use of $NaBH(OAc)_3$, on the other hand, surprisingly induced ring opening by attack with an acetate ion. The regioselectivity of the ring opening using the boron reducing agents was the same as that observed with C, N and O-nucleophiles (see Scheme 31).

Exploration into the ring opening of azetidinium salt **131e** with carbon nucleophiles was successful with both potassium cyanide and the sodium salt of diethyl malonate (**138**), generating amines **132e** and **132f** respectively (Scheme 36).[39c] Unfortunately, more basic nucleophiles such as the enolates derived from ethyl acetoacetate (**139**), acetophenone (**140**) or *tert*-butyl acetate (**141**) resulted in the formation of azetidinium ylide **142** by deprotonation at the C-2 position.



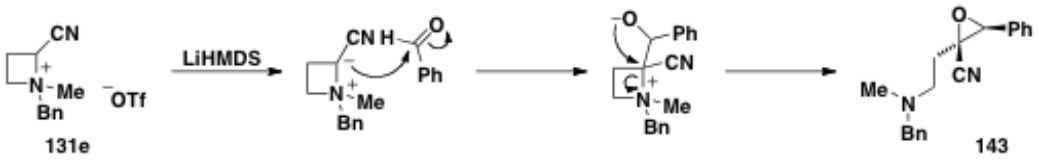

Scheme 36. Ring opening of azetidines with carbon nucleophiles

Although the authors were initially disappointed by these results they did note that the epoxide **143** was formed from the reaction of azetidine **131e** with the enolate of acetophenone (**139**, Scheme 37). In open-chained or larger heterocycles the formation of an epoxide by displacement of an ammonium leaving group is not very successful due to the high energetic barrier for ring closure. With the use of a strained azetidinium ylide, however, the energy gain associated with breaking the four-membered ring compensates for that energy barrier and increases the feasibility of such an approach.



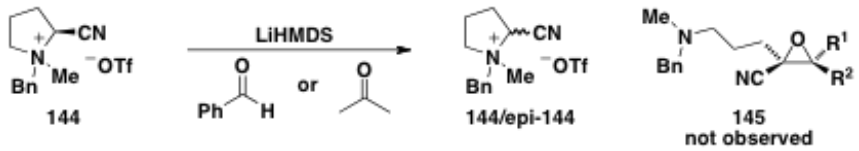

Scheme 37. Unexpected epoxide formation

This observation led to the exploration of epoxide formation/ring opening with aldehydes and ketones.[41] The proposed mechanism of the reaction is shown in Scheme 38. The reaction proceeds with the production of a single diastereomer and, when tested with enantiomerically pure starting materials produced enantiomerically pure products.



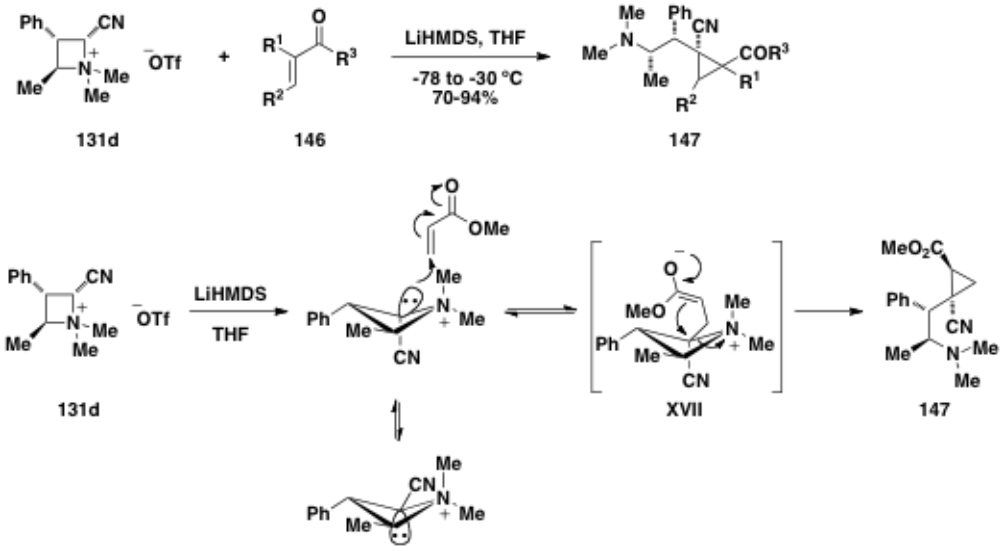

Scheme 38. Mechanism of epoxide formation

In order to confirm the importance ring strain to the success of this reaction the authors synthesized the pyrrolidine analogue **144** and subjected it to the same reaction conditions (Scheme 39). The only reactivity observed with **144** was epimerization at the α-position to a mixture of **144**/***epi*-144**. The authors state that this is due to the absense of any ring strain to help drive the reaction toward epoxide ring closure and thus results in the reversion back to the starting materials.



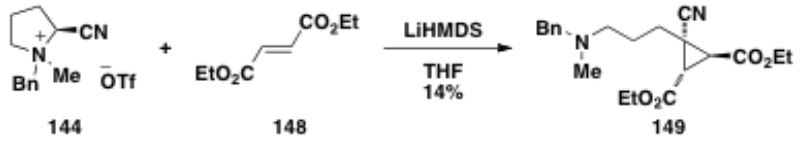

Scheme 39. Test reaction with pyrrolidine substrate

This process was further extended to the formation of cyclopropanes (**147**) by the addition of azetidinium ylide **131d** into Michael acceptors (**146**, Scheme 40).[42] The cyclopropanation was shown by the authors to proceed *via* the mechanism shown. Reversible 1,4-addition and potential ylide epimerization were found to occur during reactions performed by the authors in their search to understand the convergence of epimeric starting materials into one product.




Scheme 40. Cyclopropane formation using azetidinium salts

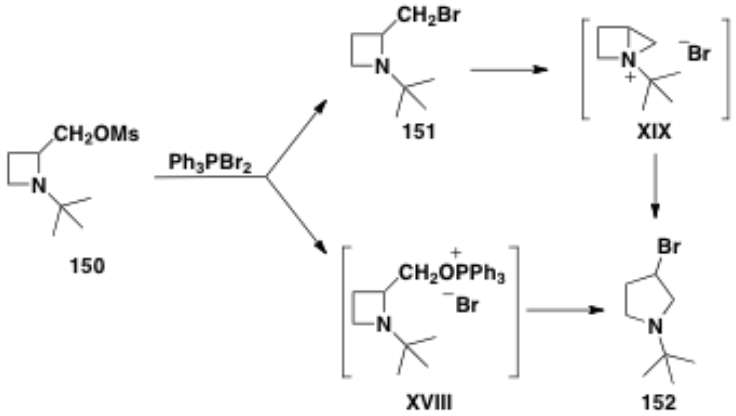
Interestingly, when the authors again tested for the importance of ring strain in the success of the reaction by subjecting pyrrolidine analogue **144** to the same reaction conditions, they were able to isolate small amounts of the homologous cyclopropanated product **149** (Scheme 41). This was in contrast to the result shown in Scheme 39, when the same pyrrolidine ylide was exposed to an aldehyde electrophile, where the only reactivity observed was epimerization at the α-position of the pyrrolidinium salt. This suggests that there are other factors, such as the lesser ability of the cyclopropane product **149** to revert back to starting materials, involved in the outcome of the reaction.




Scheme 41. Cyclopropanation with pyrrolidinium salts

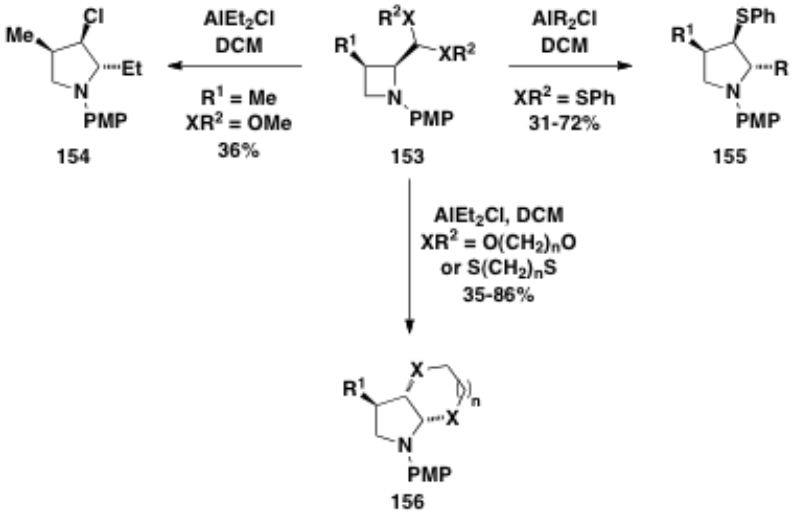
**Ring Expansion to Pyrrolidines and Other 5-Membered Heterocycles.** Although the ring expansion of azetidines to pyrrolidines was first observed several decades ago, the application of this process for synthetic purposes was not significantly developed until recently. Several research groups have explored the potential of the one-carbon ring expansion of azetidines to pyrrolidines in the last decade.

In 1970, Masuda and coworkers reported the ring expansion of *N*-*tert*-butyl-2-methanesulfonyloxy-methylazetidine **150** to pyrrolidine **152** when it was left at room temperature for a few hours.[43] A similar result was obtained when they treated **150** with triphenylphosphine dibromide. The authors proposed that the reaction could proceed *via* either the quaternary ammonium salt **XIX** or the phosphonium salt **XVIII** (Scheme 42).



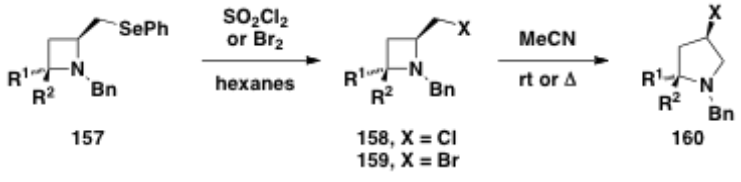

Scheme 42. Ring expansion of *N*-*tert*-butyl-2-methanesulfonyloxymethylazetidine with $Ph_3PBr_2$

Since the early observations by Masuda and coworkers several other groups have observed this ring expansion process in azetidines possessing reasonable leaving groups on the 2-methyl substutuent. In 1999, Alcaide and coworkers observed the ring expansion of azetidine **154,** with either an acetal and thioacetal-protected aldehydes on the 2-position, when treated with diethylaluminum chloride (Scheme 43).[44] In these examples the nature of the aldehyde protecting group had a large effect on the outcome of the reaction.




Scheme 43. Ring expansion of azetidines with chloroalanes

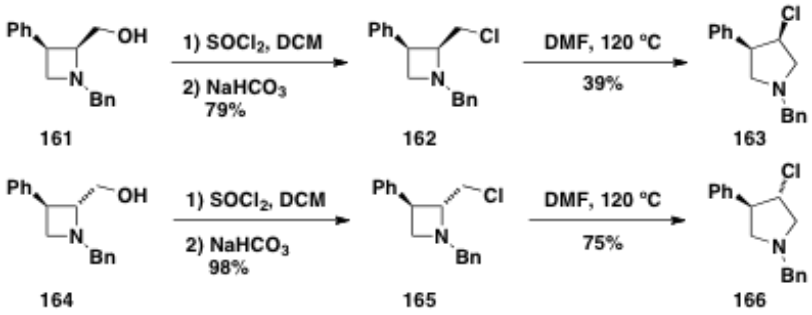
A few years later, a report concerning the formation of 1,2-dialkyl-4-halopyrrolidines (**160**) was published.[45] The authors generated 2-halomethylazetidines **158/159** from selenomethylazetidine precursors (**157**) and upon subsequent heating these substrates underwent ring expansion to give **160** (Scheme 44).




Scheme 44. Ring expansion of selenated azetidines

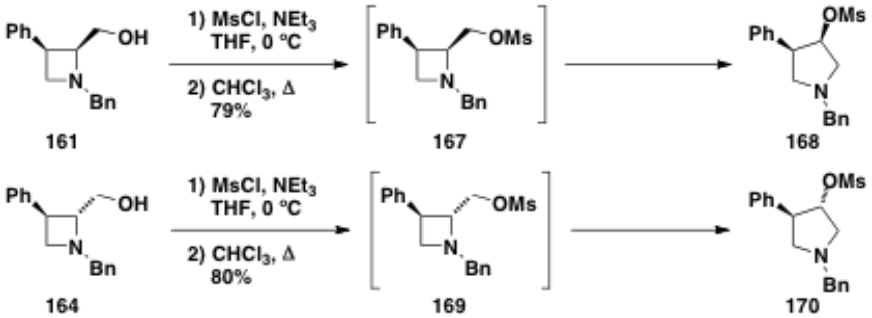
Around the same time, the Couty group had also begun an investigation into this process, looking in depth at how the nature of the leaving group, relative substitution and stereochemistry of the starting material affect the outcome of the reaction.[26b, 46] To get a good idea of the effect each factor had on the reaction the authors synthesized a variety of differently substituted, enantiopure azetidines with primary, secondary or tertiary hydroxyalkyl groups being present on the 2-position.

Conversion of primary α-hydroxymethylazetidines **161** and **164** to α-chloromethylazetidines **162** and **165** using thionyl chloride proceeded in excellent yields. Subsequent ring expansion to 3-chloropyrrolidines **163** and **166** could be initiated upon heating to 120 ºC in DMF, albeit in low to moderate yields (Scheme 45).



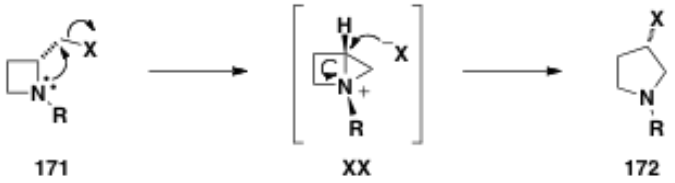

Scheme 45. Ring expansion of α-chloromethylazetidines with retention of configuration

Treatment of **161** and **164** with mesyl chloride at only room temperature, however, resulted in formation of both mesylates **167** and **169** as well as some of the pyrrolidine products. Full conversion to pyrrolidines **168** and **170,** in an overall higher yield than that observed with the chloride case, was accomplished by heating the crude mesylates in chloroform at reflux (Scheme 46).



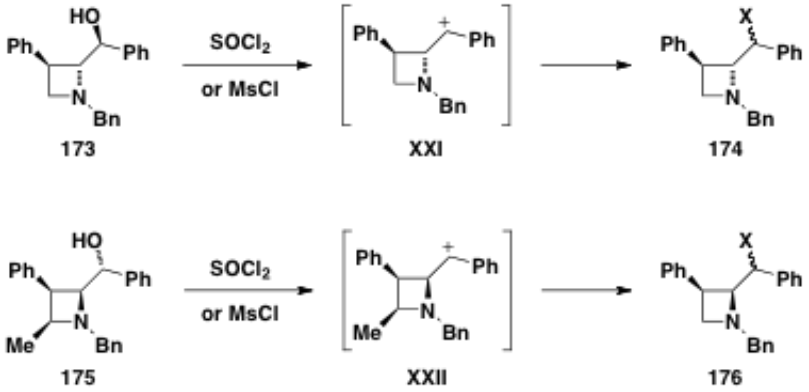

Scheme 46. Ring expansion of α-hydroxymethyl azetidines through activation with mesyl chloride

Both of the above transformations resulted in formation of a single pyrrolidine product with the same relative stereochemistry as the starting azetidines. This suggested to the authors that the ring expansion is occurring *via* the intermediate aziridinium ion **XX** (Scheme 47). Recent computational experiments performed by the same group support this mechanism.[47] Additional reactions involving other primary α-hydroxymethylazetidines suggest that multiple substituents on the ring are well tolerated and do not change the stereochemical outcome of the reaction.



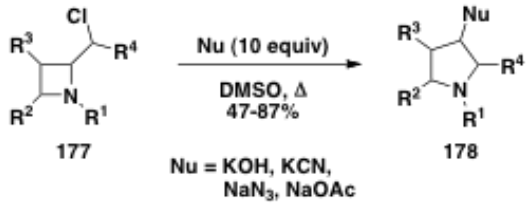

Scheme 47. Mechanism of ring expansion

Activation of the secondary α-hydroxymethylazetidines **173** and **175** with either the chlorination or mesylation conditions led to a diastereomeric mixture of activated products **174** and **176** (Scheme 48). This is may be due to the possibility of chlorination occurring *via* a $S_N1$ mechanism rather then the $S_N2$ mechanism seen with the primary α-hydroxymethylazetidines **161** and 1**64** (Schemes 45 and 46). Subsequent ring expansion of either of the separable diastereomers occurred without incident. It should be also noted that in a recent publication by De Kimpe and coworkers that this problem can be solved by setting the stereochemistry of the chloride earlier in the azetidine synthesis.[48] Unfortunately, all attempts to ring expand tertiary α-hydroxymethylazetidines only resulted in elimination products.




Scheme 48. Observation of diastereomeric products with secondary α-hydroxymethylazetidines

Addition of external nucleophiles such as hydroxide, cyanide, azide, acetate or fluoride allowed for generation of pyrrolidines (**178**) with a variety of substitutions at C-3 (Scheme 49). Most of these transformations were performed on the easily isolable chloro-substrates (**177**). The temperature of the reactions was found to be crucial for the formation of the desired products. Too low a temperature resulted in ring expansion with only chloride acting as the nucleophile while too high a temperature led to eliminative byproducts.

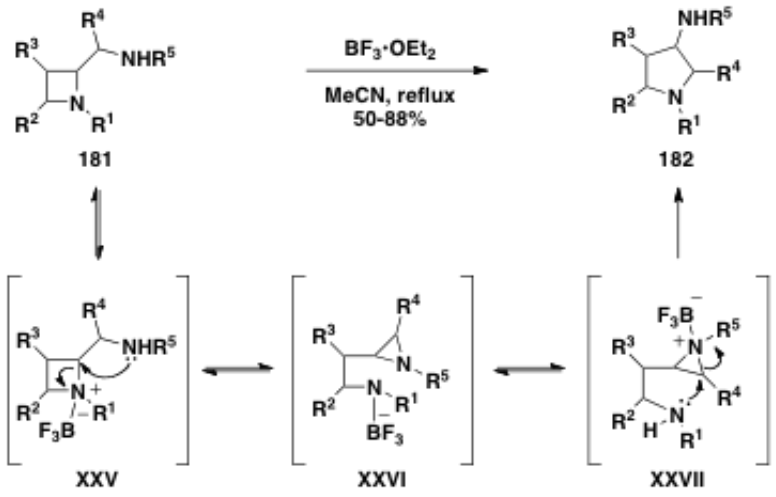



Scheme 49. Ring opening of α-chloromethylazetidines with external nucleophiles

Nucleophilic ring openings with fluoride were performed using diethylaminosulfur trifluoride (DAST), which works as both the hydroxyl activator and the source of fluoride (Scheme 50).[49]


Scheme 50. Nucleophilc ring opening with DAST

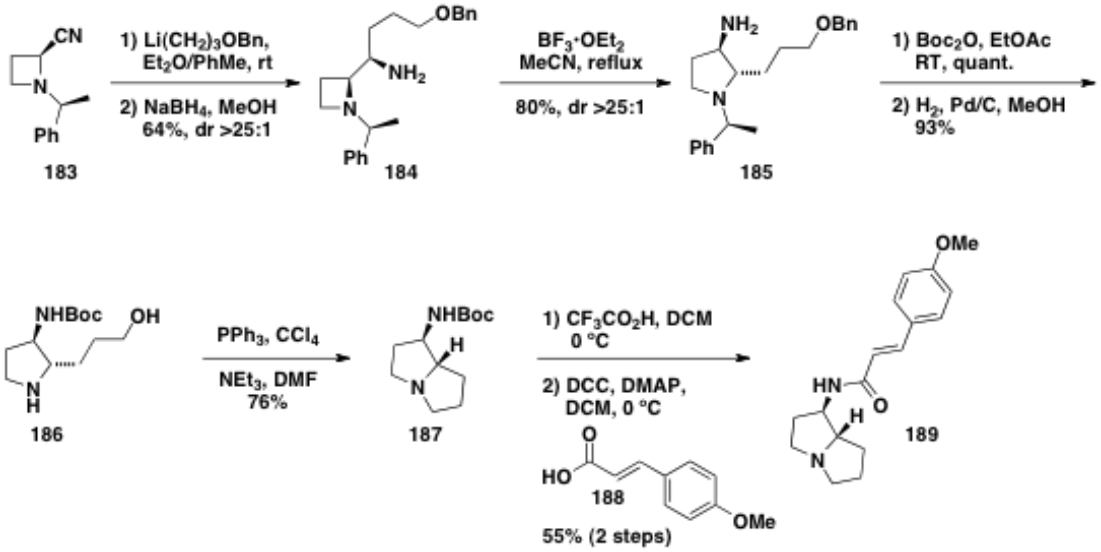
Ring-expansion of azetidines is also possible using Lewis acid activation. The $BF_3{\cdot}OEt_2$-mediated rearrangement of 2-aminomethylazetidines (**181**) provides access to 3-aminopyrrolidines **182** in moderate to good yields.[50] The mechanism for this ring expansion is shown in Scheme 51 and involves coordination of the azetidine nitrogen to the Lewis acid (**XXV**), followed by concomitant aziridination and azetidine ring opening to give intermediate **XXVI**. Migration of the Lewis acid to the aziridine nitrogen then allows for a second intramolecular nucleophilic displacement to occur, opening aziridinium intermediate **XXVII** and to provide 3-aminopyrrolidine **182**.




Scheme 51. Lewis acid activated ring expansion of α-aminomethylazetidines

This process, which provides access to highly substituted 3-aminopyrrolidines, was also applied to the synthesis of the pyrrolizidine alkaloid (-)-absouline (**189**, Scheme 52). The synthesis began with the addition of 3-benzyloxypropyl lithium to enantiomerically pure azetidine **183** followed by reduction of the resulting imine to give the desired 2-aminomethylazetidine (**184**) in 64% yield and a dr of 25:1. Activation of the azetidine nitrogen with $BF_3{\cdot}OEt_2$ initiated the ring expansion to pyrrolidine **185**, which was obtained in 80% yield with no change in the diastereomeric ratio. Protection of the primary amine as the carbamate followed by removal of the benzyl protecting groups on both oxygen and the ring

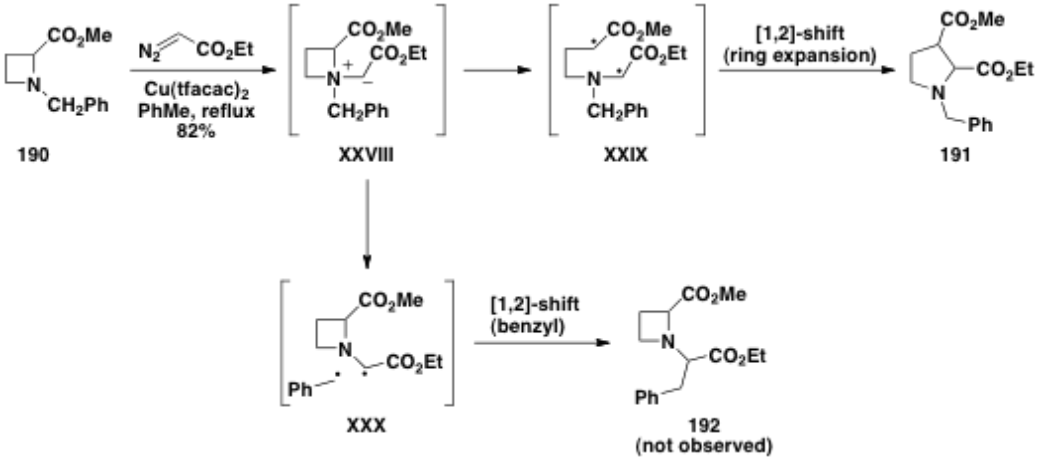
nitrogen by hydrogenolysis gave amino-alcohol **186**. Activation of the alcohol of **186** with triphenylphosphine resulted in a smooth cyclization to pyrrolizidine **187**. The synthesis was completed by standard removal of the *N*-Boc protecting group and DCC-mediated coupling of the newly revealed primary amine with (*E*)-*p*-methoxycinnamic acid (**188**).




Scheme 52. Synthesis of (-)-absouline *via* an azetidine ring-opening strategy

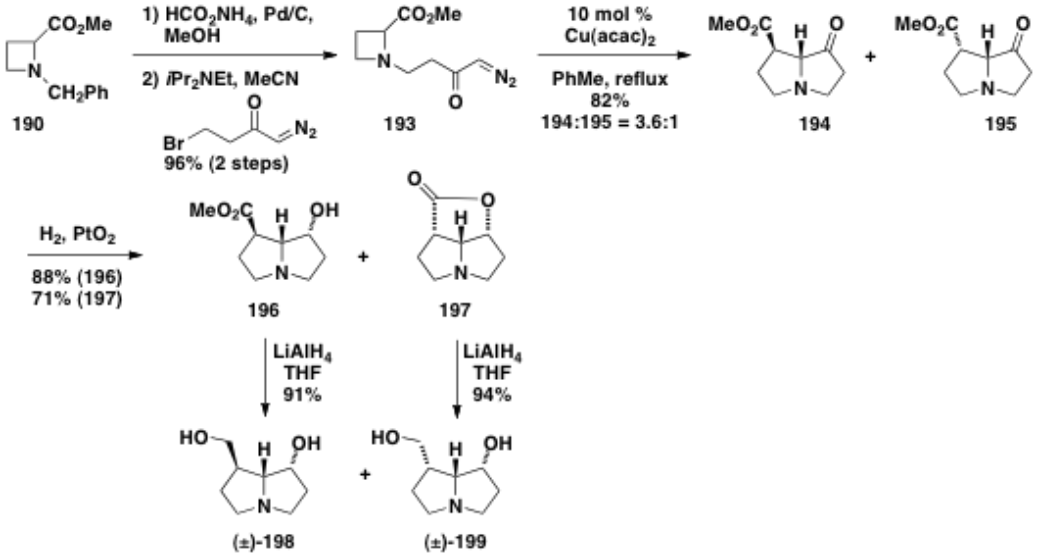
In the same year, the West group published a different approach to the pyrrolizidine alkaloid framework using the ring expansion of an azetidinium ylide and demonstrated its applicability in the synthesis of the natural products turneforcidine (**198**) and platynecine (**199**).[51] This synthesis relied on a different mode of activation for the azetidine than any of those discussed above, utilizing the *in situ* generation of an ammonium ylide through reaction of a tertiary amine with a metallocarbene, followed by ring expansion *via* a Stevens [1,2]-shift.

To examine the potential of this project the authors first decided to test the ring expansion of the azetidine in an intermolecular fashion (Scheme 53). Readily available 1-benzylazetidine-2-carboxylate **190** was reacted with ethyl diazoacetate (EDA) in the presence of a copper catalyst. In general, the Stevens rearrangement involves a migration of the group, which is best able to stabilize a radical intermediate. In unstrained systems this would result in preferential benzyl migration over ring opening (migration of a $CH_2CO_2Me$ group).[52] The authors hoped that the ring strain associated with the azetidine in this case would be a driving force for its expansion. The resulting product, pyrrolidine **191**, was the result of the Stevens [1,2]-shift of the internal C-N bond bearing the $CH_2CO_2Me$ group. This promising result convinced the authors that this process would be viable intramolecularly as well.



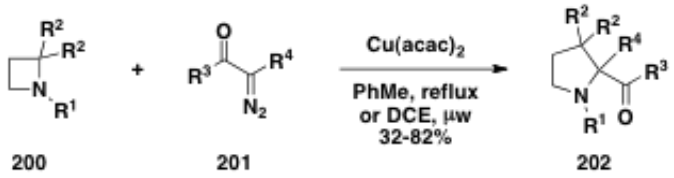

Scheme 53. Ring expansion of azetidines *via* Stevens [1,2]-shift

The synthesis of the natural products also began with 1-benzylazetidine-2-carboxylate **190 (**Scheme 54**)**. Removal of the *N*-benzyl protecting group under transfer hydrogenation conditions followed by alkylation to incorporate the tethered diazo moiety provided the desired substrate **193** in excellent yield. Next, **193** was treated with 10 mol% $Cu(acac)_2$ and heated to reflux in benzene to initiate the formation of an ammonium ylide intermediate and promote the ring expansion to diastereomeric pyrrolizidines **194** and **195** in a ratio of 3.6:1. Subsequent reduction of the ketones in the presence of Adams catalyst gave hydroxyester **196** and lactone **197** respectively. Separation and subsequent reduction of **192** and **193** with $LiAlH_4$ led to the natural products turnaforcidine (**198**) and platynecine (**199**).



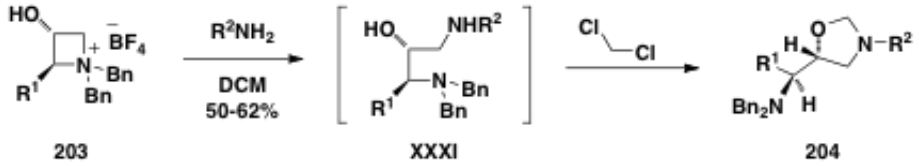

Scheme 54. Synthesis of the natural products (±)-turneforcidine and (±)-platynecine

Recently, West and coworkers have reported a more thorough examination into the ring expansion of azetidines (**200**) to pyrrolidines (**202**) *via* the Stevens 1,2-shift (Scheme 55).[53] This methodology, which is shown to tolerate a wide range of functional groups on both nitrogen and on the α-position of the ring, has led to a general procedure for the preparation of highly-substituted pyrrolidines in one step from simple building blocks.



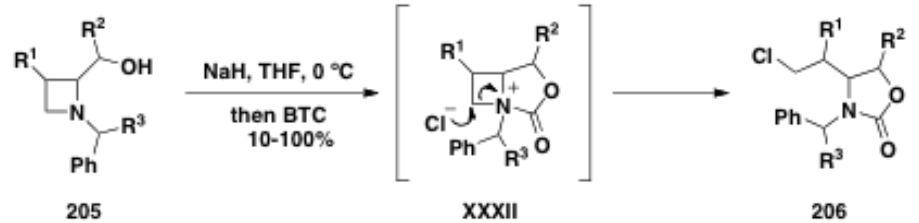

Scheme 55. One-step ring expansion of azetidines to pyrrolidines by the Stevens [1,2]-shift

Alongside the obvious success in the ring expansion of azetidines to pyrrolidines there have also been reports of the successful conversion of azetidines to other 5-membered heterocycles. In 2000, the Concellón group reported the formation of 1,3-oxazolidines **204** when primary amines were added to a solution of enantiopure 3-hydroxyazetidinium salts **203** in dichloromethane (Scheme 56).[19] The intermediate ring-opened diaminoalcohol **XXXI** reacts *in situ* with dichloromethane to generate the 1,3-oxazolidine.



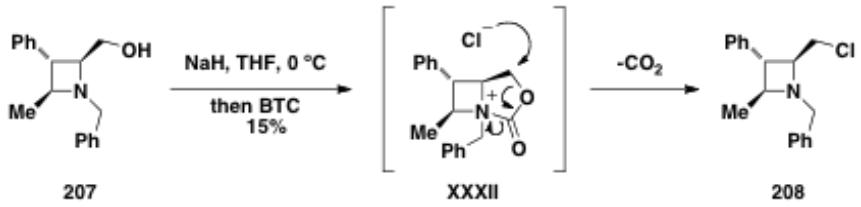

Scheme 56. Ring expansion of azetidines to 1,3-oxazolidines

Another class of 5-membered ring heterocycles that is commonly used in organic synthesis and can be accessed from azetidines is the oxazolidinones. Oxazolidinones are very important molecules for asymmetric synthesis and are commonly employed as chiral auxiliaries.[54] In 2011, the Couty group reported a synthesis of chiral oxazolidinones by activation of α-hydroxymethylazetidines **205** with bis(trichloromethyl) carbonate (BTC), which is a safer substitute for phosgene.[55] This reaction, which proceeds through bicyclic azetidinium intermediate **XXXII**, followed by nucleophilic ring opening with chloride ion, allows for the formation of a wide variety of enantiomerically pure oxazolidinones (**206)** in moderate yields (Scheme 57).



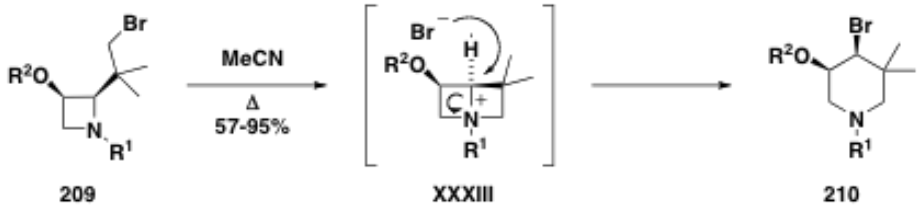

Scheme 57. Ring expansion of azetidines to oxazolidinones

One drawback the authors noted was that the placement of a substituent on the azetidine at the 4-position resulted in conversion of the α-hydroxymethylazetidine **207** into the α-chloromethylazetidine **208** without any of the desired ozazolidinone being detected. This is most likely due to steric hindrance by the substituent at C-4 preventing attack by the chloride at that position (Scheme 58).



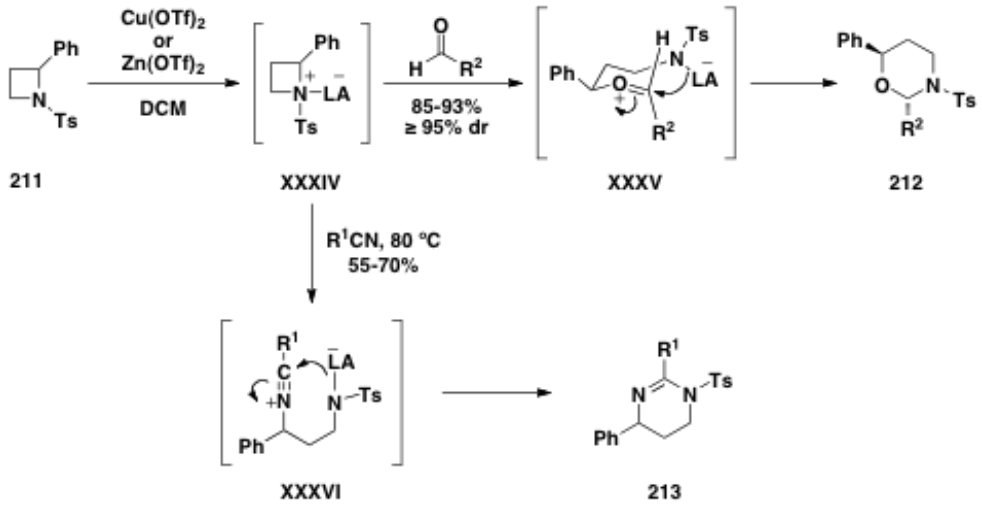

Scheme 58. Failed ring opening of 4-substitued azetidines

**Ring Expansion to Six-Membered Heterocycles.** The expansion of the azetidines to piperidines was first reported by the De Kimpe group as an extension of their work towards pyrrolidine synthesis mentioned previously.[56] The authors were able to synthesize enantiopure 2-(2-bromoalkyl)azetidines (**209)** which, upon heating, closed to the bicyclic azetidinium intermediate **XXXIII** (Scheme 59**)**. Nucleophilic attack by the bromide ion opened **XXXIII** to 4-bromopiperidine **210**. Ring opening with external nucleophiles such as hydroxide, azide or cyanide has also been successful, allowing access to other 4-substituted piperidine derivatives.




Scheme 59. Ring expansion of azetidines to piperidines

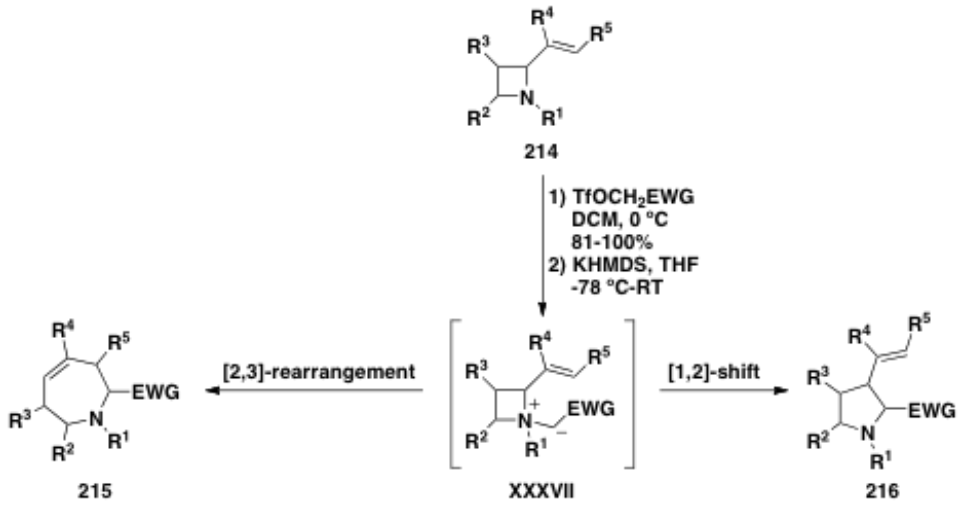
The Ghorai group has published several papers on the activation of 2-aryl-*N*-tosylazetidine **211** with either Zn(II) or Cu(II) Lewis acids followed by ring opening of the activated intermediate (**XXXIV**) with either a nitrile or carbonyl nucleophile.[57] This approach is similar to that of the activation with $BF_3{\cdot}OEt_2$ described previously and resulted in [4+2] adducts **212** and **213** (Scheme 60). Their recent expansion of this methodology to include more highly substituted and enantiopure starting materials adds a great deal of potential to this process.




Scheme 60. [4+2]-Cycloadducts by opening of azetidines with nitriles or aldehydes

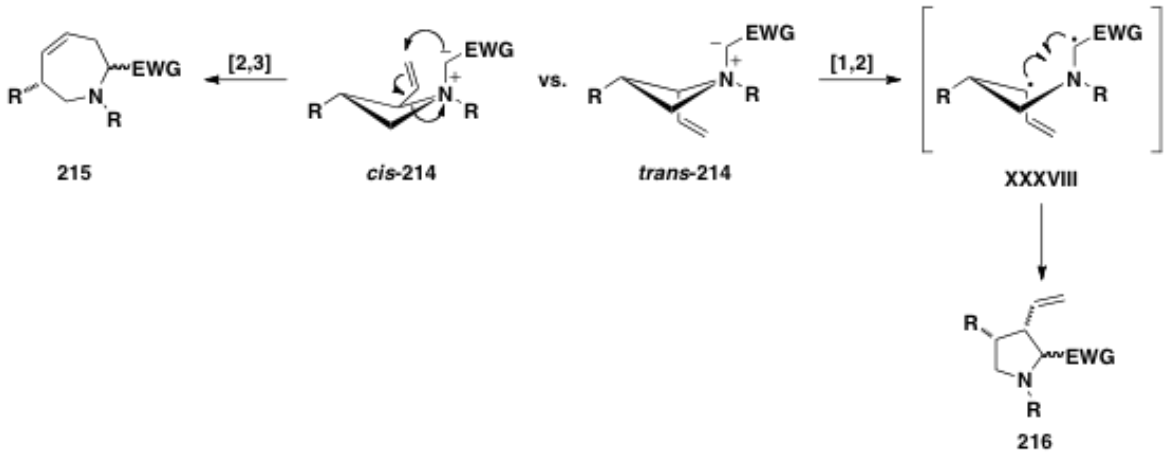
**Ring Expansion to Medium-Sized Heterocycles.** The formation of medium-sized rings (between 7-13 atoms) is one of the more challenging problems faced by synthetic chemists. This is largely due to the transannular effects (unfavourable interactions) experienced in these systems.[58] In the beginning of this chapter it was noted that the ease of forming azaheterocycles generally follows the order of 5>3>6>7≈4. This being said, there has been a great deal of interest in the formation of medium-sized 7- and 8-membered azaheterocycles, largely due to the substantial number of natural products that contain these moieties.

As discussed in the above section, the formation and subsequent ring expansion of azetidinium ylides is a viable method for the synthesis of functionalized pyrrolidines. The Couty group has reported two variations on this methodology to access both azepines and azocine dereivatives.[59] The first method, reported in 2006, was found to generate either 2,3,6,7-tetrahydroazepines (**215**) or pyrrolidines (**216**) depending on the geometry of the starting azetidine. The authors synthesized a variety of 2-alkenyl-azetidines (**214**), which were then alkylated to give the azetidinium triflate salts in excellent yields. Treatment of these salts with a strong base generated the ylide intermediate **XXXVII** which subsequently underwent a [1,2]-shift to give pyrrolidine **216** or a [2,3]-sigmatropic rearrangement to give 2,3,6,7-tetrahydroazepine **215** (Scheme 61).



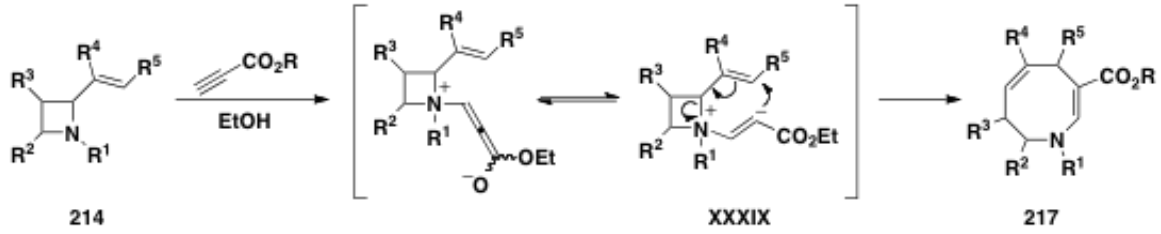

Scheme 61. Formation of 2,3,6,7-tetrahydroazepines or pyrrolidines from azetidinium ylides

The outcome of the reaction was dependent on the geometry of the alkenyl substituent on the 2-position of the azetidine ring relative to the newly formed bond to nitrogen after alkylation. The [2,3]-rearrangement occurs when these substituents are *cis* to one another while the [1,2]-shift product is the result of a *trans* relationship (Scheme 62).



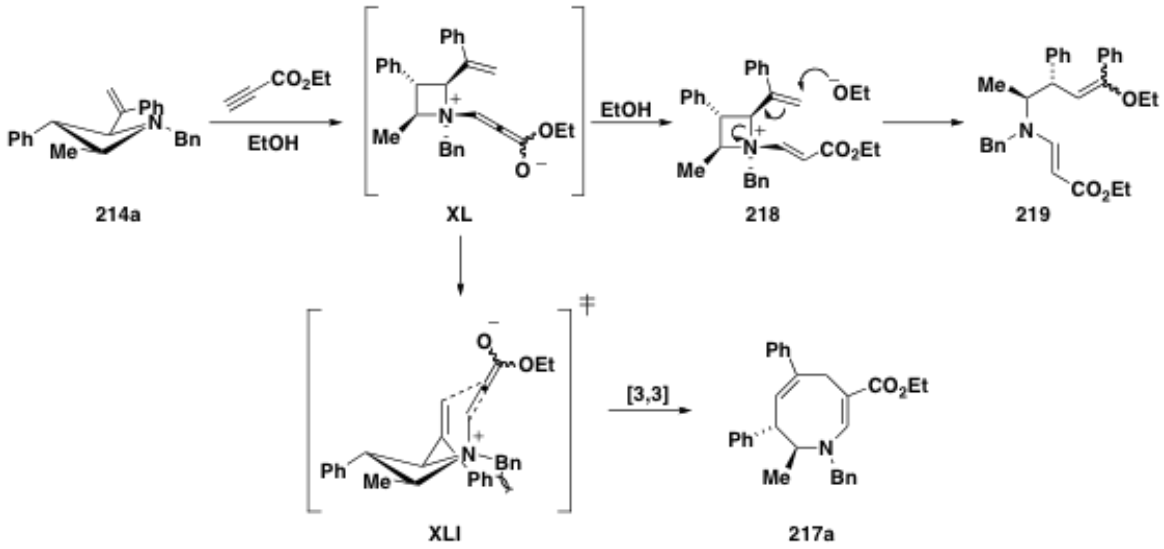

Scheme 62. Explanation for observed reactivity of *cis* and *trans* 2-alkenylazetidines

A slight modification to this procedure allowing for access to azocines derivatives with the same 2-alkenyl azetines (**214**) was reported a few years later. In this case, activation of the nitrogen by alkylation with activated alkynes leads to intermediate **XXXIX**, which can subsequently undergo a [3,3]-sigmatropic rearrangement to give the 1,2,3,6-tetrahydroazocines (**217**, Scheme 63).



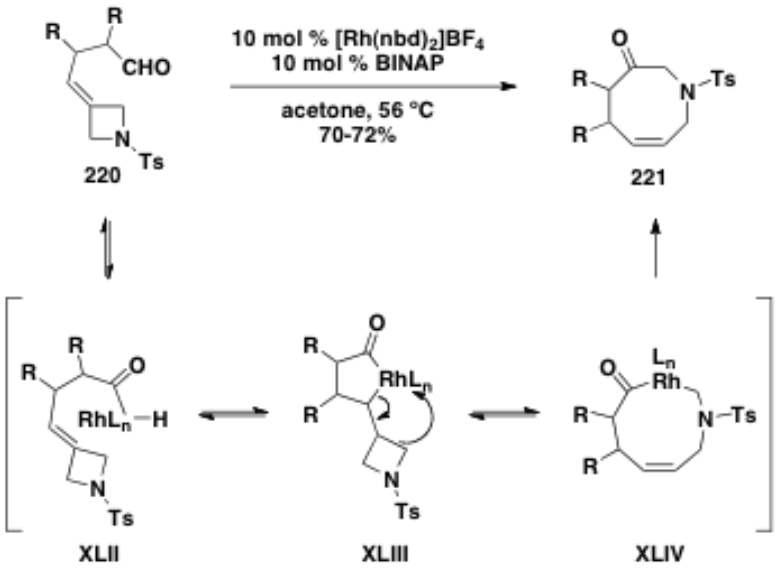

Scheme 63. Mechanism of medium-sized ring formation

The formation the desired product (**217**) was found to be sensitive to the relative configuration of the substituents on the ring. The authors found that ring opening of **214a** to give acyclic product **219** was competitive with the formation of **217a,** which was consistent in other cases where $R^4$ and/or $R^5 \neq H$ (Scheme 64). This is believed to be the result of steric congestion inpeding the requisite conformation for the rearrangement.



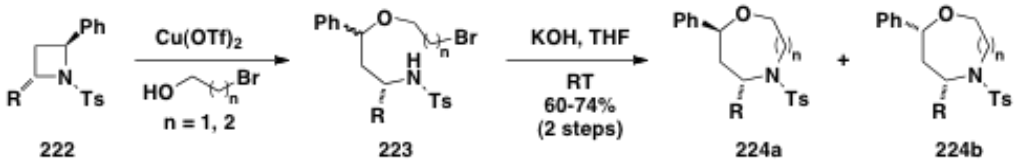

Scheme 64. Competitive formation of acyclic products using highly substituted azetidines

The formation of azocinone derivatives is also possible through the rhodium-catalyzed ring opening of 3-alkylideneazetidines (**216**, Scheme 65).[60] The ring expansion is hypothesized to occur *via* C-H activation of **220** to give **XLII**, followed by hydrometallation of the C-C double bond to give metallocyclopentanone **XLIII**. Rearrangement of **XLII** to **XLIII** followed by reductive elimination would lead to the observed product **221**.




Scheme 65. Rhodium-catalyzed ring expansion of azetidines to azocinone derivatives

In 2009, Ghorai and coworkers reported the enantioselective synthesis of 1,4-oxazepanes and 1,5-oxazocines *via* ring opening of azetidines with bromoalcohols (Scheme 66).[61] This procedure, which took enantiopure *N*-tosyl azetidines **222** and activated then with $Cu(OTf)_2$ in the presence of the alcohol, resulted in ring opening to the acyclic amine **223**. Subsequent addition of potassium hydroxide facilitated closure of the larger ring to generate diastereomers **224a** and **224b**.




Scheme 66. Ring expansion of azetidines to 1,4-oxazepanes and 1,5-oxazocines

With mono-substituted azetidines (R = H) it was found that the enantiomeric excess (e.e.) decreased during the reaction. The authors believe that this is due to partial racemization at the benzylic center of the starting azetidines in the presence of copper triflate, which has been experimentally observed with aziridines. The 2,4-disubstituted substrates, however, remained at >99% e.e. This is because the necessary epimerization of the benzylic position for racemization to occur would lead to the substituents on the ring being *cis* to one another, which is less favourable (Figure 5).

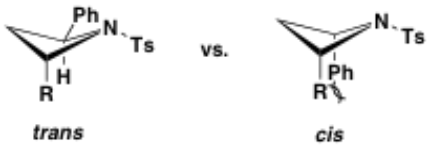
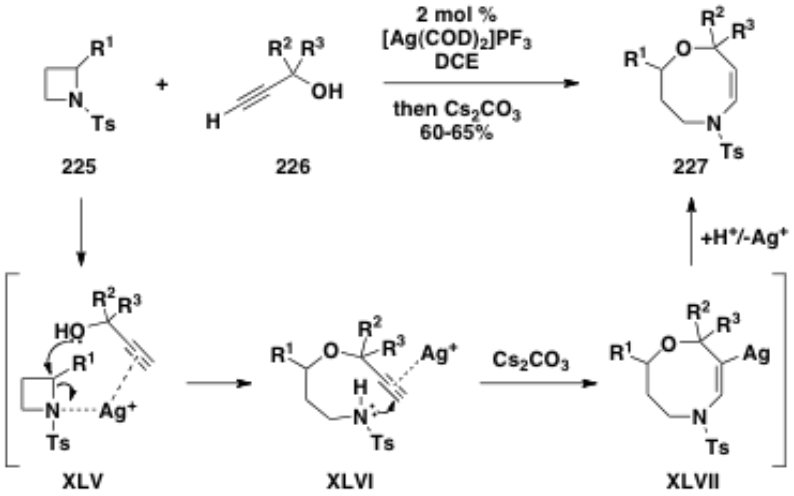



Figure 5. Steric interactions in *cis* and *trans*-2,4-disubstituted azetidines

The Roy group has also reported a ring expansion involving Lewis acid activation of 2-substituted *N*-tosyl-azetidines to give hydrooxazocenes.[62] This methodology utilizes Ag(I)-catalyzed dual activation of both azetidine **225** and propargylic alcohol **226**. This activation triggers a ring opening/closure cascade, which results in formation of 8-membered heterocycles **227** (Scheme 67).

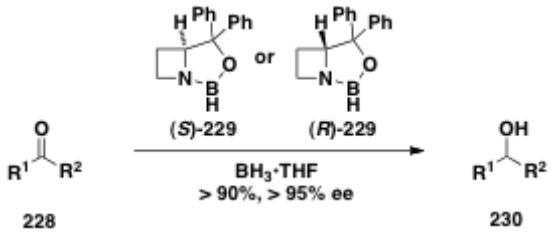



Scheme 67. Formation of hydrooxazocenes from azetidines and propargyl alcohols

The number of reports for successful ring expansion of azetidines to larger ring systems over the last few years has started to increase. This is most likely due to the ability to access a large array of enantiopure

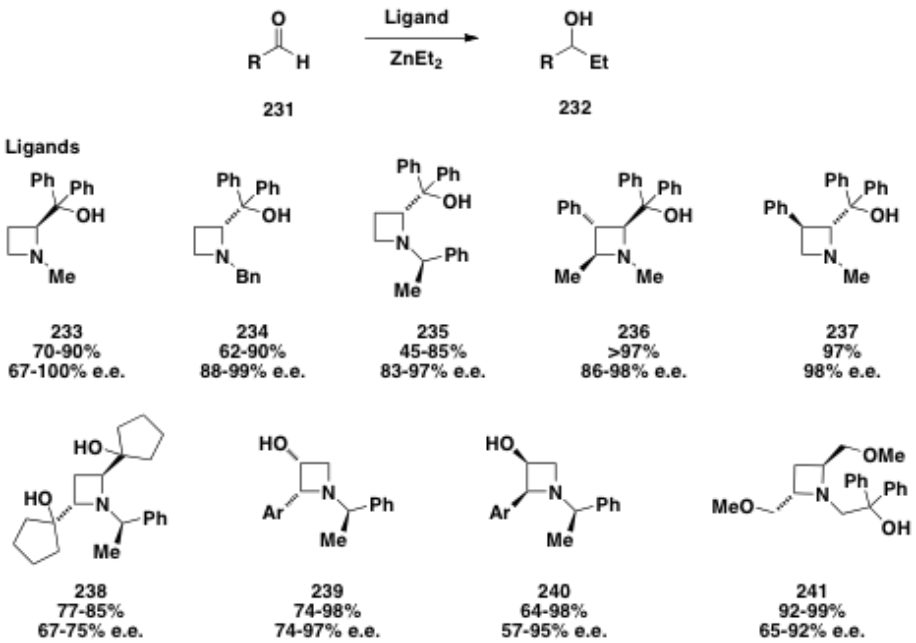
azetidines from readily available and affordable starting materials. The following section will show some of the interesting ring systems that have been accessed recently.

**Application of Azetidines in Catalysis.** With the recent development of methodologies to quickly synthesize azetidines in enantiomerically pure form, it is not suprising that their implementation as either ligands for metal-catalyzed reactions or as chiral auxiliaries in organocatalysis is increasing. The first examples of the successful application of azetidines as chiral ligands were reported in the 1990's and involved the borane reduction of aldehydes and ketones (Scheme 68).[63] The success in these cases is presumed to derive from the rigid framework of the oxaborolidines (**229**) as both acyclic and 5-memberd ring analogues resulted in lower enantiomeric excesses.



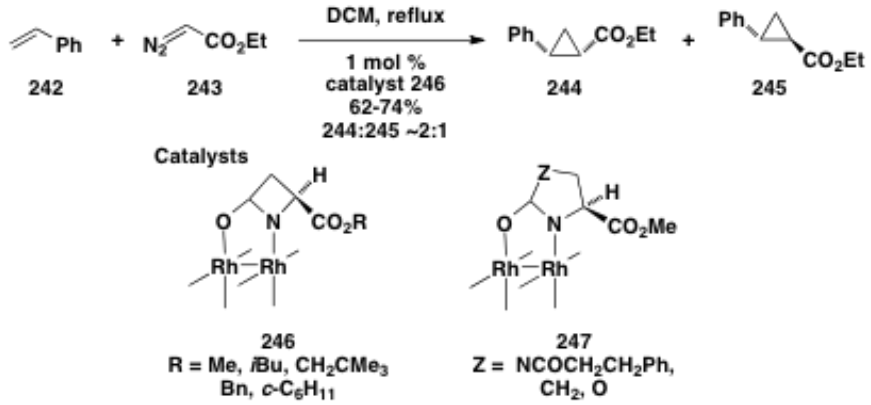

Scheme 68. Asymmetric reduction of aldehydes and ketones with oxaborolidines

Along the same lines, the asymmetric alkylation of aldehydes with diethylzinc has also been examined using azetidines with alcohol substituents as bidentate chiral ligands (Scheme 69). [26,64] Over the last decade there have been several reports in which the transformation is both highly enantioselective and high yielding with a variety of differently substituted chiral azetidines (**233**-**241**).



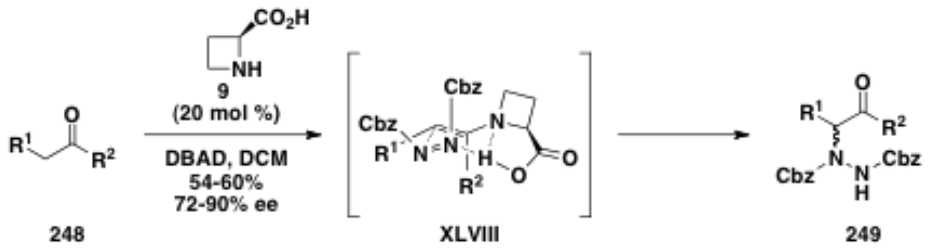

Scheme 69. Asymmetric alkylation of aldehydes with diethyl zinc and azetidine-based catalysts

Azetidines have also been used as ligands with palladium in Suzuki-Miyaura cross-coupling reactions,[65] and with rhodium for enantioselective cyclopropanation reactions.[66] The enantiocontrol observed in the cyclopropanation using azetidine-4-carboxylate-derived rhodium complexes (**246**, Scheme 70) is notable as it generally leads to the preferential formation of *cis*-cyclopropanes, which is in contrast to the preference for the *trans*-cyclopropanes observed with other similar 5-membered ring analogues **247**.



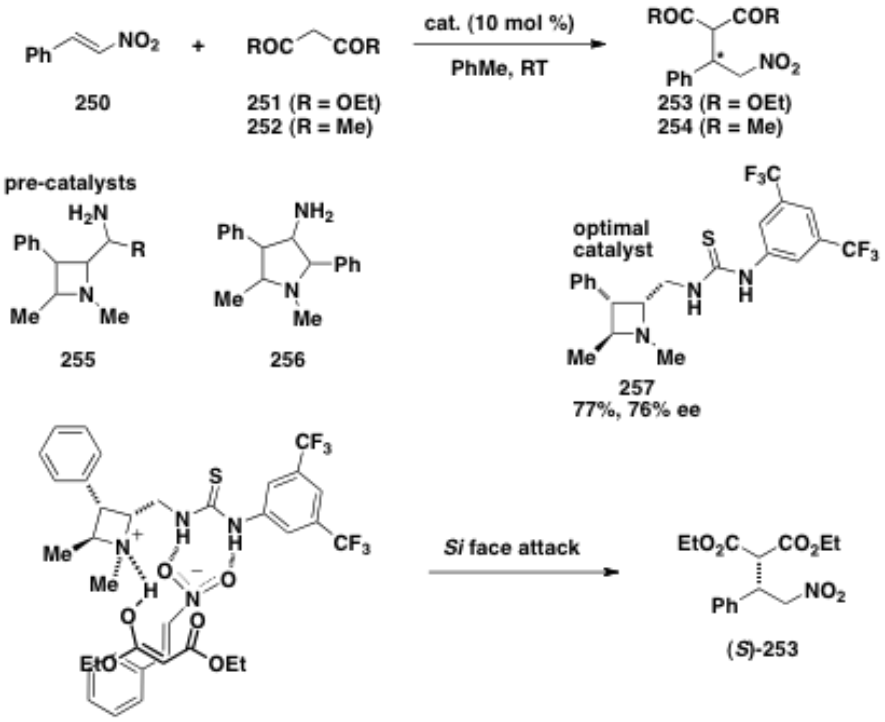

Scheme 70. Use of azetidines as ligands on rhodium for enantioselective cyclopropanations

The success of proline and its derivatives in organocatalysis is well documented in the literature.[67] Not surprisingly, the application of azetidines as organocatalysts for *in situ* formation of chiral iminium or enamine species has also been successful. In 2006, Greck and coworkers reported the asymmetric α-amidation of ketones with dibenzyl azodicarboxylate (DBAD) using L-azetidine 2-carboxylic acid (**9**) as the catalyst (Scheme 71).[68] It should be noted that the authors also performed the reactions using L-proline as the catalyst but the yields and enantiomeric excesses were lower than those observed with **9**.




Scheme 71. Use of L-azetidine-2-carboxylic acid for the asymmetric α-amidation of ketones

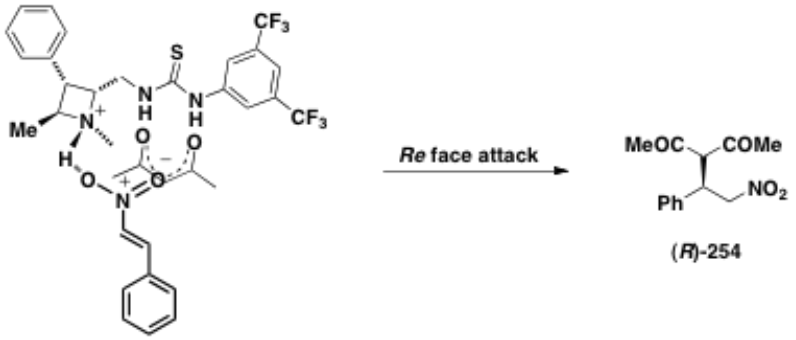
The use of azetidinic 1,2-diamines as organocatalysts for asymmetric Michael additions has also been reported recently.[69] In this paper, the authors screened a variety of thioureas derived from differently substituted primary and seconday α-aminomethyl-azetidines **255** and 3-aminopyrrolidines **256** for the addition of diethylmalonate (**251**) to β-nitrostyrene (**250**, Scheme 72). They found that only catalyst **257** showed high catalytic activity and after optimization led to the formation of the Michael adduct **253** in 77% yield and an e.r. of 68:32 (*S*:*R*).




Scheme 72. Azetidine diamine-catalyzed Michael addition to nitrostyrene with diethyl malonate

Interestingly, when diethyl malonate **251** was replaced with acetoacetone **252** the absolute configuration of the Michael adduct (**254**) was reversed (e.r. = 12:88 (*S*:*R*)). The authors believe this reversal is due to the difference in p$K_a$ of the two nucleophiles. Scheme 72 shows the proposed transitions state for the reaction with diethyl malonate, which has a p$K_a$ of 13. In this case, hydrogen bonding between the nitro group and the thiourea along with concomitant deprotonation of the enol form of diethylmalonate by the proximate tertiary amine leads to attack on the *Si* face of the nitrostyrene and generation of (*S*)-**253** as the major enantiomer.

The reaction with acetoacetone **252** (p$K_a$ = 9), on the other hand, would lead to attack on the *Re* face. This is due to the more facile deprotonation of **252** resulting in the formation of an ammonium species, which can then hydrogen bond with the nitro group. If the enolate then coordinates to the thiourea, the result is the transition state shown in Scheme 73, which illustrates how (*R*)-**254** is formed preferentially.




Scheme 73. Proposed transition state for Michael addition with acetoacetone

## CONCLUSION

Overall, the advancements made in the chemistry of azetidines in the last few decades say a great deal about the potential of these small molecules. The above summary has highlighted some of the most versatile methods for the generation of both simple and highly functionalized azetidines, as well as some of the new methods that hold potential to be so in the future. Their application in the synthesis of a wide range of molecules, from enantiopure acyclic amines to ordinarily challenging medium-sized heterocycles, shows they are great asset in multiple areas of chemistry.

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