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Recent applications of aziridine ring expansion reactions in heterocyclic synthesis

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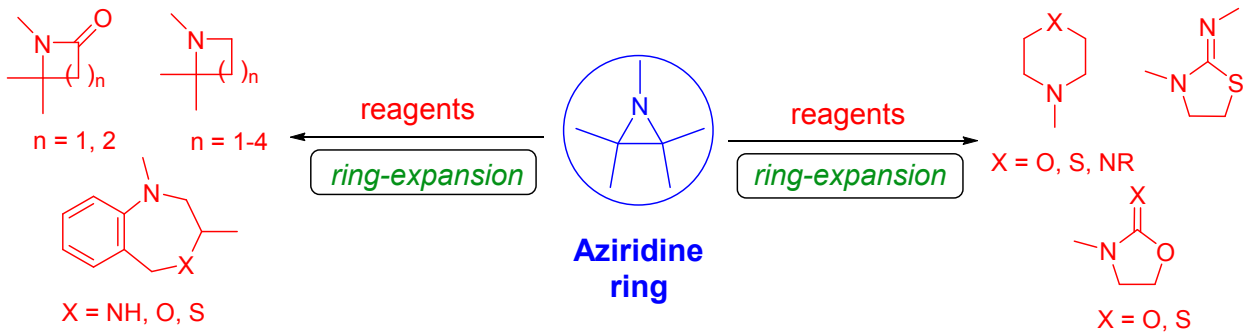
Abstract

The inherent reactivity of the aziridine ring due to ring-strain makes it valuable building blocks for the synthesis of other heterocyclic motifs of biological relevance. Of particular significance is the generation of azomethine ylides from them and cycloaddition of ylides with alkenes, alkynes, and heterocumulenes. The ring undergoes opening followed by cyclization with a variety of reagents either in the presence of a catalyst or without any catalyst. This review article discusses the recent applications of aziridines in syntheses of four- to seven-membered heterocycles of biological relevance such as azetidines, 2-azetidinones, pyrroles, imidazoles, oxazoles, thiazoles, piperidines, pyrazines, pyrimidines, benzoxazines, morpholines, azepanes, benzodiazepines, benzoxazepines, and benzothiazepines.



Keywords: Aziridines, azetidines, pyrroles, imidazoles, benzoxazines, azepanes, benzoxazepines

Table of Contents

1. Introduction

Azacyclopropanes, commonly known as aziridines, are a well-known class of compounds in the realm of heterocyclic chemistry and medicinal chemistry.[1] Aziridine ring is extremely reactive due to ring-strain associated with it which makes it a powerful building block in organic synthesis. The unique reactivity of

aziridines has been exploited by synthetic organic chemists for developing synthetic protocols to several novel heterocyclic compounds either directly or through the formation of diverse 1,2-difunctionalized compounds through ring-opening followed by cyclization or cycloaddition.

Although access to strained three- and four-membered heterocycles is a challenging endeavor aziridines having a broad range of functionalities are easily accessible by several routes described in literature. The reactivity of aziridines depends largely on type of substituents presents on the ring. The presence of a strong electron-withdrawing group on the ring activates the ring and such aziridines are referred to as activated aziridines. Aziridines bearing arylsulfonyl groups on ring nitrogen, a carboxylate group or a vinylic group on ring carbon(s) have drawn considerable interest of researchers. The synthesis and reactivity of aziridines have been reviewed from time to time.[2,3] Some review articles focusing on specific type of aziridines such as aziridine-2-carboxylates,[4] 2-haloaziridines,[5] 2-methyleneaziridines,[6] and 2-vinylaziridines[7,8] have been published. This review paper aims to describe recent applications (2008 to early 2017) of aziridines, whether activated or non-activated, in synthesis of other heterocyclic frameworks by aziridine ring expansion. It is well-known that heterocyclic compounds containing one or more nitrogen atoms, or nitrogen atom(s) together with sulfur or oxygen atoms are biologically very important class of compounds. Hence the article will focus on synthesis of different types of heterocycles rather than the different types of reactions of aziridines. Although the review of synthetic methods of aziridines is not the objective of this article it would be wise to give a brief idea about how the aziridines are accessed in laboratory. Accordingly, selected examples from different methods reported in recent literature are described here.

1.1 Synthesis of aziridines

There are a number of methods known in literature for synthesizing aziridines (Figure 1). The main approaches to construct the aziridine motif can be broadly classified as i) cyclization of 2-aminoalcohols, ii) addition of nitrenes or nitrenoids to alkenes, and iii) reactions of sulfur ylides or carbenes/carbenoids with imines. Looking at significance of asymmetry in structure of the molecules in biological systems, efforts are on to synthesize enantioenriched aziridines.[9,10]

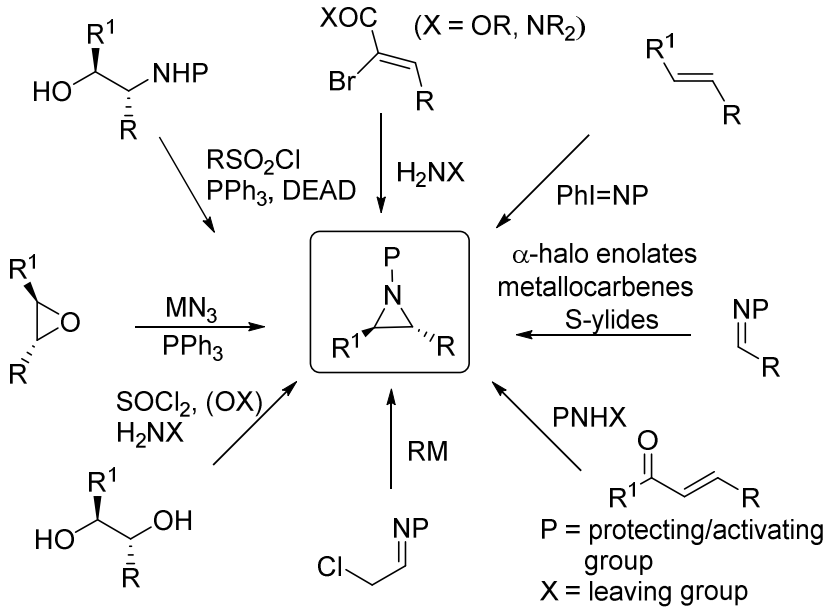
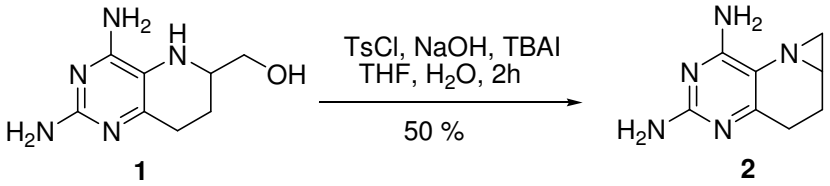


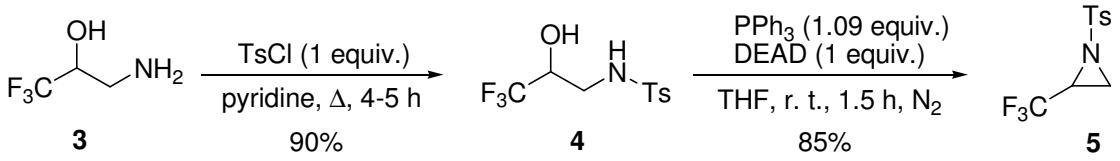
Figure 1. Main synthetic approaches to aziridines.

i) Cyclization of 2-aminoalcohols*:* A one-step cyclization of 2-aminoalcohol **1** with *p*-toluenesulfonyl chloride (TsCl), aqueous NaOH and tetrabutylammonium iodide in a biphasic system leads to the formation of a tricyclic aziridine, 2,4-diamino-5,6-methylene-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine **2** in 50% yield (Scheme 1).[11]



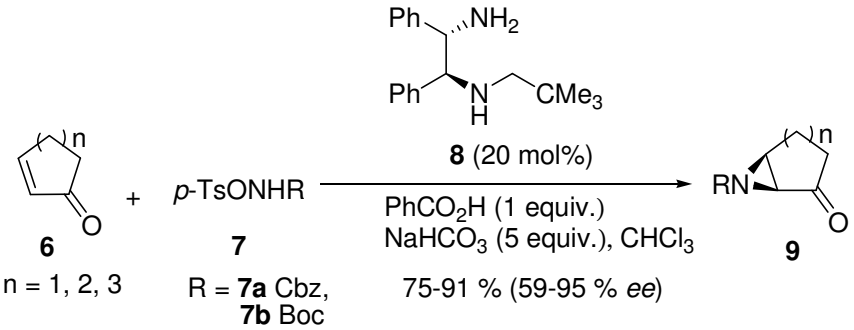
Scheme 1

The formation of *N*-tosyl-2-trifluoromethylaziridine **5** is reported from 3-amino-1,1,1-trifluoropropan-1-ol **3**.[12] The latter compound undergoes a selective *N*-tosylation on treatment with TsCl in pyridine to form *N*-sulfonamide **4**. The cyclization of the *N*-sulfonamide under the Mitsunobu conditions yielded the aziridine **5** (Scheme 2). This aziridine finds use in synthesis of pyrrolidines, piperidines and azepanes that will be dealt with in respective sections.[13]



Scheme 2

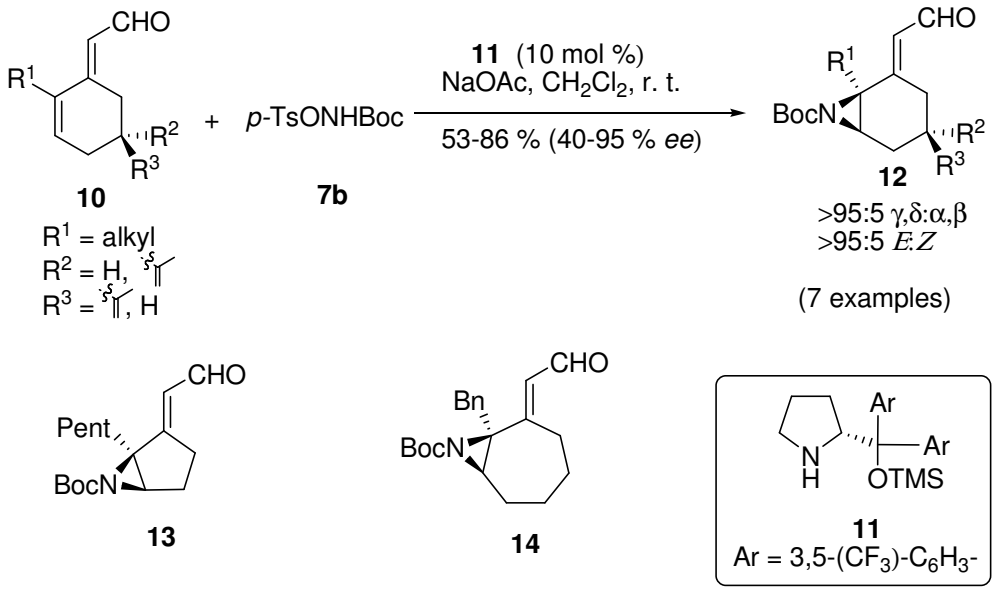
ii) Addition of nitrenes or nitrenoids to alkenes: Menjo and coworkers have reported an excellent asymmetric synthesis of fused bicyclic aziridines **9** by reaction of alkenes **6** with *N*-tosyloxycarboxybenzyl carbamate **7** in the presence of *N*-neopentyl-1,2-diphenylethylenediamine catalyst **8** (Scheme 3).[14] Recently, this group has discovered another diamine similar to **8** but CH_2CMe_3 group replaced with a 4,4-dimethylcyclohexyl group for the asymmetric aziridination using same reagent.[15]



Scheme 3

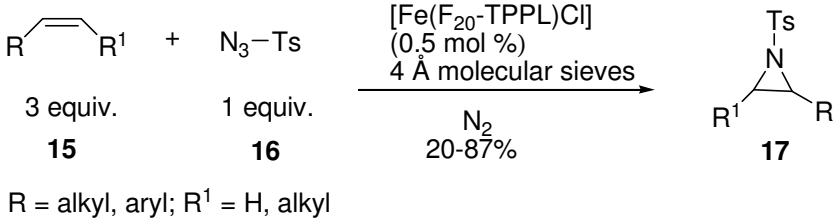
Halskov and coworkers have reported the formation of aziridines **12-14** in very good yields and excellent enantioselectivity (except for aziridine **14** that had only 40% ee) by the reaction of *N*-tosyl-*tert*-

butyloxycarbonyl carbamate, **7b**, with five- to seven-membered cyclic 2,4-dienals **10** using trimethylsilyl (TMS)-protected prolinol catalyst **11** (Scheme 4).[16]



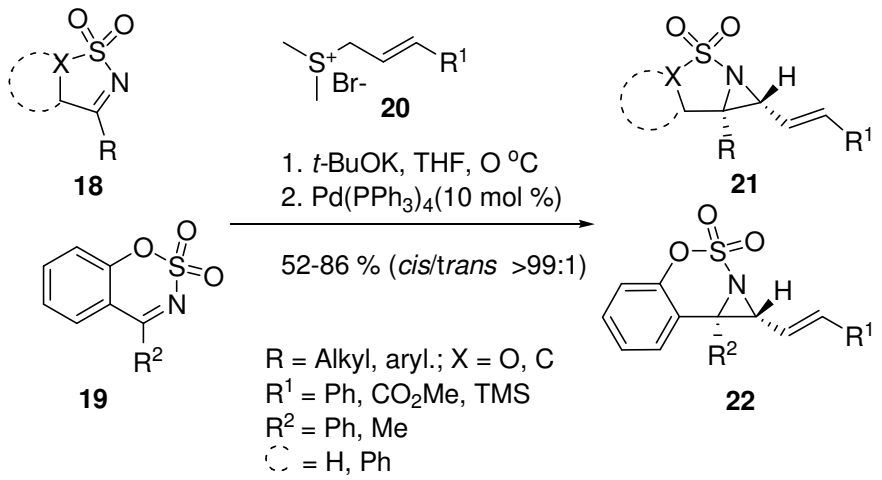
Scheme 4

Liang and coworkers have reported the formation of *N*-tosylaziridines **17** by reactions of olefins **15** with *p*-toluenesulfonyl azide **16** in the presence of iron porpholactone, (*meso*tetrakis-(pentafluorophenyl)porpholactonato dianion, [Fe(F_{20}-TPPL)Cl]) as a catalyst (Scheme 5).[17] However, *p*-methoxystyrene and α-methylstyrene furnished tetrahydropyrrole and allylic amidation products, respectively, instead of aziridine derivatives from this reaction.



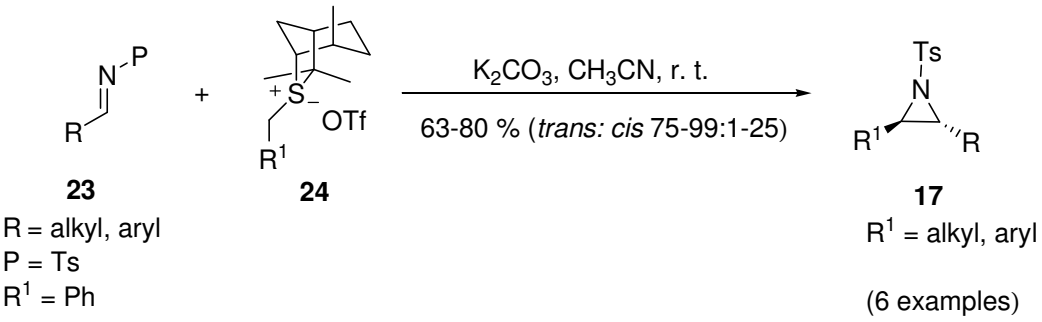
Scheme 5

iii) Reactions of sulfur ylides or carbenes/carbenoids with imines: A one-pot, highly diastereoselective synthesis of functionalized *cis*-vinylaziridines, **21** and **22** containing a quaternary carbon center is reported through a sulfur ylide-mediated aziridination of five- and six-membered cyclic imines **18** and **19** in the presence of a palladium catalyst (Scheme 6).[18]



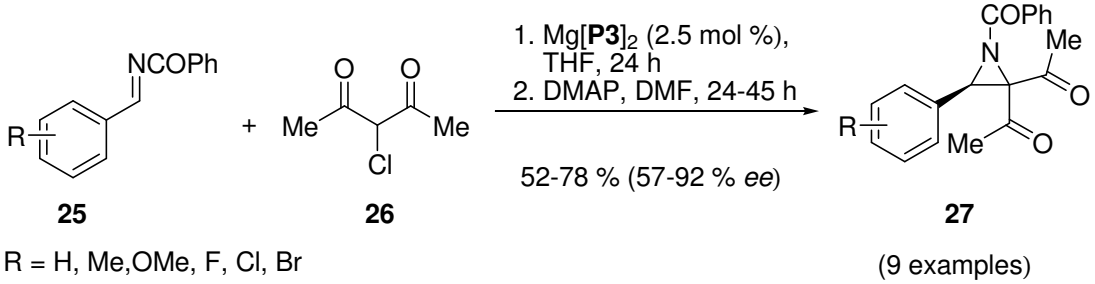
Scheme 6

In another example, Aggarwal and coworkers used dissolved sulfonium salt **24** in acetonitrile before adding the imines **23** and potassium carbonate.[18] The solution was then stirred at room temperature overnight. The reaction led to the formation of aziridines **17** in good yields with good *trans* selectivity (Scheme 7).[19]



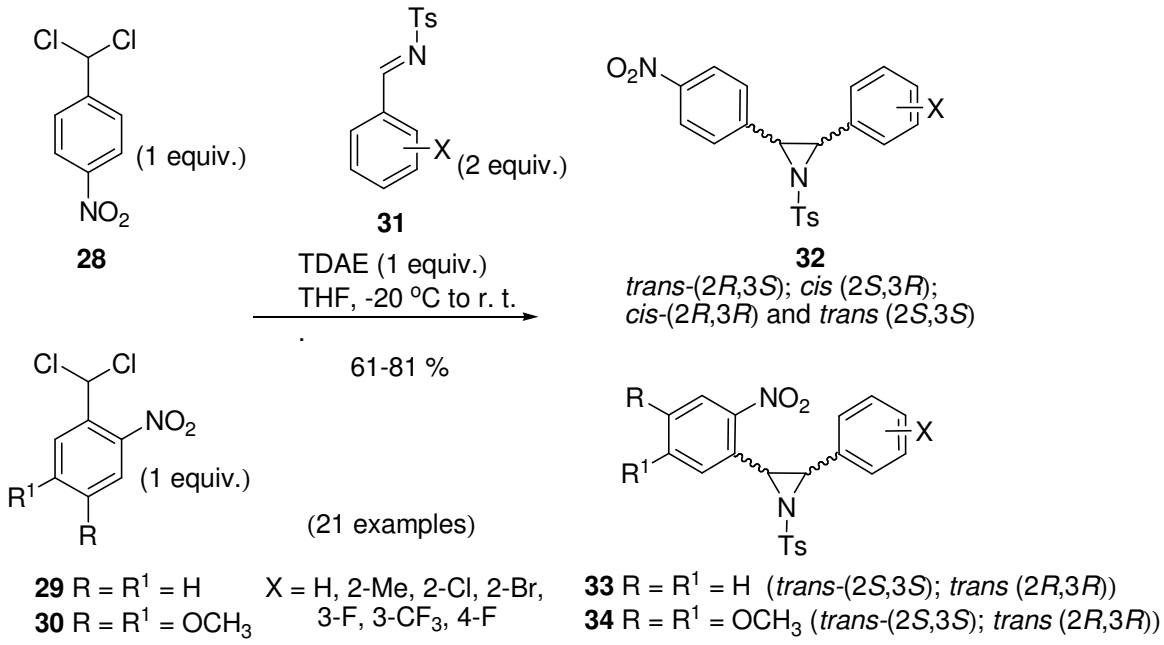
Scheme 7

The Aza-Darzens reaction is reported as a convenient method to access aziridnes.[20] Aza-Darzens reaction involves an α-haloenolate or an α-halocarbanion and an imine. Stockman and coworkers have reported the synthesis of 2,3-disubstituted and 2,2',3-trisubstituted aziridines by an aza-Darzens reaction of the *tert*-butanesulfinyl imines with ethyl bromoacetate.[20] Larson and co-workers reported the first asymmetric aza-Darzens addition using 3-chloropentane-2,4-dione **26** and *N*-benzoyl imines **25** to give *N*-benzoyl-2,2-diacetyl-3-arylaziridines **27** using vaulted biphenanthrol magnesium salt (Mg[P3]$_2$) as a catalyst (Scheme 8).[21]



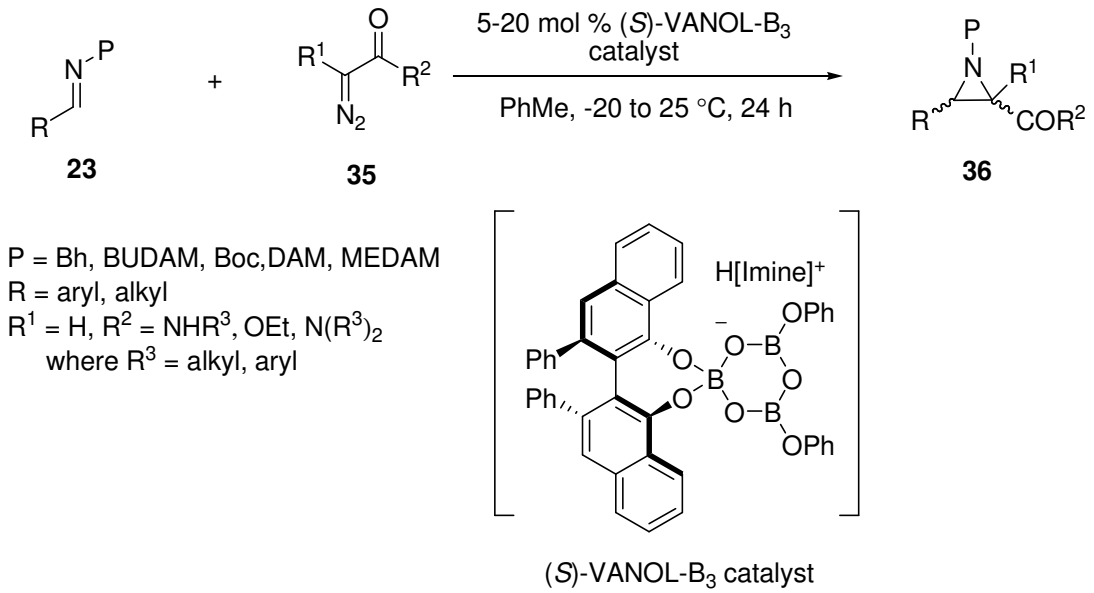
Scheme 8

Khoumeri and coworkers have synthesized a mixture of *cis/trans* 2,3-diaryl *N*-tosylaziridines **32**, with *cis*-isomers being the major products by reaction of 1,1-dichloromethyl-4-nitrobenzene **28** with aromatic *N*-tosylimines **31** in the presence of tetrakis(dimethylamino)ethylene (TDAE) (Scheme 9).[22] However, when the nitro group was on *ortho*-position, as in 1,1-dichloromethyl)-2-nitrobenzene **29** and 1,1-(dichloromethyl)-4,5-dimethoxy-2-nitrobenzene **30**, only the *trans*-aziridines **33** and 3**4**, respectively, are obtained.



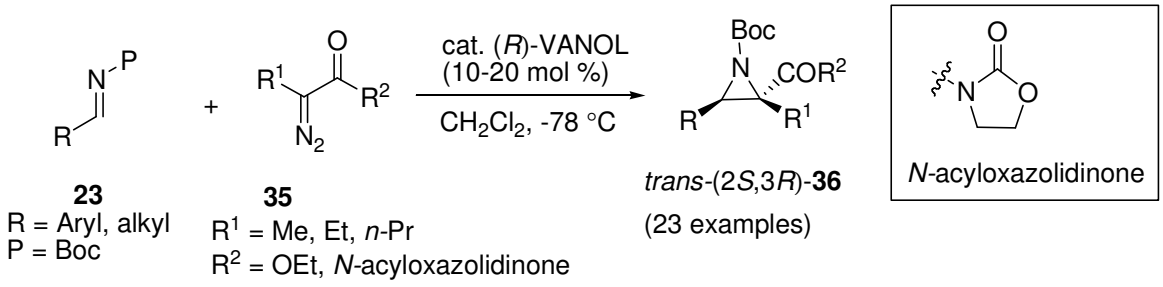
Scheme 9

Wulff`s research group has carried out several studies on catalytic reactions of diazo compounds with imines, mediated by boroxinate catalysts derived from VANOL and VAPOL ligands mainly for achieving aziridines in enantiopure forms.[23-25] The reactions of imines with diazoacetates[26] and with diazomethyl ketones,[27] catalyzed by either a VAPOL or VANOL catalysts, have been reported to provide *cis*-aziridines. The reaction of *sec*-diazoacetamides with imines, however, results in formation of *trans*-aziridines.[28] The reaction of imines **23** with α-diazo compounds **35** in the presence of the VANOL/ VAPOL-B_3 catalyst furnishes either *cis*- or *trans*- aziridines **36** depending on the reaction conditions (Scheme 10).[29] For example, a *N*-BUDAM-protected imine **23** reacts with α-diazoacetamides **35** in toluene at -20 °C to give pure *trans*-aziridine acetamides **36** in 90% yield and 96% ee. The same imine **23** reacts with ethyl diazoacetate **35** under similar reaction conditions to give a 99% isolated yield of the pure *cis*-aziridine acetate **36** in 98 % ee. Hence, the face selectivity is caused by the catalyst or diazo compound rather than the imine.



Scheme 10

The α-diazo compounds **35** without amidic protons, furnish *cis*-aziridines **36** selectively whereas those with amidic proton afford *trans*-aziridines **36** under similar reaction conditions.[30] Thus, the presence or absence of an amidic proton plays an important role in diastereoselection. The *N*-Boc-protected imines **23** react with α-diazopropanoate **35** (R^2 = OEt) and α-diazo-*N*-propanoyloxazolidinone **35** (R^2 = *N*-acyloxazolidinone) in dichloromethane at -78 °C in the presence of VANOL-B_3 catalyst to give *trans*-trisubstituted aziridines **36** selectively (Scheme 11).[25]

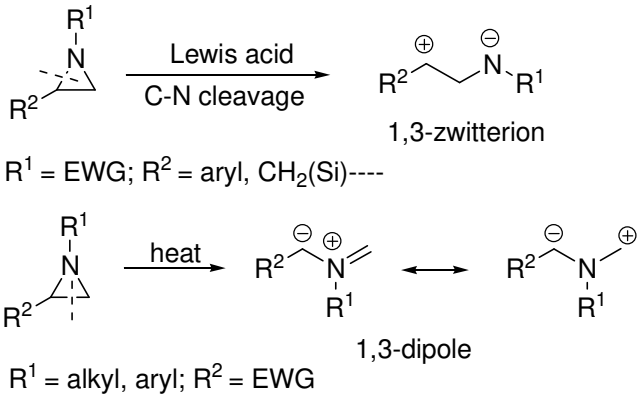


Scheme 11

2. Ring-Opening of Aziridines: Synthetic Methods for Heterocycles from Aziridines

The chemistry of aziridines has drawn considerable interest in recent years with an objective to construct medium-size aza-, diaza-, oxoaza- and thioaza- heterocycles (Figure 1). A brief account of synthetic methods in preceding section has shown that aziridines with different types of substituents are easily accessible in laboratory by a number of methods. Aziridine ring, however, has inherent reactivity due to high ring-strain associated with it. As a result, a number of nucleophiles have been employed successfully for aziridine ring-opening. Both C-C and C-N bonds of aziridine ring can undergo cleavage (Scheme 12).[31] The regioselectivity in

ring-opening depends on substituents present on the ring.[32,33] Usually the electron-withdrawing groups on ring favor the cleavage of C-N bond. The presence of an electron-releasing group favors the cleavage of C-C bond. Besides electronic effects, sometimes steric effect also governs the nucleophilic attack on the ring.[32] De Kimpe and coworkers observed that in non-activated 2-substituted aziridines, the ring-opening depends on the nature of nucleophile, the type of activation of the aziridine ring, and nature of the substituent on the ring.[32] Paasche and coworkers have performed computational analysis of the underlying potential energy surfaces and reaction paths to get an insight into the thermodynamic and kinetic factors governing the cleavage of C-C and C-N bonds in differently substituted aziridines.[34] This study revealed that the C-C bond cleavage and nucleophilic attack is a stepwise reaction while the C-N bond cleavage and nucleophilic attack is a concerted process. The substitution pattern on the aziridine ring did not affect the reaction course but affected the reaction barrier. The barrier for the C-C bond cleavage decreased on replacing hydrogen atom with electron-withdrawing substituents such as nitrophenyl or carboxylate. The barrier for the C-N bond cleavage, however, increased with cumulative substitution. The computed data predicted that a shift from C-N to C-C bond cleavage required stabilizing substituents at both carbon atoms.



Scheme 12

The 1,3-dipole, generated by cleavage of aziridine ring, can be trapped with diverse types of dipolarophiles to synthesize heterocyclic compounds. The ring-opening of aziridines and subsequent cyclization or cycloaddition have led to discovery of interesting synthetic methodologies for four- to seven-membered heterocyclic motifs (Figure 2) such as azetidines, β-lactams, pyrroles, imidazoles, oxazoles, pyrimidines, pyrazines, oxazines, morpholines, thiomorpholines azepanes, benzodiazapines, benzoxazepines, and benzothiazepines. In the succeeding sections, the synthesis of these heterocyclic frameworks from aziridines by different methods is described. The literature is arranged here according to the ring size. Within a particular ring size, the synthetic methods are discussed according to ring-type.

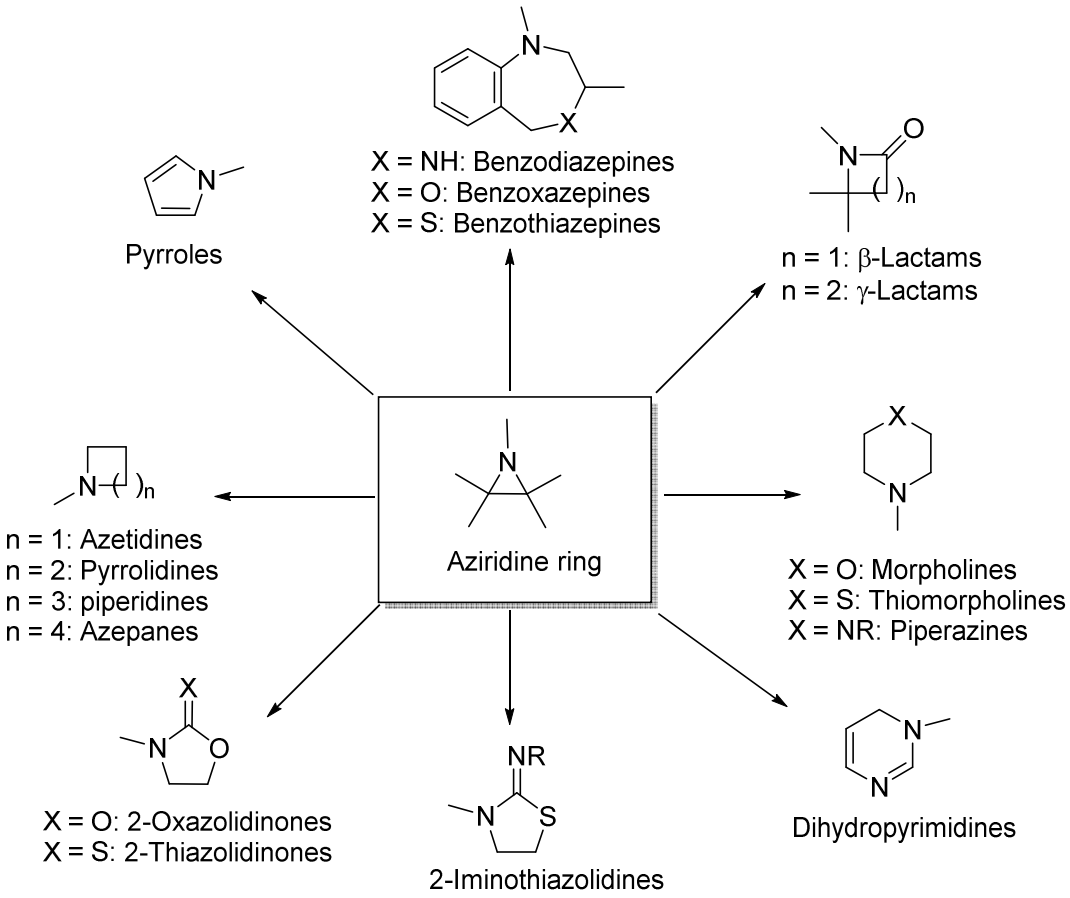


Figure 2. Heterocyclic compounds from aziridines.

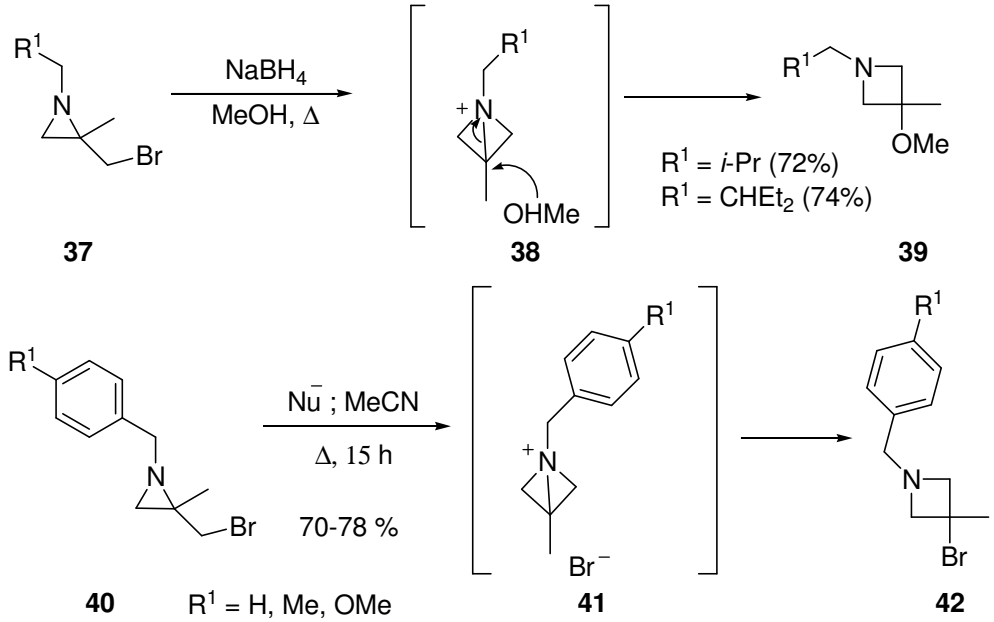
3. Synthesis of Four-membered Heterocycles

3.1 Synthesis of azetidines

The transformation of a three-membered ring to a four-membered ring is a difficult to achieve endeavor and hence the literature is scarce on this type of transformation. Azetidines constitute an important class of azaheterocyclic compounds from synthetic, mechanistic, and biological points of views.[35]

De Kimpe and coworkers have designed and developed the synthesis of several novel aziridines and investigated their reactivity towards different reagents for entry into other heterocyclic systems of biological relevance. A novel aziridine to azetidine rearrangement protocol has been developed by the conversion of 2-bromomethyl-2-methylaziridines **37**.[36] Treatment of aziridines **37** with sodium borohydride is suggested to form a bicyclic intermediate **38** that undergoes reaction with methanol to form the azetidines **39** (Scheme 13). The cyclization of aziridines **37** to the bicyclic intermediate **39**, which is in contrast with the well-known chemistry of 2-(bromomethyl)aziridines **37** bearing no additional substituent at C-2-position, was interpreted as the Thorpe-Ingold effect due to *the gem*-disubstitution at the aziridine carbon atom, resulting in a more favorable geometric positioning of the nucleophilic nitrogen atom with respect to the halogenated carbon atom.

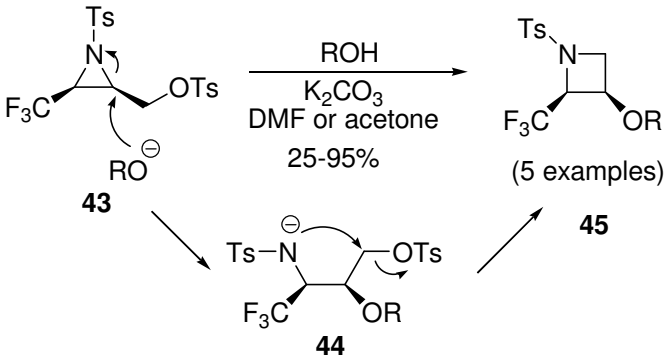
De Kimpe group has extended their work with *N*-benzylaziridines **40** towards different anionic nucleophiles such as oxygen, sulfur and carbon.[37] The solvent had a significant influence on the reaction outcome, enabling the selective formation of either functionalized aziridines in dimethylformamide or azetidines **42** in acetonitrile (Scheme 13).



Scheme 13

A regioselective ring-opening of the *cis*-*N*-tosyl-2-tosyloxymethyl-3-trifluoromethylaziridines **43** with phenols, followed by rearrangement leads to an easy entry to azetidine ring system (Scheme 14).[38] A similar treatment of these aziridines with aryl thiols leads to the formation of *N*-tosyl-2-arylthiomethyl-3-trifluoromethylaziridines. The phenolate ion attacks at C-2 position of the aziridine ring leading to cleavage of the C-N bond resulting into formation of an intermediate **44**. An intramolecular displacement of the tosylate group from intermediate **44** leads to the formation of *cis*-azetidines **45**.

The cleavage of alkyl 2-(bromomethyl)aziridine-2-carboxylates by HCl is reported to occur by the reaction at sterically more hindered carbon atom (C-2) leading to cleavage of the C-N bond. A subsequent base-promoted cyclization of the ring-opened product gives alkyl 3-chloroazetidine-3-carboxylates.[39]

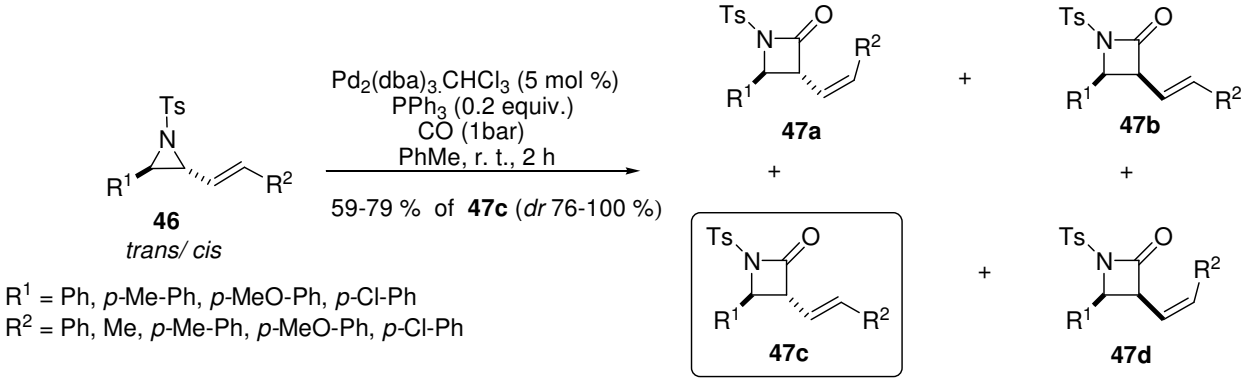


Scheme 14

3.2 Synthesis of β-lactams

β-Lactams are four-membered cyclic amides that constitute the most famous group of antibiotics. Besides being used as antibiotics,[40,41] they are also used as β-lactamase inhibitors,[42] and cholesterol absorption inhibitors.[43]

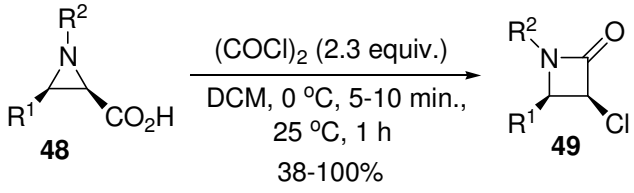
Fontana and coworkers have reported the palladium-catalyzed carbonylative ring-expansion of vinylaziridines for the synthesis of β-lactams.[44] The reaction of 3-aryl-2-vinylaziridines **46** with carbon monoxide in the presence of trisdibenzylideneacetone palladium(III) trichloromethane catalyst and triphenyl phosphite afforded four isomeric β-lactams **47a-d** at room temperature (Scheme 15). The *trans*-*E*-β-lactams **47c** were the major products. Alkyl substituents on vinyl aziridines did not give any β-lactam except in the presence of 50 bar of carbon monoxide, where *trans*-*Z*-β-lactams **47a** were obtained. However, a full chirality transfer to the *trans*-*E*-β-lactam **47c** could be achieved by using enantioenriched alkyl substituted vinyl aziridine **46**. A palladium(0)-mediated isomerization of vinyl aziridines followed by carbonylation and ring closure was proposed as the plausible mechanism for the formation of major product.



Scheme 15

Wulff and coworkers have reported the reactions of 3-alkylaziridine-2-carboxylic acids **48** with oxalyl chloride leading to an exclusive formation of 2-azetidinones **49** (Scheme 16).[45] The ring-expansion occurs in stereospecific manner with high yields and diastereoselection. The reaction with *trans*-1-benzyl-3-

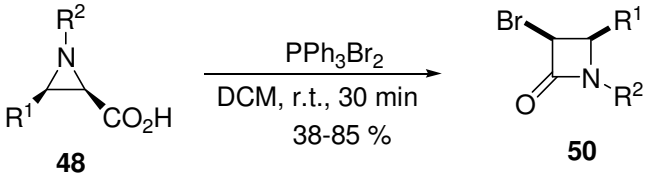
cyclohexylaziridine-2-carboxylic acid yielded exclusively the *trans*-β-lactam. The reaction also provided β-bromo-β-lactams with oxalyl bromide but some isomerization to *trans*-β-lactam was observed.



R^1 = *C*-hex, Et, *n*-Pr, *i*-Pr, *i*-Bu, *tert*-Bu
R^2 = $CHPh_2$, CH_2Ph, $(3,5\text{-}Me_2\text{-}4\text{-}MeOC_6H_2)_2CH$,
$(3,5\text{-}tert\text{-}Bu_2\text{-}4\text{-}MeOC_6H_2)_2CH$,

Scheme 16

A highly diastereoselective synthesis of 3-halogenated-4-trifluoromethyl *cis* and *trans*-β-lactams **50** is reported from 1-alkyl/aryl-3-(trifluoromethyl)aziridine-2-carboxylic acids **48**. The latter compounds are converted into *cis* and *trans*-β-lactams by different halogenating reagents, such as $POCl_3$, PCl_5, $SOBr_2$, PPh_3/NBS, PPh_3Br_2 (Scheme 17).[46]



R^1 = CF_3
R^2 = CH_2Ph, *p*-MeO-CH_2Ph, Ph_2CH, *p*-MeO-Ph

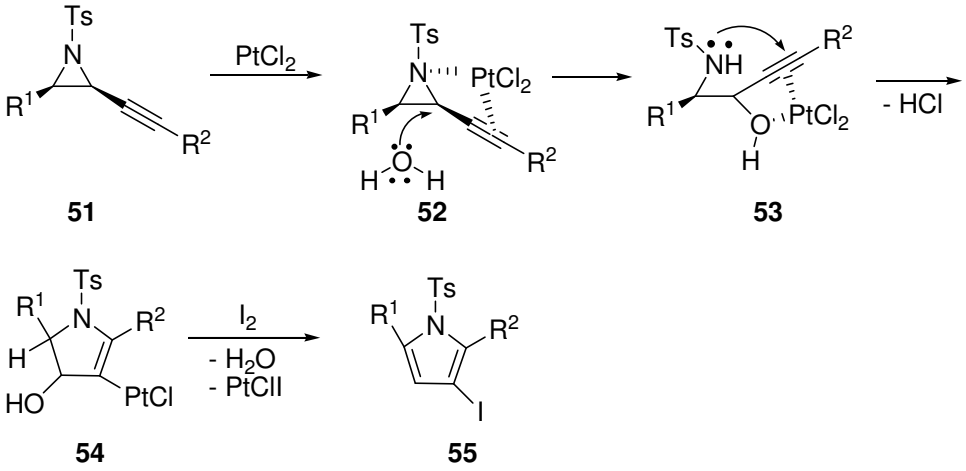
Scheme 17

4. Synthesis of Five-membered Heterocycles

4.1 Synthesis of pyrroles and indoles

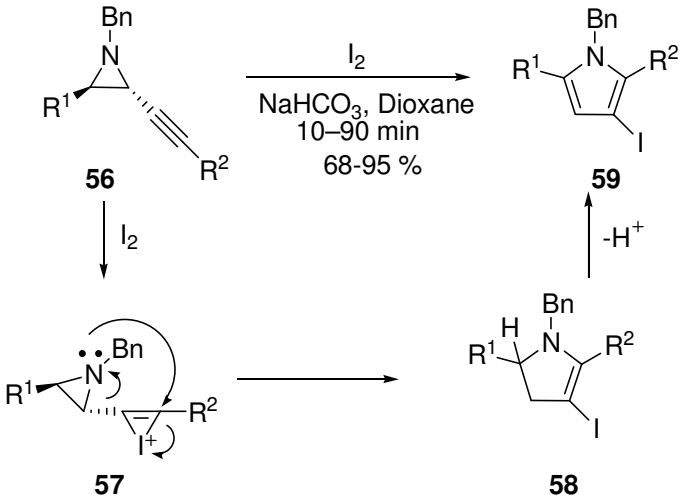
Pyrroles are well-known structural subunits in natural products and in compounds for industrial purposes. Polypyrroles have applications in material science, non-linear optics and supramolecular chemistry as molecular sensors and devices.[47] Yoshida and coworkers have reported the synthesis of 3-iodopyrroles by an electrophilic cyclization of *N*-tosyl or *N*-benzyl-substituted propargylic aziridines.[48] The annulation of *N*-tosyl-substituted substrates required a platinum catalyst while, the *N*-benzyl-substituted aziridines could be annulated through iodine-promoted cycloisomerization. In the case of *N*-tosyl compounds **51**, the aziridine is activated by coordination of platinum with ring-nitrogen and alkynyl group forming complex **52**, which promotes the aziridine ring-opening by nucleophilic attack of water on ring-carbon bearing the alkynyl group. The attack of the sulfonamide nitrogen in resulting product **53** on the distant alkyne carbon leads to the formation of a dihydropyrrole **54** that undergoes aromatization by elimination and subsequent iodo-demetalation with iodine to form 3-iodopyrroles **55** (Scheme 18). The mechanism for *N*-benzyl substrates suggested by the authors involved the formation of a cyclic iodonium ion **57** by the coordination of the

propargylic triple bond to an iodine cation followed by the attack of the aziridine nitrogen producing the cyclized cationic intermediate **58,** which then underwent aromatization by elimination of a proton to furnish 3-iodopyrroles **59** (Scheme 19). This group has further reported the platinum-catalyzed cascade cyclization/ring expansion of alkynyl-aziridines, spiro-fused to cyclobutane, forming bicyclic pyrroles **61** (Scheme 20).[49]



51 **52** **53** **54** **55**

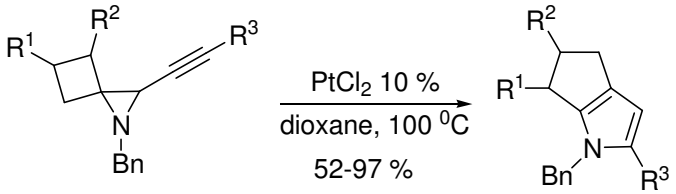
Scheme 18



56 **59** **57** **58**

R^1 = *C*-hex, *n*-Bu, *t*-Bu, Naphthyl
R^2 = Ph, CH_2Ph, allyl, -$(CH_2)_3OH$, siloxypropyl, *i*-Pr

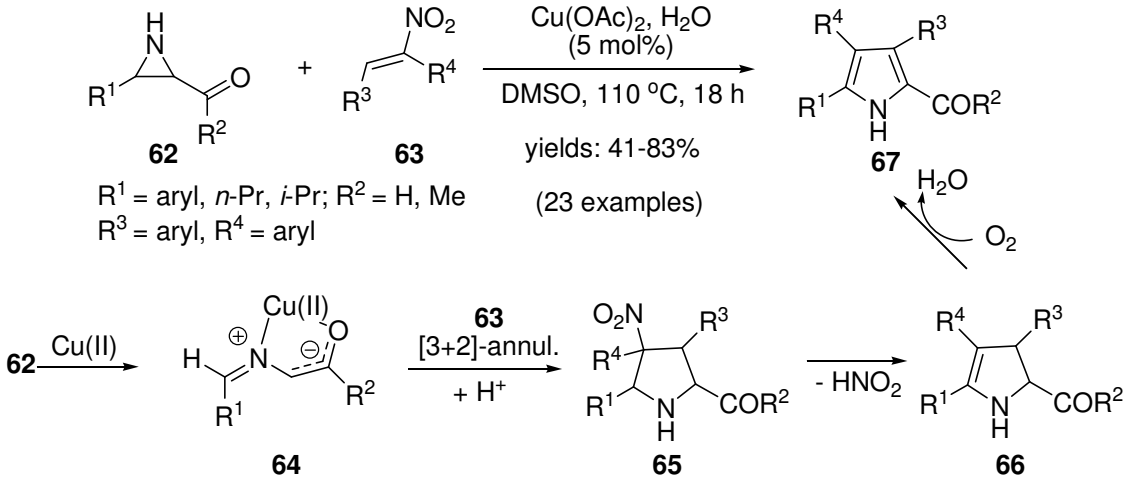
Scheme 19



60 R^1 = H, alkyl; R^2 = H, alkyl; R^3 = alkyl **61**

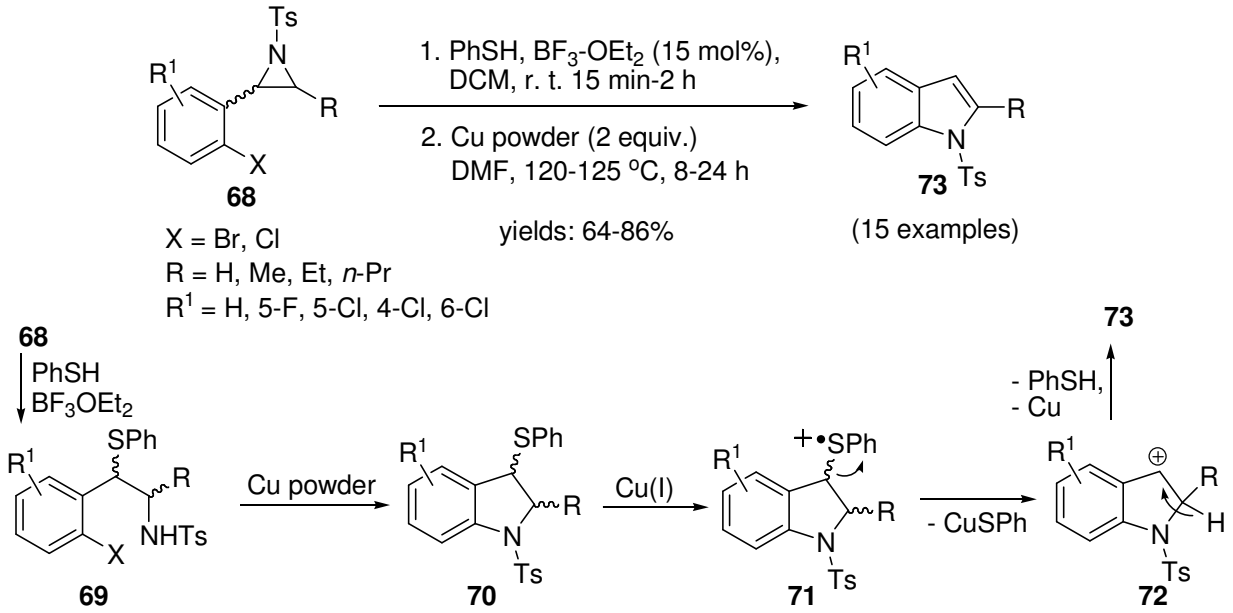
Scheme 20

Wang and coworkers have reported an efficient method for the synthesis of polyfunctionalized pyrroles **67** by a cascade of regioselective ring-opening of N-H aziridines **62** followed by [3+2]-cycloaddition with β-nitroolefins **63** under aerobic conditions (Scheme 21).[50] The reaction is assumed to proceed through an azomethine ylide, generated by a regioselective C-C bond cleavage. A copper-catalyzed regioselective [3+2]-annulation of the ylide **64** with nitroalkenes forms pyrrolidines **65**. An elimination of HNO_2 from pyrrolidines **65** followed by dehydrogenation of the resulting dihydropyrroles **66** leads to the formation of pyrroles **67**. When the reaction was carried out in an inert atmosphere, a significantly low yield of the product was obtained suggesting the necessity of oxygen for dehydrogenative aromatization step.



Scheme 21

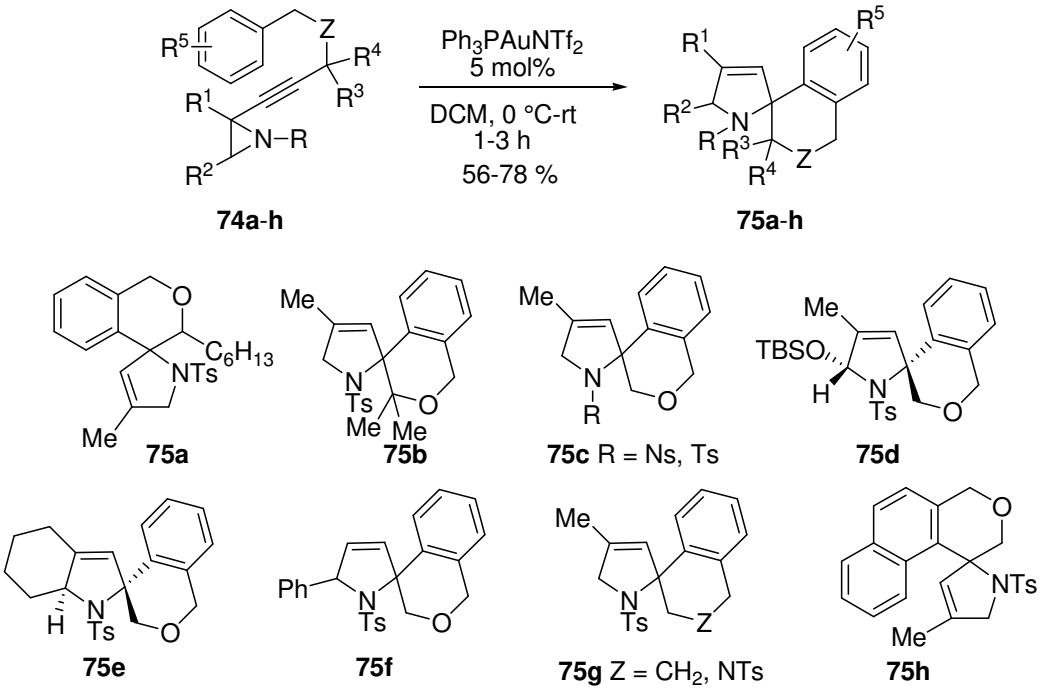
Ghorai and coworkers have reported recently a regioselective ring-opening of *N*-tosyl-substituted 2-(2-haloaryl)-3-alkylaziridines **68** with thiophenol, followed by copper-powder-mediated intramolecular cyclization/aromatization to access 2-alkylindoles in good yields (Scheme 22).[51] The reaction was also extended to 3-(2-chlorophenyl)-1-tosylaziridine-2-carboxylate to get an indole with a carboethoxy group on C-2 position. The authors proposed a Lewis acid-catalyzed S_N2-type ring-opening with thiophenol as proposed in an earlier study published same year.[52] The ring-opening product **69** undergoes C-N cyclization under influence of copper powder to give product **70**. The Cu(I)-mediated generation of radical cation **71** from product **70**, followed by its desulfonylation gives a cationic intermediate **72** which undergoes aromatization to give the final product.



Scheme 22

4.2 Synthesis of dihydropyrroles

The dihydropyrrole structural unit makes up the functional core of some natural products and pharmaceutical agents as well as serves as precursors for many *N*-heterocycles of synthetic and biological interest.[53] Gold catalysts have been applied in cascade-type reactions for the conversion of various 2-(aryloxyprop-1-ynyl)aziridines **74a**-**h** to spiro[isochroman-4,2'-pyrrolines] **75a**-**h** (Scheme 23).[54] The reaction exploited both the σ- and π-Lewis acid properties of the gold salt for a Friedel–Crafts type intramolecular rearrangement followed by the cyclization of an aminoallene intermediate. In case of more hindered aziridines, however, the cascade reaction stopped at aminoallene intermediate product stage.



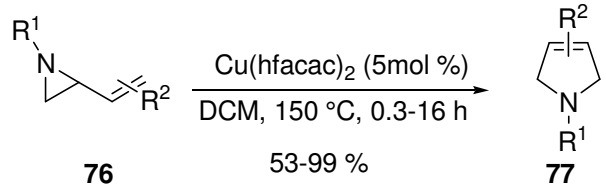
74a-**h** **75a**-**h**

75a **75b** **75c** R = Ns, Ts **75d**

75e **75f** **75g** Z = CH_2, NTs **75h**

Scheme 23

Njardarson and coworkers have reported annulation of several *N*-tosyl- and *N*-phthalimide-protected vinyl aziridines **76** to dihydropyrroles **77** in high yields using $Cu(hfacac)_2$ as a Lewis acid catalyst (Scheme 24).[55] The formation of the product has been explained through the Lewis acid-catalyzed [1,3]-sigmatropic rearrangement. Later, they applied the same methodology to reveal the stereospecificity of this arrangement.[56] The mechanistic studies concluded that several key factors impacted the rate of this catalytic reaction.[57] The reaction was significantly accelerated by using an electron-poor sulfonamide (nosyl instead of tosyl) and modestly accelerated when electron-rich olefins were employed, compared to electron-poor olefins. Moreover, a $M(hfacac)_2$ additive could accelerate the reaction, with $Zn(hfacac)_2$ providing the optimal results.

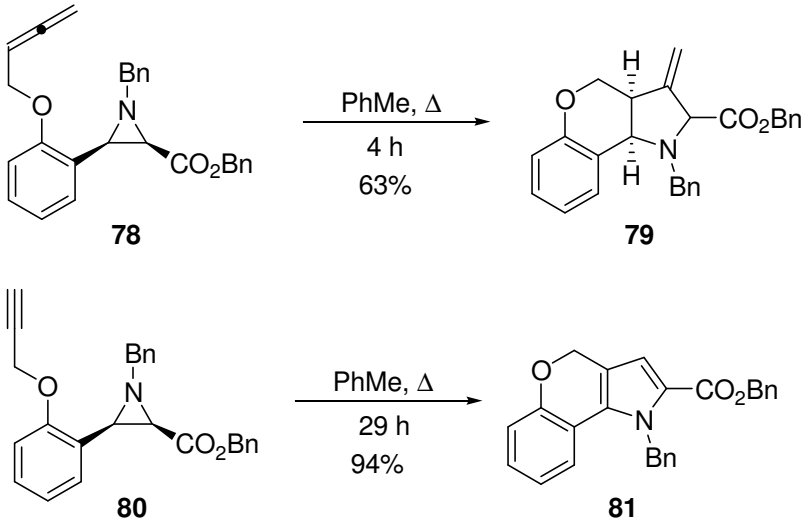


76 **77**

R^1 = Ts, Phth; R^2 = H, Ph, OTBS, CO_2Me,

Scheme 24

The reactions of aziridines with buta-2,3-dienoate are reported to form pyrrolidines and pyrroles by C-C bond cleavage and C-N bond cleavage of aziridines, respectively, followed by [3+2]-cycloaddition.[58,59] The preference for cleavage depends on substitution pattern of aziridines, and solvent used. In a recent communication, Laia and Pinho e Melo have reported the thermal reactivity of an alkyne or allene-bearing aziridines, derived from salicylaldehyde. Thermolysis of aziridines results into a pericyclic ring-opening generating azomethine ylides. The latter intermediate undergoes an intramolecular [3+2]-cycloaddition with the allene or alkyne moiety present in it to form the pyrrole derivatives.[60] The two representative examples of formation of pyrrolidine **79** and dihydropyrrole **81** from aziridines **78** and **80**, respectively, are shown in scheme (Scheme 25). According to the report, aziridine-2-carboxylates furnished higher yields in comparison to 2-benzoylaziridines. Also, the carbon-carbon triple bond was observed to be more activated dipolarophile in comparison to allene.

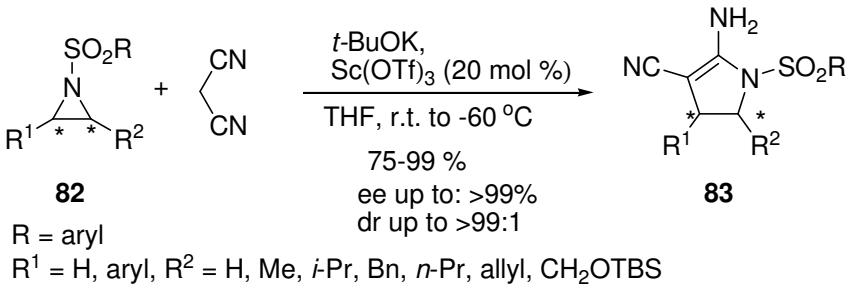


78 **79**

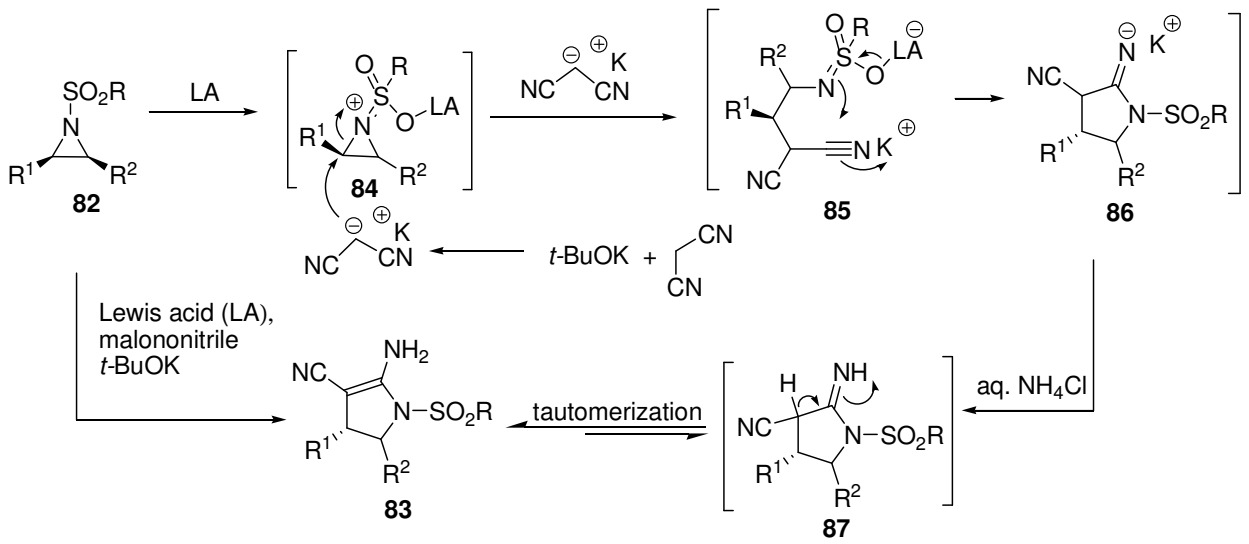
80 **81**

Scheme 25

Activated aziridines **82** containing sulfonyl, nosyl, and tosyl groups on ring-nitrogen has been reported to undergo a Lewis acid-catalyzed domino ring-opening cyclization reaction with malononitrile at low temperatures to give 4,5-dihydropyrroles **83** in excellent yields (Scheme 26).[61] The formation of products has been explained by an S_N2-type pathway. A malononitrile anion, formed after proton abstraction from malonate by *t*-BuOK, attacked the Lewis acid-activated aziridine intermediate **84** to generate another intermediate **85**, which cyclized to intermediate **86**. Subsequent protonation of intermediate **86** by aqueous NH_4Cl gave intermediate **87** which then tautomerized to dihydropyrrole products **83** (Scheme 27).[61]



Scheme 26



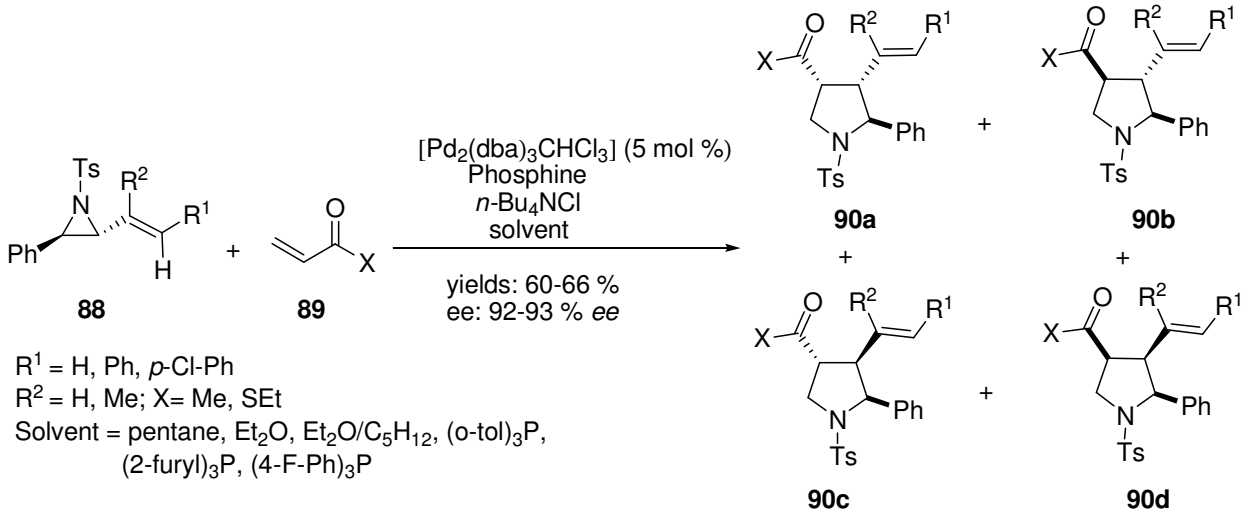
Scheme 27

4.3 Synthesis of pyrrolidines

Pyrrolidine motif occurs in alkaloids from natural resources such as nicotine, epibatidine and hygrine.[62] They are also found in the leaves of tobacco and carrots.[63] In addition, pyrrolidines are compounds of medicinal importance. The drugs like procyclidine and bepridil are pyrrolidine derivatives.[63] L-Proline and its derivatives having pyrrolidine ring are well-known chiral organocatalysts.[64] Obviously, the construction of pyrrolidine ring is of utmost importance to synthetic and medicinal organic chemists.

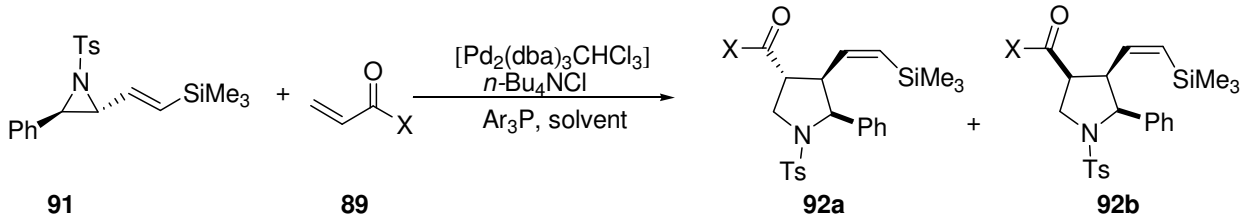
Aziridines as masked azomethine ylides are well-known precursors for synthesis of pyrrolidines by [3+2]-cycloaddition. Many research groups have reported palladium-catalyzed [3+2]-cycloaddition of aziridines leading to pyrrolidines. Lowe and coworkers have reported the reaction of *trans*-3-styryl-2-phenyl-*N*-tosylaziridines **88** with methyl vinyl ketone (X = Me) or with ethyl thioacrylate (X = SEt) **89** in the presence of a

palladium catalyst, a phosphine and an additive to give a diastereomeric mixture of pyrrolidines **90a-d** in 60-66% yields with excellent enantioselectivity (ee 92-93%) (Scheme 28).[65] The reaction was promoted by nonpolar solvents - pentane, diethyl ether or mixtures of diethyl ether/pentane, and sterically hindered phosphines; (*o*-tol)$_3$P, (2-furyl)$_3$P and (4-F-Ph)$_3$P. The presence of a styryl group on C-2 position of the aziridine furnished excellent diastereoselectivities but moderate yields. Replacing the styryl group with a 4-chlorophenyl group or 1-propenyl group lowered both the diastereoselectivity and yield. In addition to lowering the diastereoselectivity, the prop-1-enyl group switched the stereoselectivity to compound **90c** as the major diastereomer. The 2-vinyl-3-phenyl-aziridine **88** offered only two diastereomers, 2,3-*cis*-3,4-*trans*-substituted pyrrolidine **90c** as the major diastereomer and 2,3-*cis*-3,4-*cis*-substituted pyrrolidine **90d** as the minor one.



Scheme 28

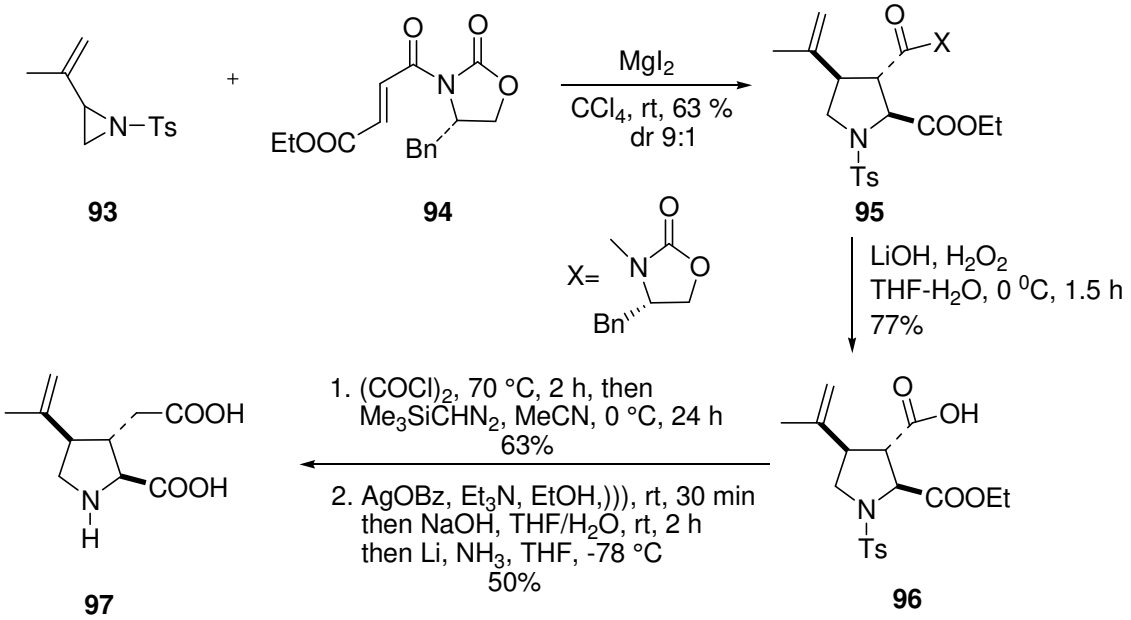
The scope of the reaction was extended to *trans*-2-(trimethylsilyl)vinyl-3-phenyl-*N*-tosylaziridine **91** to get 2,3-*cis*-3,4-*trans* substituted pyrrolidine bearing a *Z* olefin side chain **92a** as the major product.[65] Aziridine **91** also reacted with ethyl thioacrylate **89** to give the diastereomer **92a** as the major product (Scheme 29).



Solvent	X	% Yield (**92a**:**92b** *ee*) major product
(2-furyl)$_3$P, pent/TBME	Me	60 % (94:6 *ee*)
(2-furyl)$_3$P, Et$_2$O	SEt	73 % (20:80 *ee*)

Scheme 29

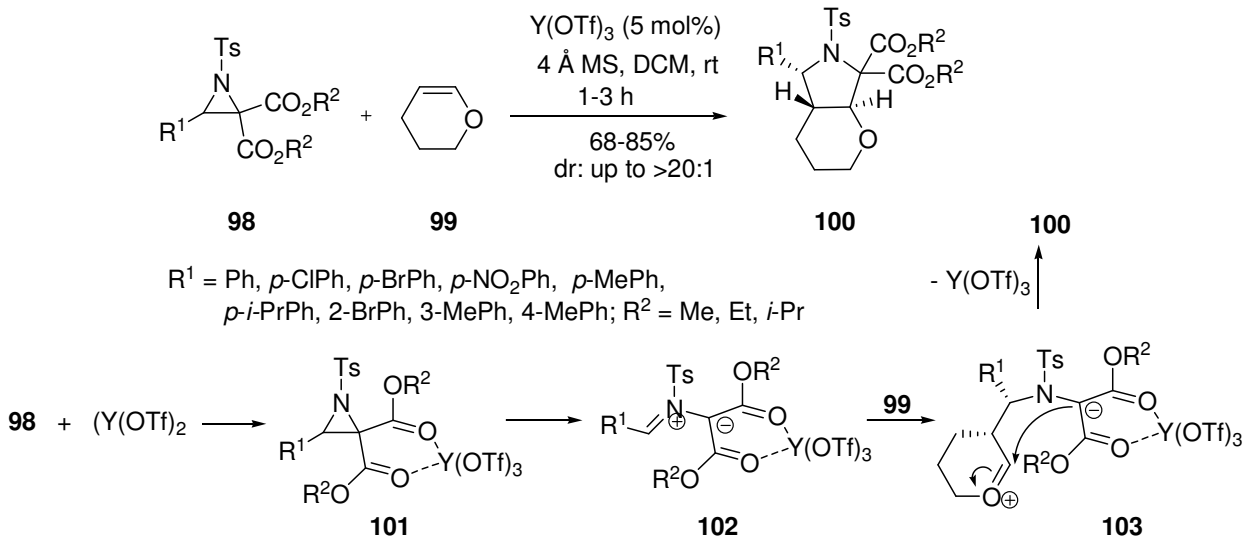
Aggarwal and coworkers have demonstrated the application of pyrrolidines, synthesized from the reaction of 2-vinylaziridine with Michael acceptors in the total synthesis of (-)-α-kainic acid and (+)-allo-kainic acid, pharmacological tools used in neurological disorders.[65,66] The reaction of vinylaziridine **93** with fumarate **94** furnished trisubstituted pyrrolidine **95** in the presence of MgI_2 (Scheme 30).[66] The latter promoted the S_N2-type ring-opening and concomitant cyclization with fumarate Michael acceptors forming 2,3,4-trisubstituted pyrrolidine **95**. The auxiliary was then removed by basic hydrolysis to afford acid **96** that was then converted into a diazoketone by treatment with oxalyl chloride and trimethylsilyldiazomethane. Sonication of this intermediate in the presence of silver benzoate promoted the Arndt-Eistert homologation to furnish the diester. The saponification of the ethyl esters and removal of the tosyl group gave (+)-allo-kainic acid **97.** Sengoden and Punniyamurthy, have employed 2-arylaziridines with free NH- or *N*-alkyl and *N*-aryl group in a highly efficient [3+2]-cycloaddition reaction with different heterocumulenes resulting into formation of 2-iminopyrrolidines, 2-iminooxazolidines, and 2-iminothiazolidines, etc. in very good yields.[67] The reaction was catalyzed by an iron catalyst ($Fe(NO_3)_2.9H_2O$) in water as a solvent.



93 **94** **95** **96** **97**

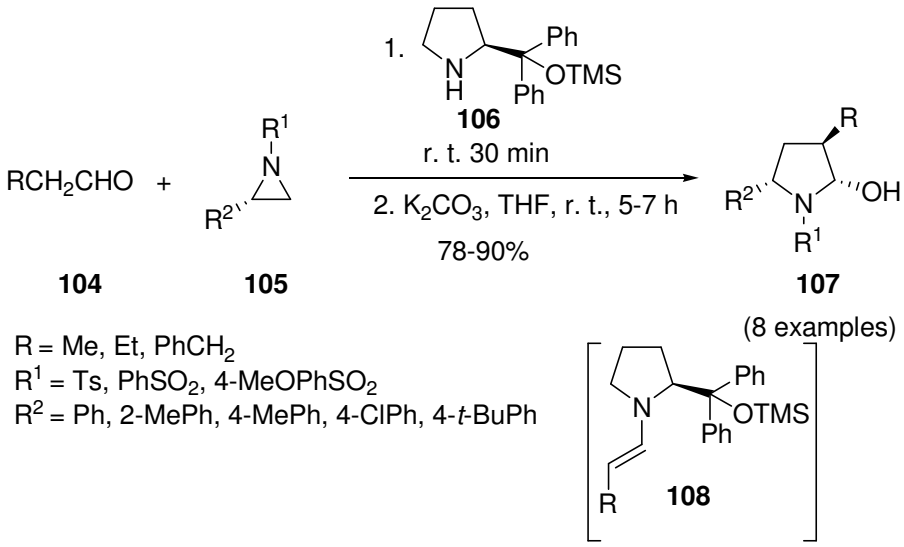
Scheme 30

Lei and coworkers have reported the Lewis acid $Y(OTf)_3$–catalyzed ring-expansion of *N*-tosyl aziridine dicarboxylates **98** with electron-rich olefin 3,4-dihydro-2*H*-pyran **99** leading to the formation of functionalized pyrrolidines **100** in good yields with moderate to excellent diastereoselectivities (Scheme 31).[68] The use of commercially available chiral ligand Pybox in the reaction offered moderate enantioselectivity (ee 57-59%) in the reactions. The selective coordination of the Lewis acid with dicarboxylates of aziridines led to the cleavage of C-C bond of aziridines **98** through intermediate **101** forming metalloazomethine ylides **102**. The ylides went into the formal [3+2] dipolar cycloaddition with electron-rich acyclic olefins or 3,4-dihydro-2*H*-pyran **99** *via* a stepwise reaction pathway involving intermediate **103** to produce substituted pyrrolidines **100**.



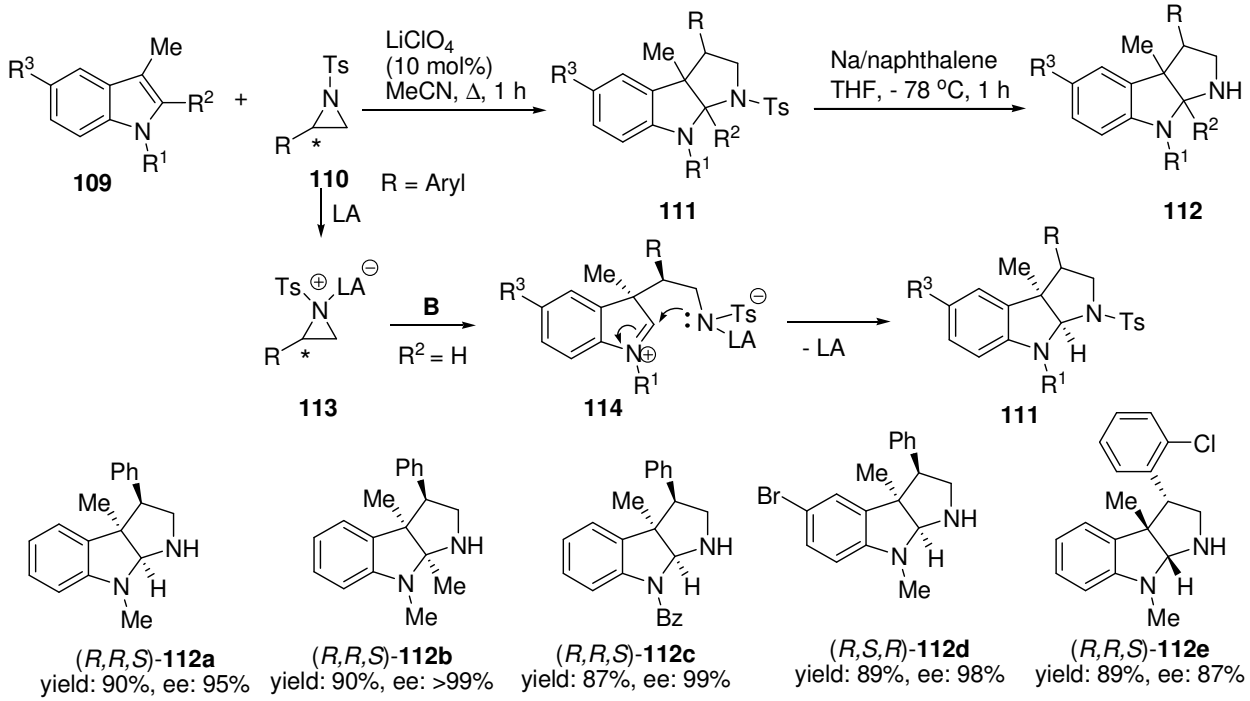
Scheme 31

Yadav and coworkers have exploited the application of organocatalysts in synthesis and reactions of aziridines.[69] Rai and Yadav have reported the reaction of enamines **108**, generated *in situ* from the reaction of aldehydes **104** and a pyrrolidine derivative **106**, with 2-arylaziridines **105** forming pyrrolidines **107** as a single diastereomer in very good yields (Scheme 32).[70] The presence of a chiral carbon in aziridines was the main driving force in formation of a single diastereomer. Usually in such aziridines, the nucleophilic attack occurs at benzylic carbon of the ring. The present study, however, revealed the nucleophilic attack at other carbon atom presumably due to bulky nucleophile (steric control). The authors have explained the C-C bond formation step between the β-carbon of enamine and methylene carbon (CH_2) of aziridine as the origin of stereoselectivity. This bond-formation took place from the *Si*-face of the *trans*-enamine because the *Re*-face was covered by the bulky $(Me_3SiO)Ph_2$ group.



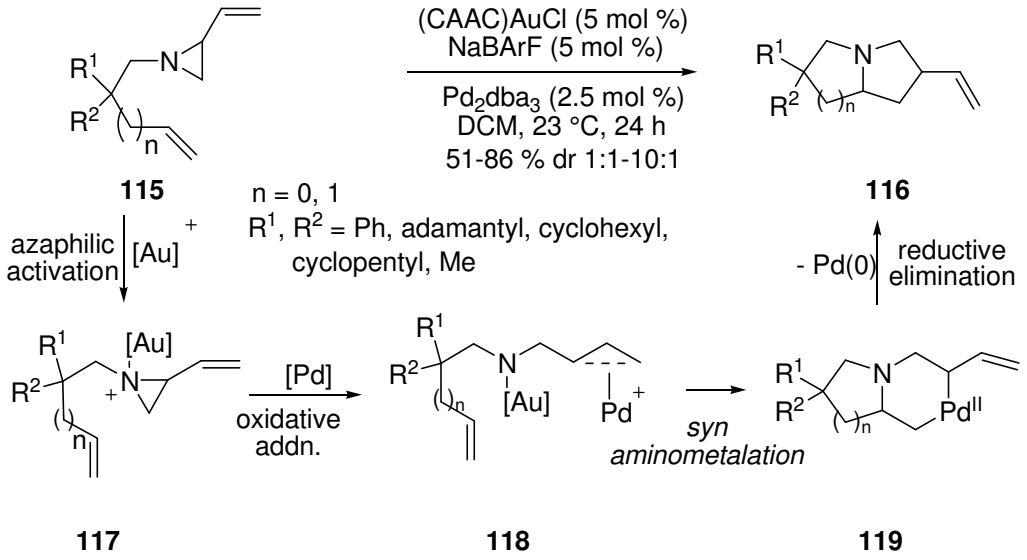
Scheme 32

More recently, Mal and coworkers have reported a one-pot method for the synthesis of indoline-fused pyrrolidines **112** (Scheme 33) by a domino ring-opening cyclization of activated aziridines **110** with indoles **109** having substituents at C-3 and other positions.[71] A Lewis acid-catalyzed S_N2-type ring-opening followed by cyclization leads to the formation of hexahydropyrrolo[2,3-*b*]indoles **109**. The latter compounds, on detosylation, afforded the corresponding products with a free NH group in excellent yields (up to 95%) with very high enantioselectivity (up to >99%). According to proposed mechanism, the Lewis acid coordinates to aziridine ring nitrogen, generating a highly reactive intermediate **113**. A S_N2-type nucleophilic attack by indole through its C-3 position on intermediate **113** leads to the formation of an iminium ion **114**. The product **111** is then formed by an intramolecular nucleophilic attack by nitrogen on iminium ion.



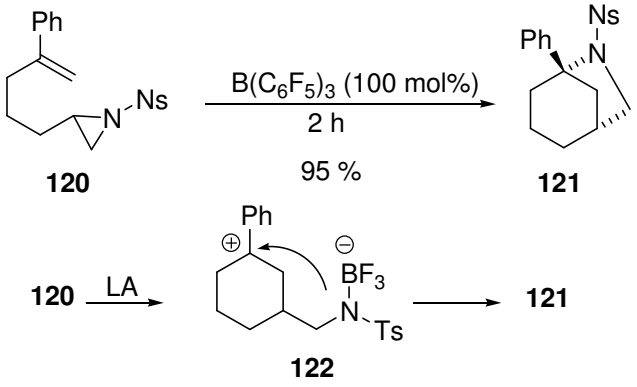
Scheme 33

Hirner and coworkers have demonstrated a palladium(0) and gold(I) Lewis acid dual-catalysis in rearrangement of vinyl aziridines **115** installing a C-C bond and C-N bond in one step to form pyrrolizidine and indolizidine products **116**.[72] According to proposed mechanism (Scheme 34), the gold complex (Lewis acid) attaches to aziridine nitrogen forming an aziridinium ion **117**. The latter undergoes a Lewis acid-promoted oxidative addition by Pd(0) resulting into formation of a palladium(II) intermediate **118**. A *syn* aminometalation in intermediate **118** released the Lewis acid and formed a palladacyclic intermediate **119**. A reductive elimination from the palladacycle led to the formation of observed product. A gold/palladium transmetalation occurred with complete retention of stereochemistry. A variety of substrates such as adamantyl (86%), cyclohexyl (56%), and cyclopentyl (51%) were tolerated in this reaction. Methyl substitution at the internal position of the tethered alkene also afforded the corresponding indolizidine in 67% yield. Increasing the olefin tether length in diphenyl vinyl aziridine provided indolizidine in good yield (74%) with an increased diastereomeric ratio (10:1). However, it was not efficient with *gem*-dimethyl group, probably due to a reduced rate of cyclization from a diminished Thorpe-Ingold effect.



Scheme 34

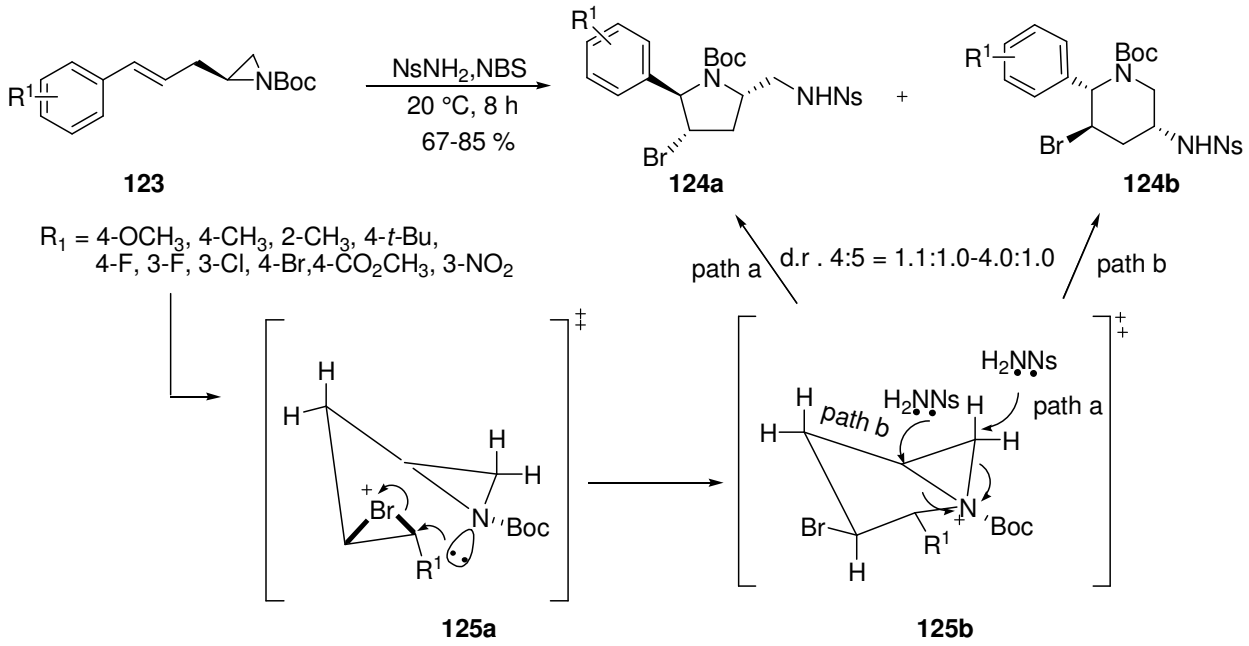
Aziridines react with π-nucleophiles to give both bicyclic and monocyclic compounds under acidic conditions as governed by *N*-substitution.[73] The *p*-nitrophenylsulfonyl (*N*-Ns)-protected aziridine **120** gave 6-azabicyclo[3.2.1]octane **121** in 95% yield in the presence of a Lewis acid $B(C_6F_5)_2$ (Scheme 35). The *N*-diphenylphosphinyl (Dpp)-protected aziridine furnished a mixture of aminomethyl-substituted cyclohexenes with Lewis acids; BF_3OEt_2 and $B(C_6F_5)_2$, respectively. The formation of product was explained via an initial attack of the Lewis acid on the olefinic linkage of the aziridine **120** leading to a carbocationic intermediate **122** that cyclized by nucleophilic attack of nitrogen on the carbocation. Azabicyclooctanes are found in natural products and pharmacologically active molecules.[74] They are useful as antitumor agents.[75] Azabicyclooctane based antagonists have been shown to decrease viability of breast cancer cells without affecting normal mammary epithelial cells as well as inhibiting tumor growth in a breast cancer xenograft model.[75]



Scheme 35

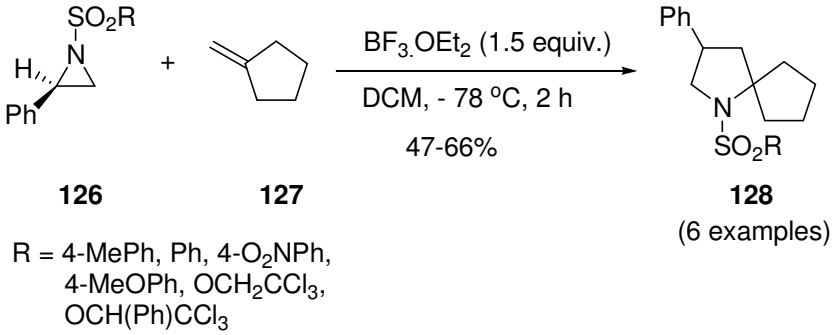
A novel *N*-bromosuccinimide-induced aminocyclization–aziridine ring-expansion cascade leading to the formation of functionalized pyrrolidines **124a** as the major products is reported.[76] The mechanism proposed by the authors involved addition of bromine on C=C of aziridines **123** by the NBS/$NsNH_2$ protocol to produce an intermediate **125a**. A subsequent reaction of aziridine in **125a** with the bromonium ion led to the generation of another intermediate **125b**, which then transformed to either pyrrolidines 1**24a** or piperidines **124b**

depending on the $NsNH_2$ attack on C-5 or C-4, respectively (Scheme 36). The substrates with electron-rich substituents afforded better regioselectivity. The best selectivity was observed in substrate bearing a *tert*-butylphenyl group. Compared to other substrates, *ortho*-CH_3 phenyl system gave slightly lower yield. This was attributed to the steric repulsion.



Scheme 36

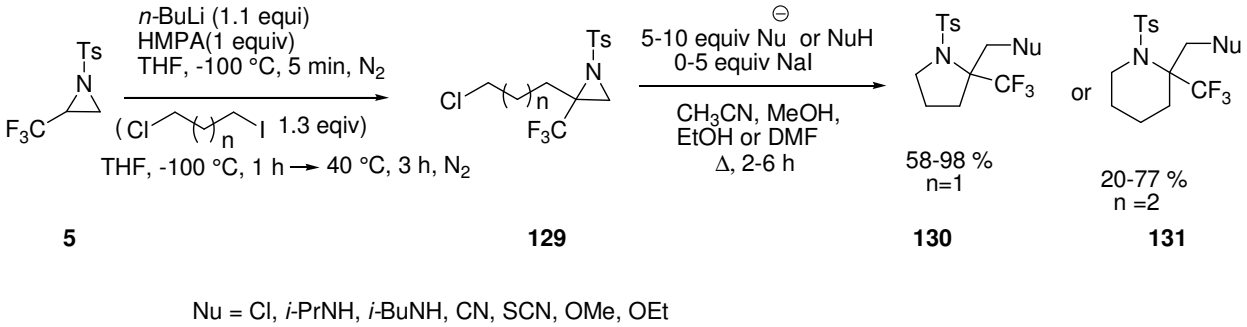
Martinand-Lurin and coworkers have reported the Lewis acid-catalyzed ring-opening and cycloaddition of *N*-sulfonylaziridines with methylenecycloalkanes such as methylenecyclobutane, methylenecyclopentane, and methylenecyclohexane to achieve the synthesis of spiro-fused pyrrolidine ring. For example, the reaction of *N*-arylsulfonylaziridines **126** with methylenecyclopentane **127** afforded pyrrolidines **128** (Scheme 37).[31] The study revealed that the substituent on nitrogen had little influence on [3+2] cycloaddition reaction that was rationalized by theoretical studies. The DFT calculations revealed that the formation of 1,3-zwitterionic species was probably the rate-determining step.



Scheme 37

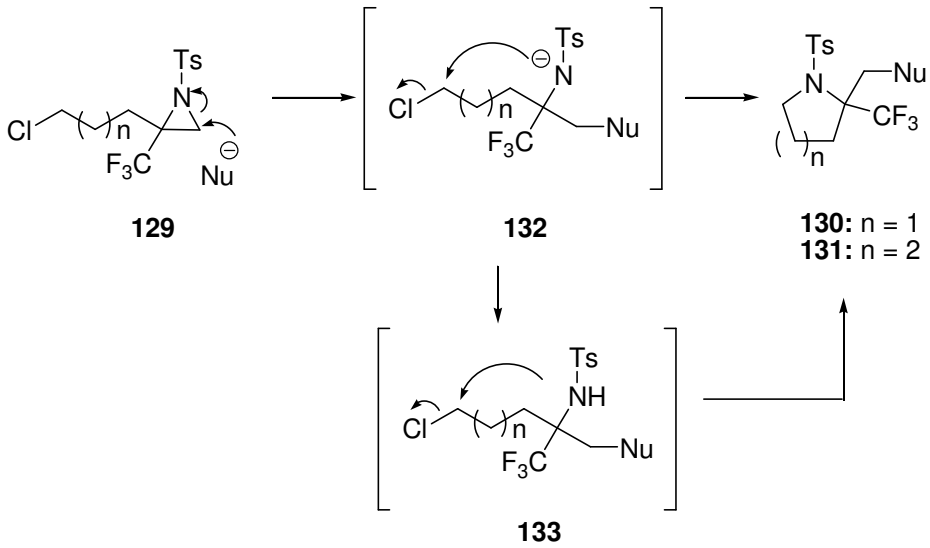
Dolfen and coworkers have reported synthesis of functionalized 2-(trifluoromethyl)pyrrolidines, from 1-tosyl-2-(trifluoromethyl)aziridine **5**.[13] **Error! Bookmark not defined.** They have extended this study to the synthesis of

piperidine and azepane as well. Deprotonation and subsequent alkylation of 1-tosyl-2-(trifluoromethyl)aziridine **5** afforded the aziridines **129**, which upon treatment with nucleophiles, triggered rearrangements of aziridines toward pyrrolidines **130** and piperidines **131** (Scheme 38). In this case, the Cl^- serves as a requisite leaving group for the ring-expansion process.



Scheme 38

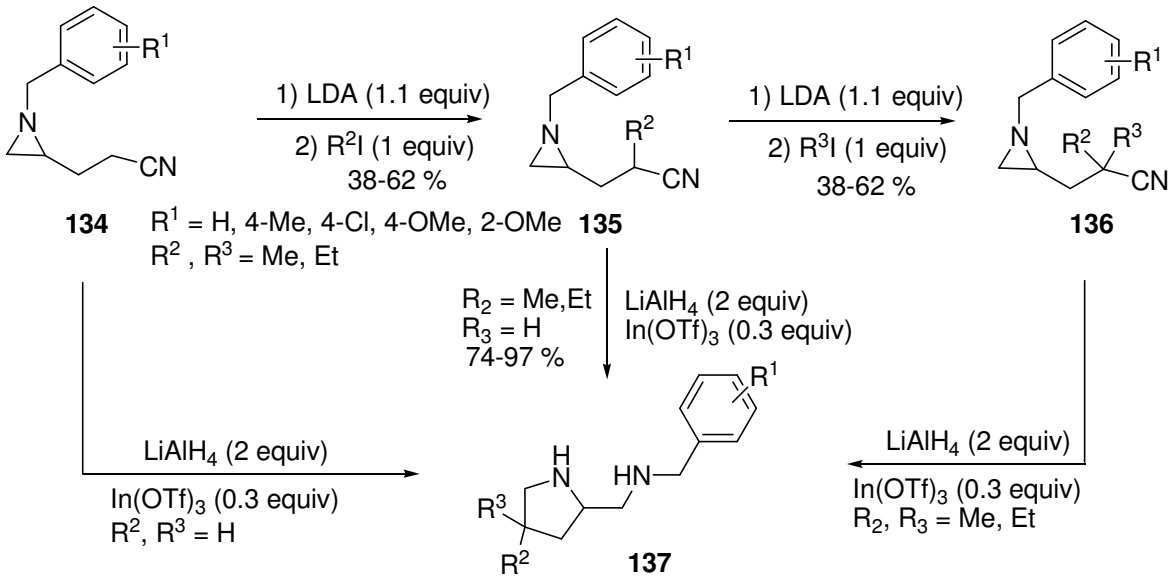
The mechanism proposed by the authors involved the ring cleavage of aziridines **129** under the action of the nucleophile to form the corresponding anions **132,** followed by either direct ring-closure or protonation to amines **133** (in protic solvents) followed by ring-closure, thus affording pyrrolidines **130** or piperidines **131** (Scheme 39). Ring rearrangements towards piperidines occurred in the presence of a higher boiling solvent dimethylformamide. Treatment of aziridine **129** (n = 2) with equimolar amounts of *i*-$PrNH_2$ and NaI afforded piperidines (see Section 5.1) while the treatment of **129** (n = 3) with 5 equiv of *i*-$PrNH_2$ or *i*-$BuNH_2$ and NaI (1 equiv) in acetonitrile afforded the 1-isoalkyl-3-tosylamino-3-(trifluoromethyl)azepanes (see Section 6.1) instead of piperidines. Addition of an equimolar amount of NaI appeared to be necessary to induce ring-closure in these cases.



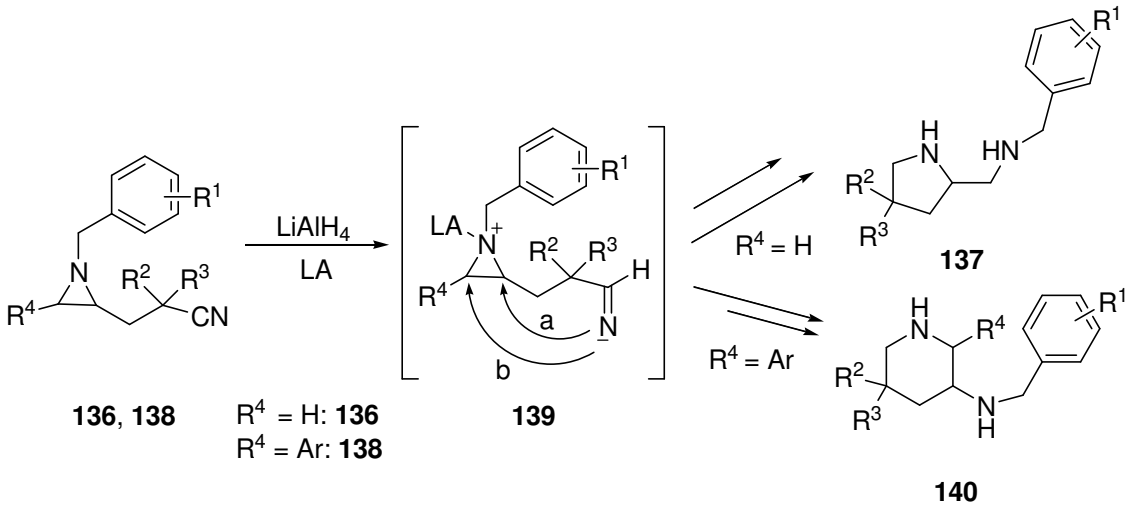
Scheme 39

Dolfen and coworkers have reported the Lewis acid-mediated regio- and stereoselective ring-opening of different 2-(2-cyanoethyl)aziridines **134** to pyrrolidines **137** either directly or via other aziridines **135** and **136** obtained by alkylation of side-chain in aziridines and **135**, respectively (Scheme 40).[77] The pyrrolidines were

obtained through a ring-opening of the aziridine moiety at the more hindered carbon atom of intermediate **139** (Route a, Scheme 41), while 3-aryl-3-(2-cyanoethyl)aziridines **138** furnished 3-aminopiperidines **140** (see section 5.1) through a regioselective ring-opening at the benzylic position of the same intermediate due to the resonance stabilization of the developing benzylic carbenium ion at the C-3 position (route b, Scheme 42). The regioselectivity of ring opening process, according to the routes a and b, could be controlled by the selection of the substituents on the aziridine core.



Scheme 40

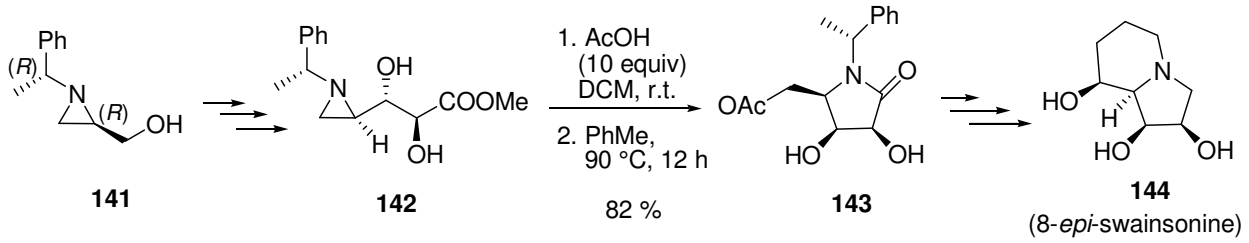


Scheme 41

4.4 Synthesis of 2-pyrrolidinones

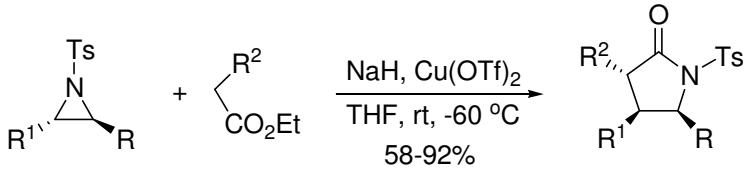
The 2-pyrrolidinones or γ-lactam ring occurs in many secondary metabolites and is pharmacophore in many biologically important natural and synthetic compounds.[78] It has also been used as a building block for the synthesis of naturally occurring compounds. Lee and coworkers have reported the synthesis of (-)-8-*epi*-swainsonine **144** that is an indolizidine derivative from a commercially available 1-(*R*)-α-methylbenzylaziridine-2-methanol **141**.[79] Aziridine-diol **142**, obtained from the aziridine **141** in three steps, undergoes a

regioselective ring-opening under influence of acetic acid in dichloromethane at room temperature. Heating the crude product mixture in toluene led to the formation of pyrrolidinone **143** (Scheme 42) bearing adjacent hydroxyl groups in *cis*-configuration. This compound was used for synthesizing (-)-8-*epi*-swainsonine **144** in a number of steps.



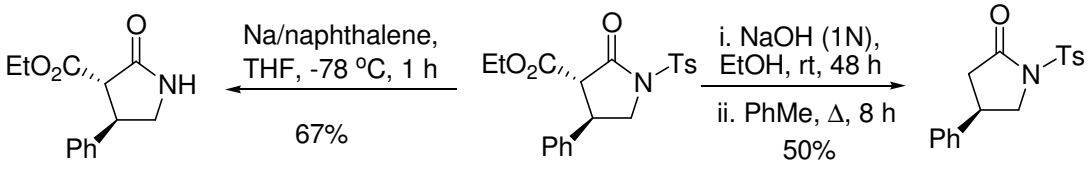
Scheme 42

The approaches for synthesis of γ-lactams using transition metals as catalysts in various reactions have made considerable progress in recent years.[80] Ghorai and Tiwari have reported the synthesis of γ-lactams from *N*-tosyl, *N*-sulfonyl and *N*-nosylaziridines by transition metal catalysis (Scheme 43).[81] The mono- and disubstituted aziridines **17** undergo an S_N2-type ring-opening under an influence of the Lewis acid in a highly enantio- and diastereoselective manner that is followed by cyclization with active methylene compounds **145** in domino fashion to afford the functionalized chiral γ-lactams **146** in good yields. It was observed that the electronic effect of the phenyl ring on *N*-tosyl-2-phenylaziridine **17** had a vital role in determining the regio- and diastereoselectivity. The authors have demonstrated the synthetic utility of such compounds by synthesizing pyrrolidinone-3-carboxylate **147** and *N*-tosylpyrrolidinone derivatives **149** by desulfonation and decarboxylation, respectively, of a pyrrolidinone **148** (Scheme 44).



a. R = Et, R^1 = Ph, R^2 = CO_2Et; b. R = *n*-Pr, R^1 = Ph, R^2 = CO_2Et;
c. R = vinyl, R^1 = Ph, R^2 = CO_2Et; d. R = allyl, R^1 = Ph, R^2 = CO_2Et;
e. R = Et, R^1 = Ph, R^2 = COMe

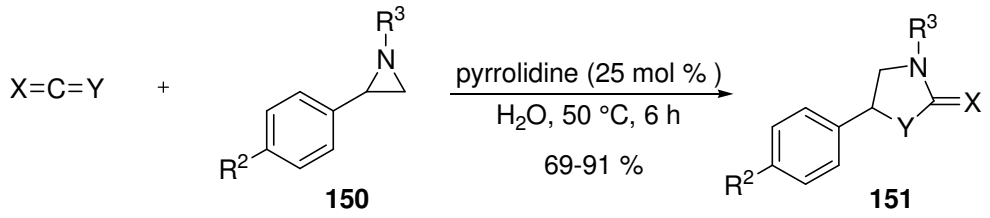
Scheme 43



Scheme 44

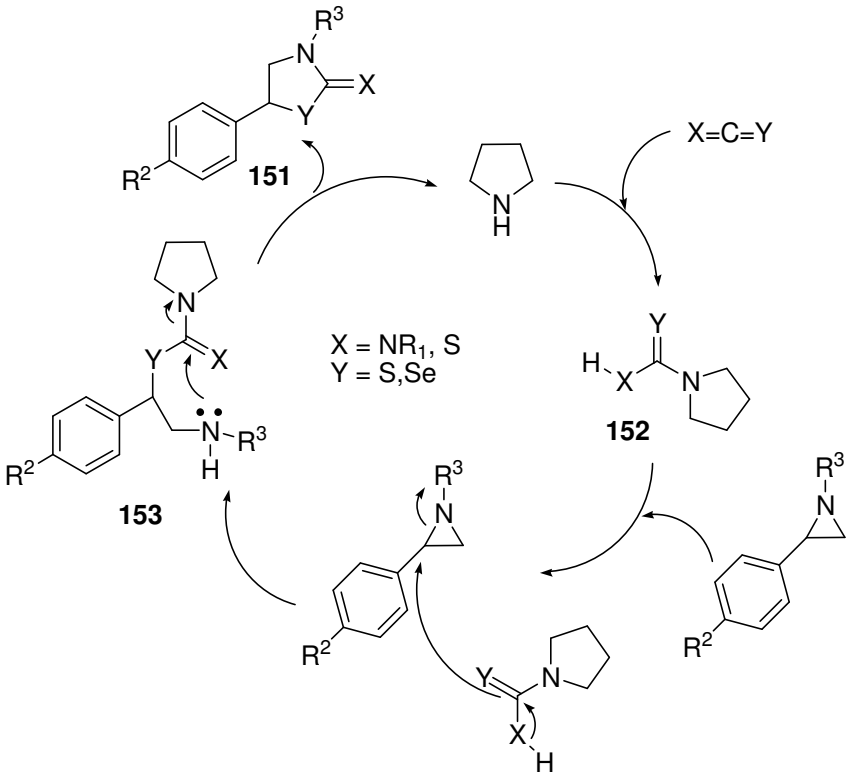
A pyrrolidine-catalyzed [3+2] cycloaddition of substituted aziridines **150** with isocyanates, isoselenocyanates and carbon disulfide forming five-membered heterocycles **151** including pyrrolidinones is

reported by Sengoden and coworkers (Scheme 45).[82] This reaction goes through a urea-type intermediate **152**, which on reaction with aziridine through an S_N2 reaction afforded product **153**. The intramolecular cyclization of the product **153** provided heterocycles **151** (Scheme 46). The same group also reported similar reactions of aziridines with heterocumulenes on water using iron(III) catalysis.[83]



a. X = NR^1, Y = S; R^2 = H, R^3 = *i*-Pr. R^1 = 2-MeO, 3-F-Ph, 4-Et-Ph, *p*-MeO-Ph, 4-Me-Ph,4-NO_2, 2,4-Me_2-Ph, 3,4-Me_2-Ph, 3,5-Me_2-Ph α–methylbenzyl, 1-naphthyl
b. X= NR^1, R^1 = 2-MeO-Ph, Y = S, R^2 = H, Br, F, MeO, Me, 2,4-Me_2, R^3 = Allyl, Bn, *n*-Bu, *C*-hex, Tosyl, *i*-Pr
c. X = NPh,N(2-MeO-Ph), N(3-Me-Ph),N(4-Cl-Ph), N(*p*-MeO-Ph) Y = Se, R^2 = H.R^3 =*i*-Pr
d. X= S, Y = S, R^2 = Br, MeO, Me, R^3 = *i*-Pr

Scheme 45

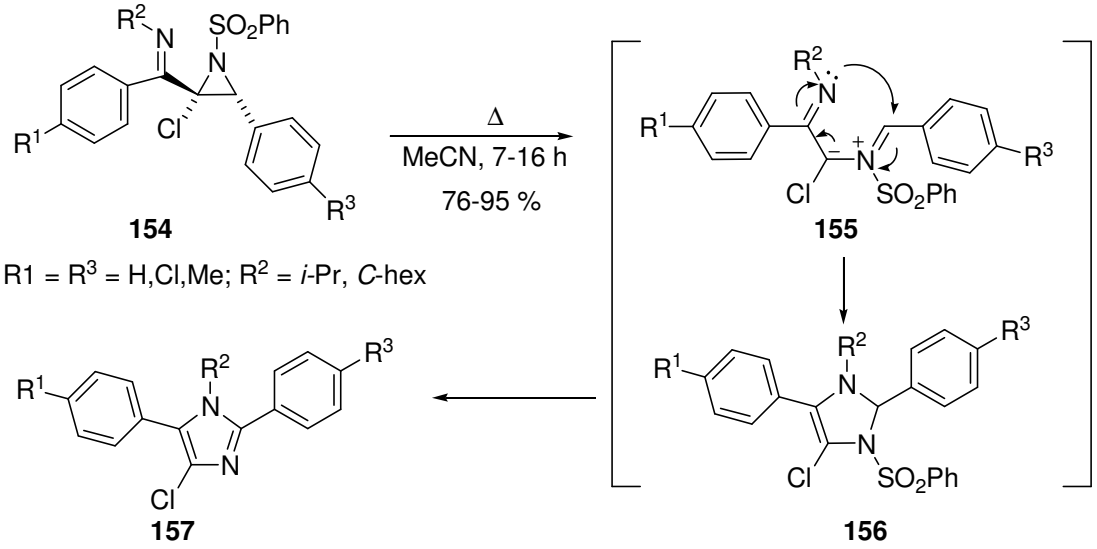


Scheme 46

4.5 Synthesis of imidazoles

The 2-chloro-2-imidoylaziridines **154**, prepared via an aza-Darzens type reaction of 3,3-dichloro-1-azaallylic anions and *N*-sulfonylaldimines, undergo a thermal rearrangement via C-C bond cleavage to produce 4-chloro-

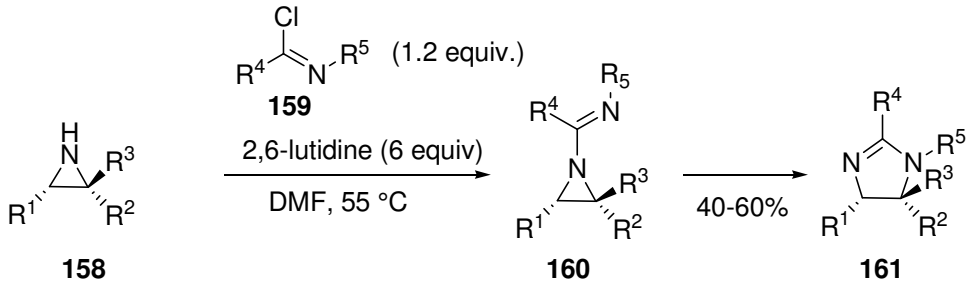
2,5-diarylimidazoles **157** on heating under reflux in acetonitrile.[84] The reaction involves the conversion of 3-aryl-2-chloro-2-imidoylaziridines **154** to azomethine ylides **155** and their subsequent 1,5-dipolar electrocyclization to imidazolines **156** (Scheme 47). The latter products, after loss of benzenesulfonate, afforded imidazoles **157**.



Scheme 47

4.6 Synthesis of imidazolines

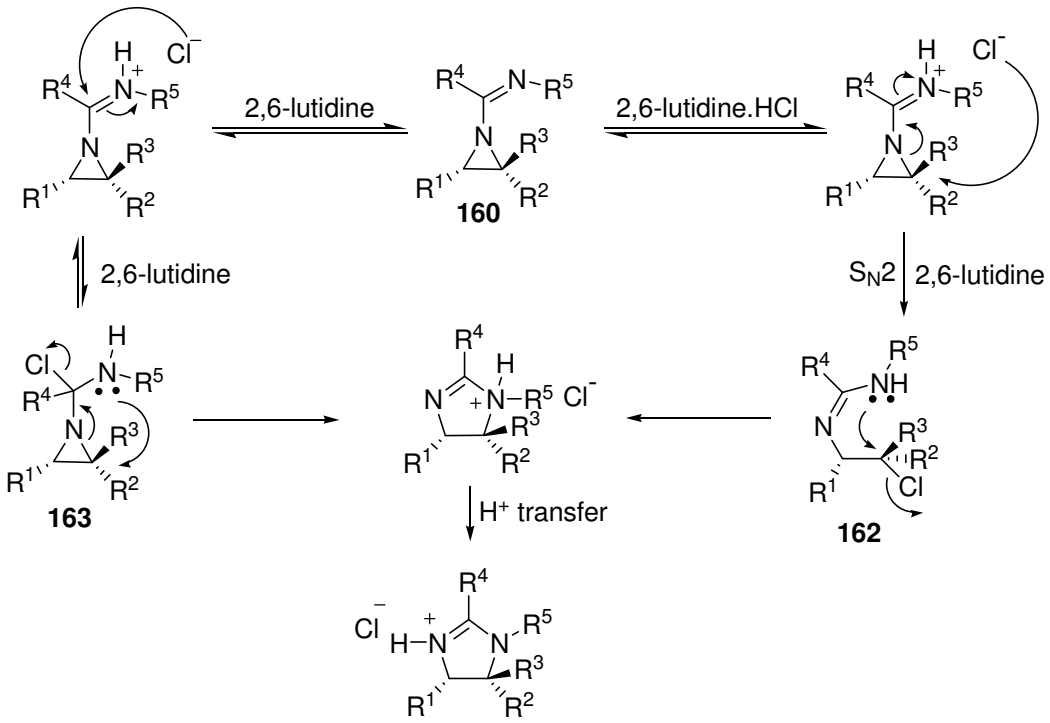
The reaction of imidoyl chlorides **159** with aziridine derivatives **158** in a single-pot Heine process have led to the synthesis of functionalized 2-imidazolines **161** (Scheme 48).[85] The reaction is highly regio- and stereospecific. The imidoyl aziridine **160** is most likely activated by the Bronsted acid, 2,6-lutidine.HCl. An S_N2 attack of the chloride ion at the C-2-position of the imidoyl aziridines **160** may form intermediate **162** that can cyclize through a second S_N2 reaction. Alternatively, the attack of the imidoyl carbon atom by the chloride ion to form product **163** and ring-expansion of the latter product by a 4-*endo*-tet ring-closure either by a S_Ni or stepwise process may lead to the formation of product (Scheme 49). There are evidences in support of both mechanisms.



a. $R^1 = R^3$ = Ph, R^2 = H; R^4 = *p*-MeO-Ph , Ph, *p*- F-Ph, *p*- NO_2-Ph, *C*-hex, Me; R^5 = CH_2Ph, Me, *p*-MeO-Ph, *C*-hex

b. R^1 = *p*-MeO-Ph, Ph, *p*- NO_2-Ph, PhCH=CH, *n*-C_6H_{13}; R^2 = H,Me, CH_2Ph; R^3 = CO_2Et, COPh, H; R^4 = Ph; R^5 = CH_2Ph

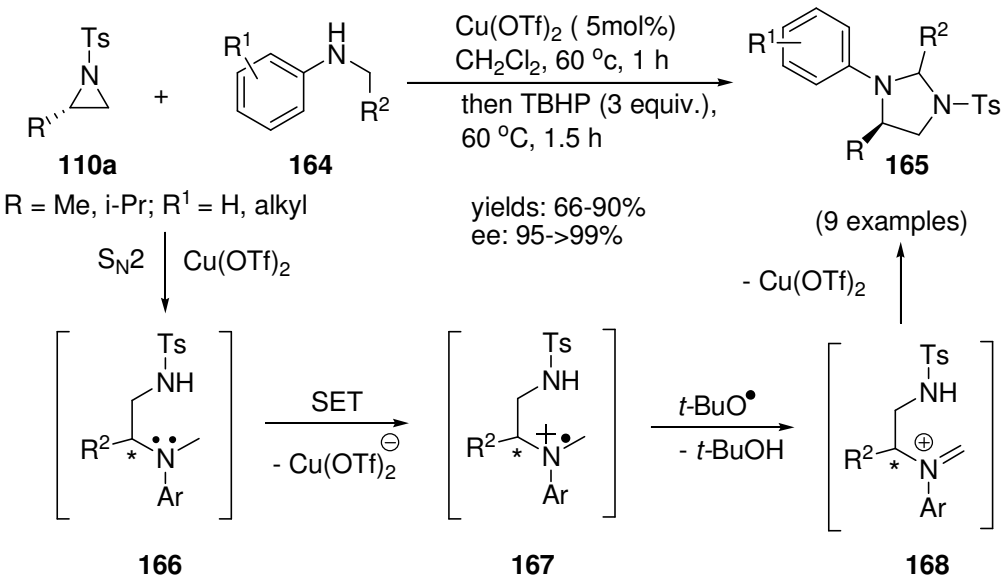
Scheme 48



Scheme 49

4.7 Synthesis of imidazolidines

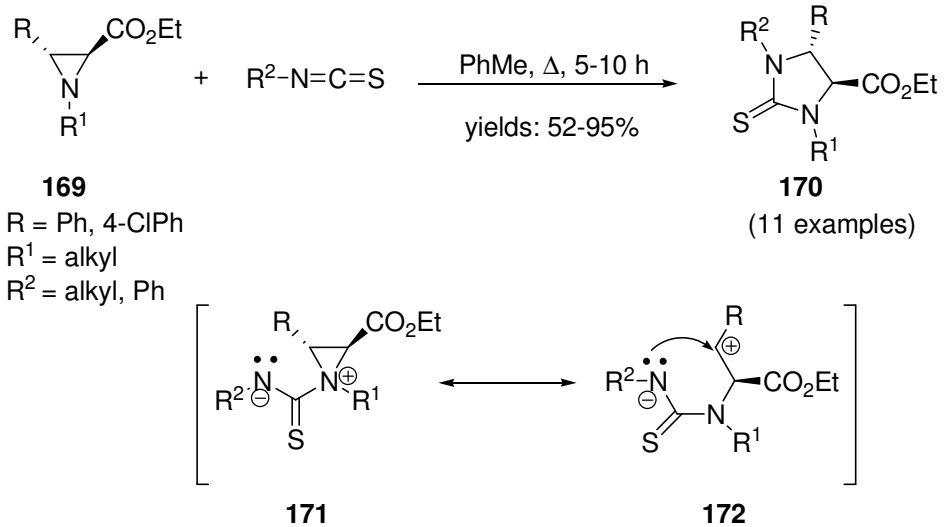
Sengoden and coworkers have reported a stereospecific copper-catalyzed domino ring-opening of activated aziridines and their sp^3 C-H functionalization with *N*-alkylanilines resulting into the formation of functionalized imidazolidines.[86] Anilines with bulky group on nitrogen such as *N*-benzylaniline and *N*-isopropylaniline failed to react with 2-phenyl-1-sulfonylaziridine due to steric hindrance. The reaction of an optically active aziridine **110a** with a series of *N*-methylanilines **164** afforded imidazolidines **165** with excellent optical purity (ee >99%) (Scheme 50). The plausible mechanism for the formation of products involves coordination of $Cu(OTf)_2$ with the nitrogen lone pair of aziridine and its subsequent ring-opening leading to the formation of intermediate **166**. Another intermediate **167** may be formed by single electron transfer reduction of $Cu(OTf)_2$ using the nitrogen lone pair of **166.** Homolysis of *N*-methyl C-H bond by *tert*-butoxy radical is suggested to form imine **168** that may cyclize to give the observed products.



Scheme 50

4.8 Synthesis of imidazolidin-2-ones, imidazolidine-2-thiones, and 2-iminoimidazolidines

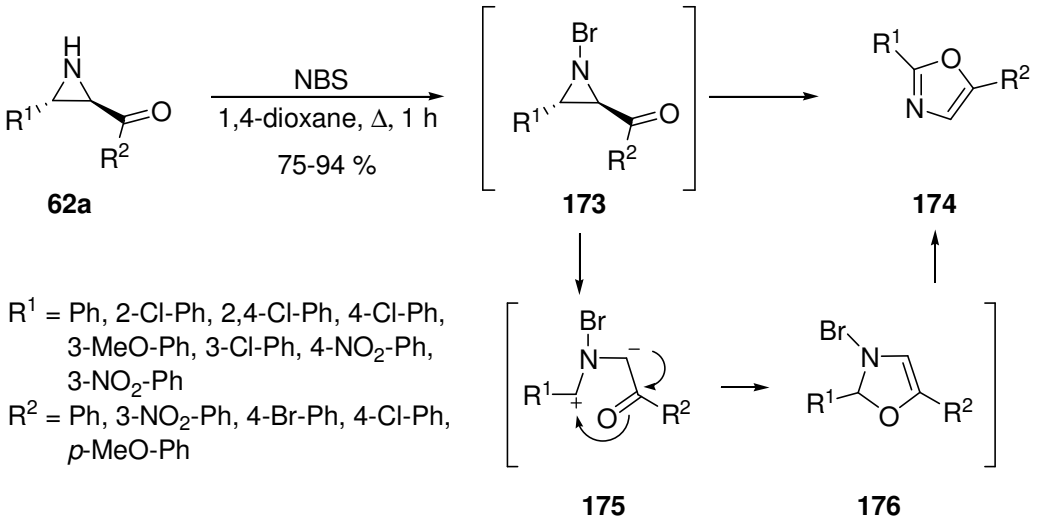
Takeda group has employed Lewis base for the ring-expansion of aziridinofullerenes with aryl isothiocyanates forming imidazolidinone-fused fullerenes.[87] A ring-expansion of *trans*-aziridine-2-carboxylates with isocyanates results into formation of imidazolidin-2-ones.[88] A similar reaction of *trans*-aziridine-2-carboxylates **169** with isothiocyanates leads to the formation of *trans*-imidazolidine-2-thiones **170** in regioselective and stereoselective manners (Scheme 51).[89] The steric and electronic effects in substrates play a role resulting into epimerization of starting aziridines in some cases and/or formation of imidazolidin-4-ones. The formation of *trans*-imidazolidine-2-thiones is suggested via a *zwitterionic* key intermediate **171**, generated by a nucleophilic attack of lone pair on aziridine nitrogen onto the electrophilic carbon of isothiocyanates. The *zwitterionic* intermediate **171** undergoes a regiospecific C-N bond cleavage to give a linear *zwitterionic* intermediate **172** that cyclizes to form the final product. The formation of 2-iminoimidazolidines is reported by a Lewis acid-catalyzed [3+2]-cycloaddition of carbodiimides with 2-substituted *N*-sulfonylaziridines and 2-phenylaziridines.[90] The reaction, catalyzed by zinc bromide, occurs in dichloromethane at room temperature.



Scheme 51

4.9 Synthesis of oxazoles

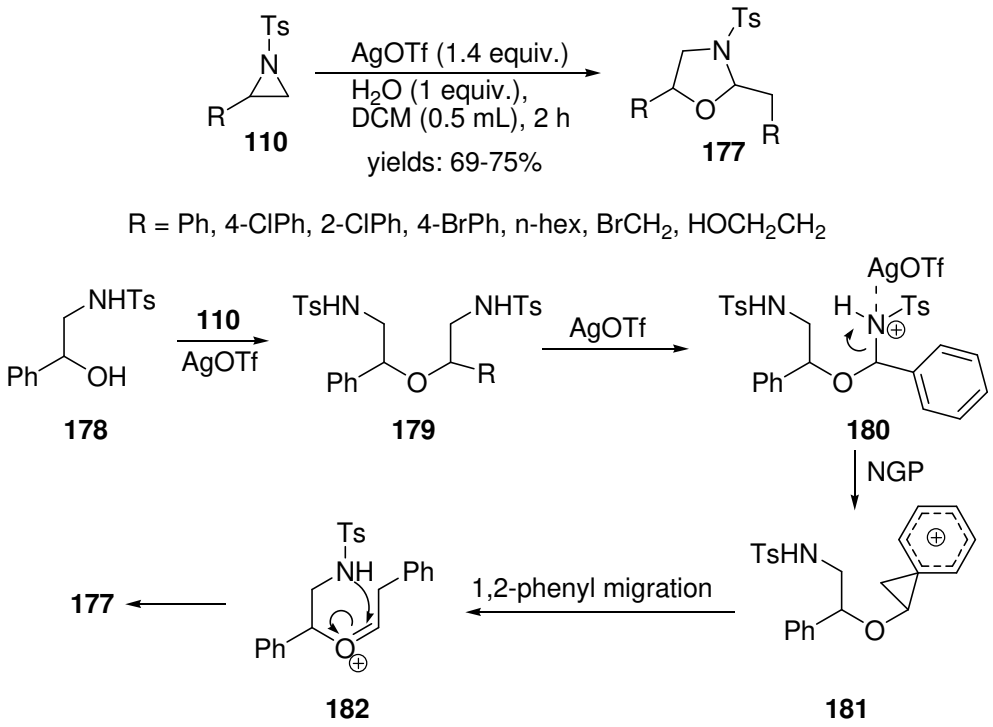
It was very recently demonstrated that N-H ketoaziridines **62a** could be rearranged to 2,5-diaryloxazoles **174** via an *in situ* formation of *N*-bromoketoaziridines **173** in the presence of *N*-bromosuccinimide.[91] Under thermal conditions, *N*-bromo substituted ketoaziridines **173** are converted into an azomethine ylide **175** via C-C bond cleavage that is followed by the ring-closure of the latter leading to a cyclized intermediate **176**, which then undergoes thermal elimination of hydrogen bromide to produce oxazoles **174** (Scheme 52). The authors have also reported that the presence of electron-withdrawing R^1 groups and electron-donating R^2 groups favored the formation of azomethine ylide. It was also observed that the bromine group on the aziridine nitrogen had a stabilizing effect on the formation of azomethine ylide and was crucial for the thermal C-C bond cleavage of the ketoaziridine ring.



Scheme 52

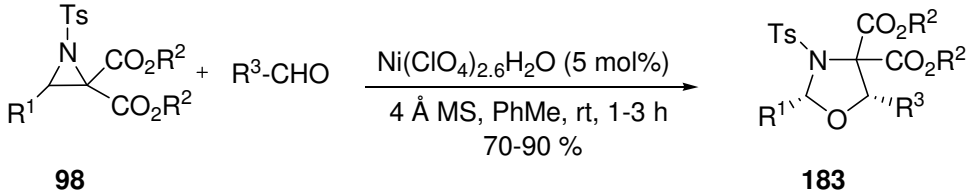
4.10 Synthesis of oxazolidines

A tandem ring opening/cyclization of aziridines leads to the formation of oxazolidine derivatives.[92] A silver triflate, AgOTf-catalyzed ring-opening of *N*-tosyl-2-arylaziridines **110** with water and subsequent reaction of the ring-opened product with another molecule of aziridine gives the product **177** (Scheme 53). 2-(2-Chlorophenyl)/alkyl-1-tosylaziridines failed to afford the desired oxazolidine products. The ring opens by a nucleophilic attack of water at the benzylic ring carbon (C-2). The resulting 1-aryl-2-aminoethanol **178** reacts with aziridine again by a nucleophilic attack of its hydroxyl group on benzylic carbon of the aziridine generating a bis-aminoether **179**. The latter compound, in the presence of AgOTf, gives another intermediate **180** that is stabilized to intermediate **181** by neighboring group participation of aromatic ring. A 1,2-phenyl migration in intermediate **181** forming another intermediate **182** followed by cyclization forms the final product.



Scheme 53

The Lewis acid-catalyzed [3+2]-cycloaddition of carbonyl compounds to aziridines has been investigated by many researchers recently. Wu and coworkers demonstrated an efficient [3+2]-cycloaddition of aldehydes and azomethine ylides, obtained from a Lewis acid catalyzed C–C bond cleavage of *N*-tosylaziridines **98** under mild conditions, providing highly substituted 1,3-oxazolidines **183** with high diastereo- and regioselectivity (Scheme 54).[93] It is worthy to note that moderate enantioselectivity (60% ee) is achieved by the use of Pybox as a chiral ligand. In yet another recent report, Yang and coworkers have reported the BF_3-OEt_2-catalyzed cycloaddition of *N*-sulfonylaziridinofullerenes with various aromatic-, heteroaromatic-, and aliphatic aldehydes, and some ketones forming fullerooxazolidines.[94] The reaction of ethyl formate, however, led to elimination of ethoxy group in an unprecedented manner forming fullerooxazole bearing no substituent at C-2 position of oxazole ring.



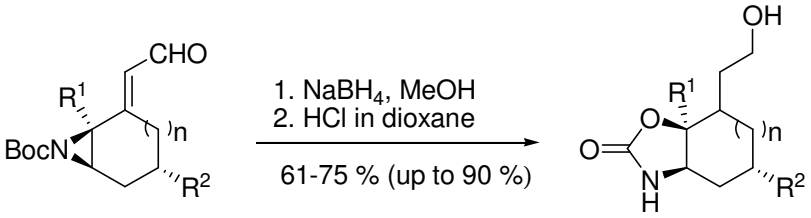
R^1 = 4-NO_2-Ph, 4-Cl-Ph, 4-Br-Ph, 4-Me-Ph 4-*i*-Pr-Ph, 3-Me-Ph, 2-Br-Ph, Ph
R^2 = Me, Et, *i*-Pr
R^3 = Ph, 3-Me-Ph, 4-MeO-Ph, 4-Cl-Ph,

Scheme 54

4.11 Synthesis of oxazolidin-2-ones and oxazolidine-2-thiones

Oxazolidinones are useful as protected vicinal amino alcohols and as Evans auxiliaries.[95] They have been reported to exhibit biological activity, especially optically active oxazolidinones.[96] Some oxazolidinones inhibit bacterial protein synthesis by preventing binding of the aminoacyl-tRNA to the A site of the ribosome.[97] For example, Linezolid (LZD) (Zyvox) has gained wide use clinically for treating infections caused by gram-positive pathogens.[98] In that regard, many protocols for synthesizing oxazolidinones have been developed, including the use of aziridines.

N-Boc-protected aziridines undergo an intramolecular Lewis acid-catalyzed reaction to give oxazolidinones.[99] The reaction involves reduction of the aziridine aldehydes **184** with sodium borohydride followed by treatment with HCl in dioxane to furnish a single regioisomer of oxazolidinones **185** (Scheme 55).[16] The products were obtained in good yields with high enantiomeric excess with retention of configuration.

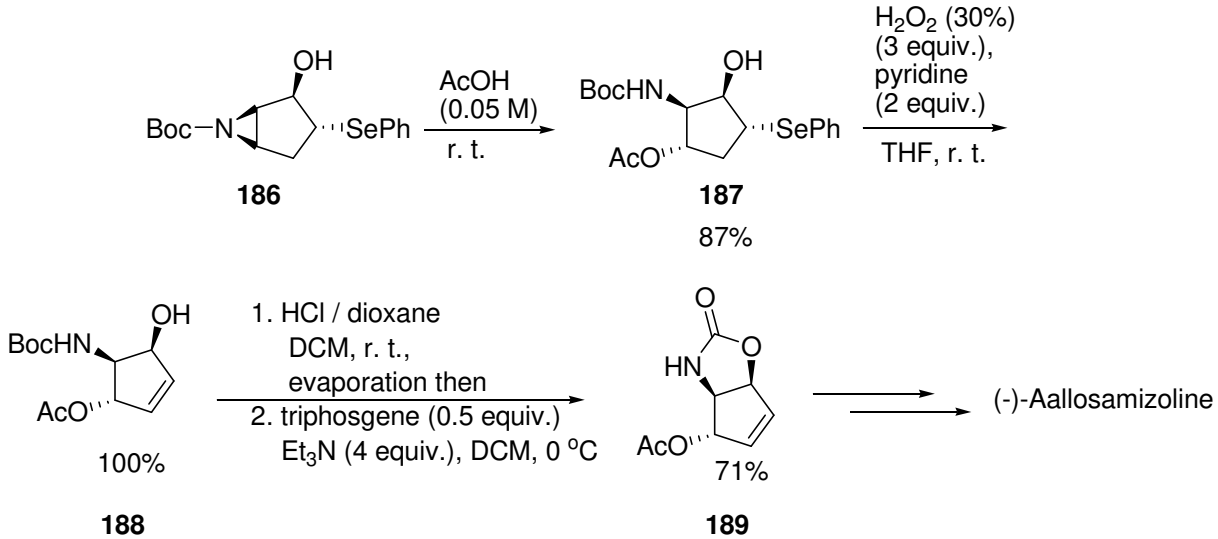


184 **185**

R^1 = pentyl, Me
R^2 = H,
n = 0, 1

Scheme 55

Hamada group has also synthesized an oxazolidinone **189** from an *N*-boc-protected aziridine **186** (Scheme 56).[15Error! Bookmark not defined.] The oxazolidinone was then utilized to access a key intermediate required for the synthesis of (-)-allosamizoline, an aglycon unit of the potent chitinase inhibitor allosamidin. The aziridine ring-opening with acetic acid leading to formation of cyclopentane **187** followed by creation of an olefinic system **188** in the cyclopentane ring, and cyclization led to an entry into an oxazolidinone ring system.

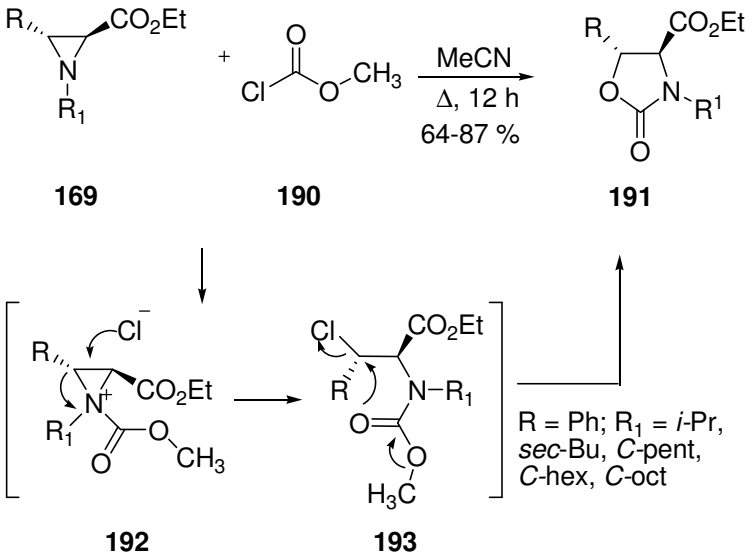


186 **187** 87%

100% **188** 71% **189**

Scheme 56

Very recently Kaabi and coworkers reported the regio- and stereoselective transformation of *trans*-*N*-alkylaziridine-2-carboxylates **169** to the corresponding *trans*-1,3-oxazolidin-2-ones **191** in good yields (Scheme 57).[100] It is noteworthy to mention that the reaction conditions and *N*-substituent had little influence on the course of the reaction. Upon reaction with methylchloroformate **190**, a regioselective nucleophilic ring-opening by the attack of *in situ* liberated chloride anion on the benzylic carbon of the electrophilic aziridinium ion **192** formed the chloride intermediates **193**. This compound could be cyclized to *trans*-*N*-alkyl-1,3-oxazolidin-2-ones **191** through an intramolecular nucleophilic attack of the carbonyl oxygen atom and subsequent displacement of chloride ion.



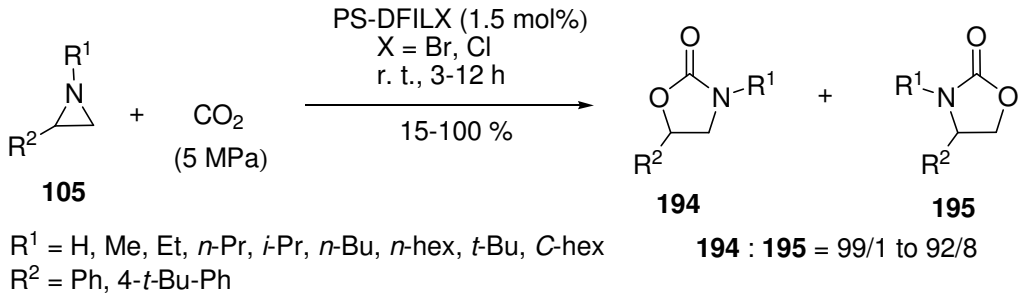
169 **190** **191**

192 **193**

Scheme 57

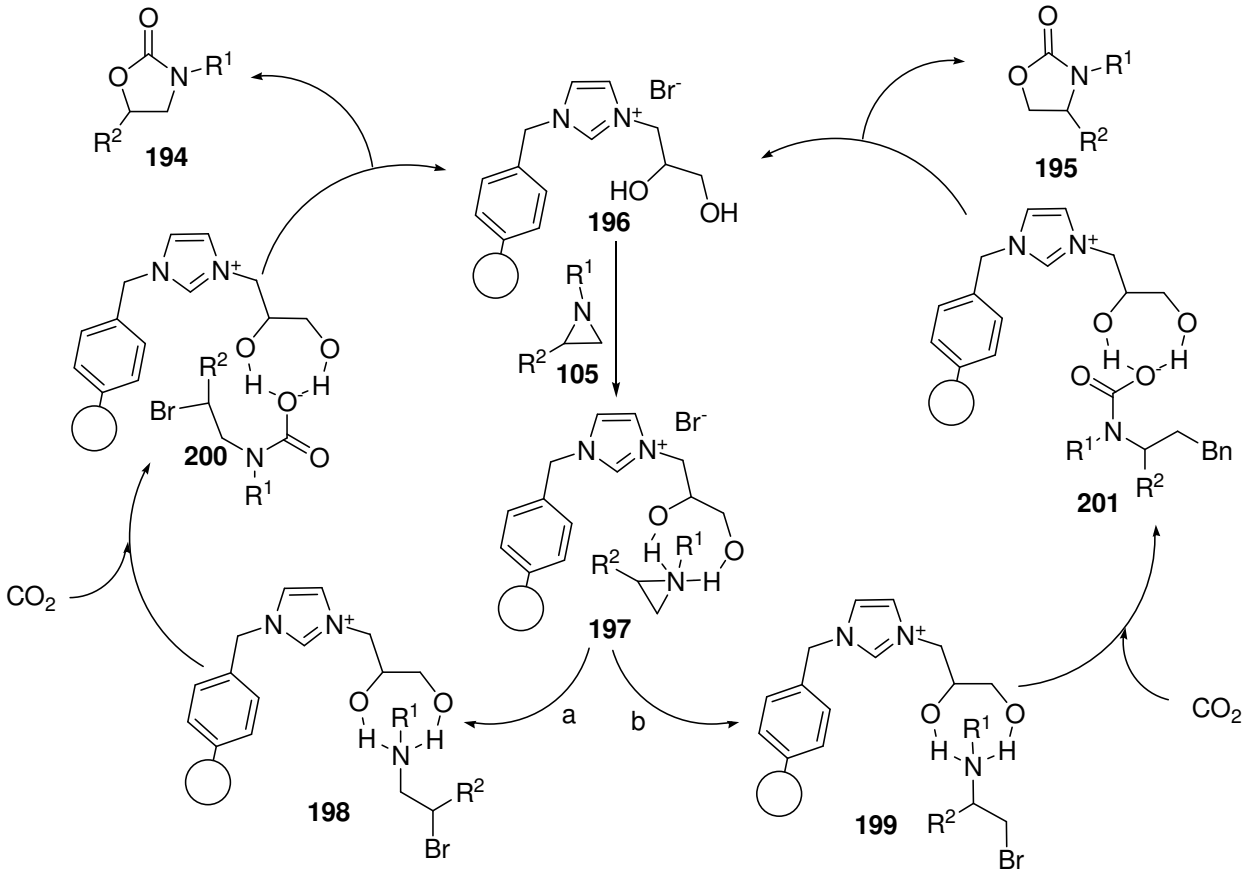
A commercial approach that is very efficient as well to construct oxazolidinone ring from aziridine is the insertion of CO_2 molecule in aziridine ring. A number of catalysts are known in literature to ease the reaction. Some of these involve quaternary ammonium bromide-functionalized polyethylene glycol,[101] zirconyl chloride,[102] alkali metal halide,[103] Lewis basic ionic liquids,[104] protic onium salt,[105] polyethylene glycol-functionalized phosphonium salts,[106] DBN,[107] polyethylene glycol functionalized ionic liquids,[108] 2,2',2''-terpyridine,[109] and mesoporous zirconium phosphonates.[110] A very few selected examples are described in succeeding paragraphs.

An insertion of CO_2 in aziridine ring of NH-aziridine or 1-alkyl-2-arylaziridines **105** in the presence of polymer-supported diol-functionalized ionic liquids (PS-DFILXs) as catalysts gives 4- and 5-aryl-2-oxazolidinones **194** and **195** (Scheme 58).[111] The reaction offers high conversions with excellent regioselectivities under mild solvent-free conditions. The yield of the major product **194** increases with an increase in size of alkyl chain on nitrogen atom of aziridine. On the contrary, the increase in bulkiness of the *N*-substitution (*t*-butyl, *C*-hex) tends to lower yields. However, the problem of steric hindrance could be overcome by increasing the temperature of reaction.



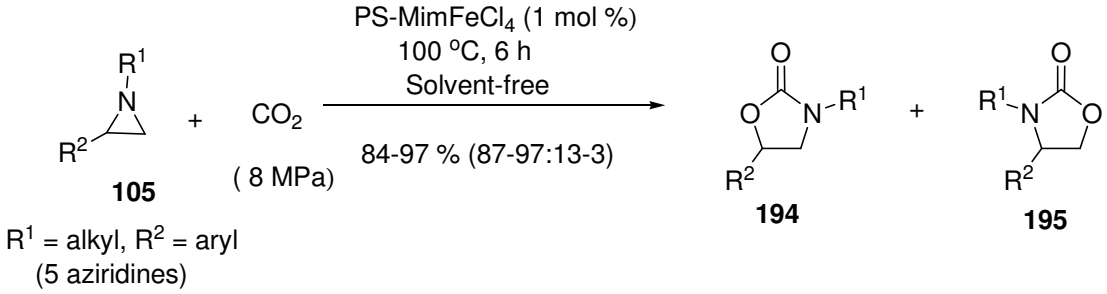
Scheme 58

The reaction is believed to be initiated by activation of the aziridine ring through hydrogen bonding between the hydroxyl groups of the polymer-supported diol-functionalized ionic liquid **196** and the *N*- atom of aziridines **105** to form an intermediate **197**. This tends to polarize the C-N bond of aziridines, resulting in ring-opening via two pathways, a or b to give intermediates **198** and **199**, respectively. A subsequent cyclization leads to the formation of 2-oxazolidinones **194** and **195** and regeneration of the catalyst. The major product **194** could originate from ring- opening of the aziridine at the most hindered carbon, path a,[112] whereas the minor product **195** may be formed from the less hindered position, path b. The hydroxyl groups on vicinal carbon atom of the ionic liquid do not only initiate activation of the aziridine, but also stabilize intermediates **200** and **201** during the reaction (Scheme 59).



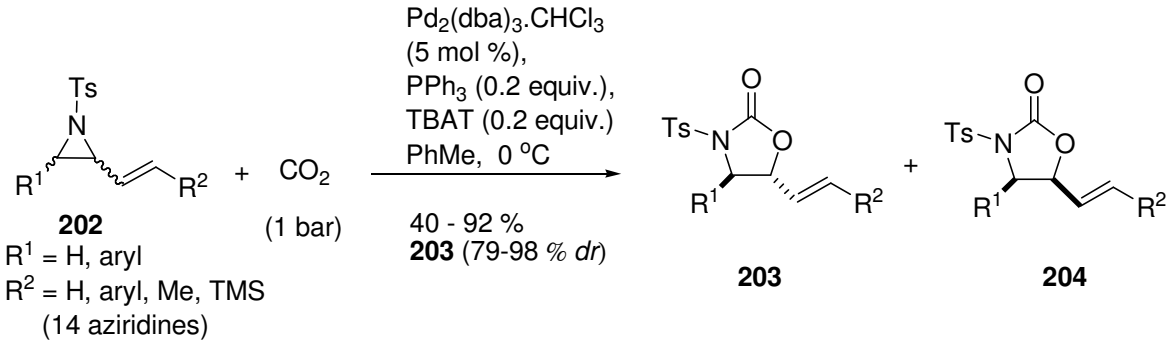
Scheme 59

A similar carbonylation reaction of unactivated aziridines **105** was reported by Gao *et al* whereby polystyrene-supported Lewis acid Fe(III) ionic liquid catalyst was used.[113] Oxazolidinones **194** and **195** were selectively formed in good to excellent yields as well as high regioselectivities (Scheme 60).



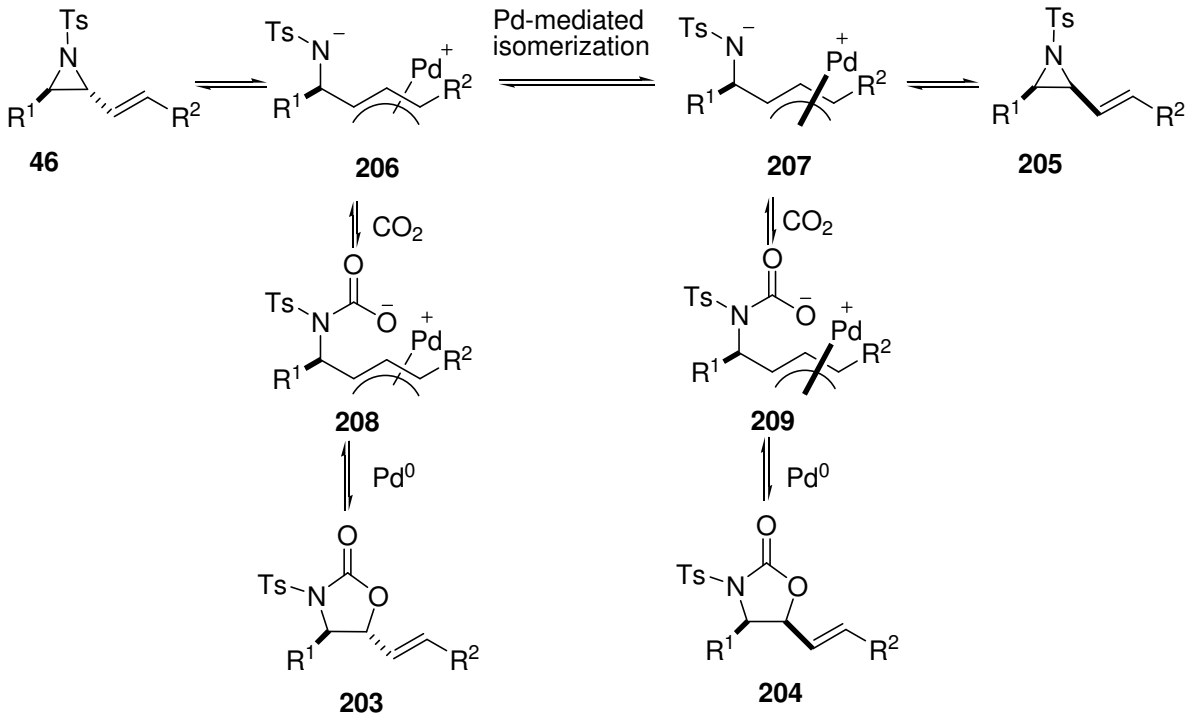
Scheme 60

2-Vinyl aziridines **202** react with carbon dioxide (1 bar) in the presence of triphenylphosphine (PPh_3) and palladium catalyst to furnish 5-vinyloxazolidinones **203** and **204** with no erosion in enantio-purity (Scheme 61).[114] Tetrabutylammonium difluorotriphenylsilicate adduct (TBAT) was required to hinder ion-pairing between the amide ion and the cationic Pd, thus increasing the yields of the products **203** and **204**. The process is both regio- and stereoselective. Both the electron-donating and electron-withdrawing *para* substituents on the *trans*-aziridine core were tolerated. However, alkyl groups on the vinyl moiety resulted in lower yields.



Scheme 61

The mechanism involves the reaction of Pd(0) complex with *trans*-*E*-vinylaziridines **46** or *cis*-*E*-vinylaziridines **205** to form a π-allyl palladium intermediate **206** which then isomerizes to another complex **207**. The intermediates **206** and **207** are then captured by carbon dioxide to afford the intermediates **208** and **209**, respectively, which cyclize to the corresponding 5-vinyloxazolidinones **203** and **204** (Scheme 62).[114]

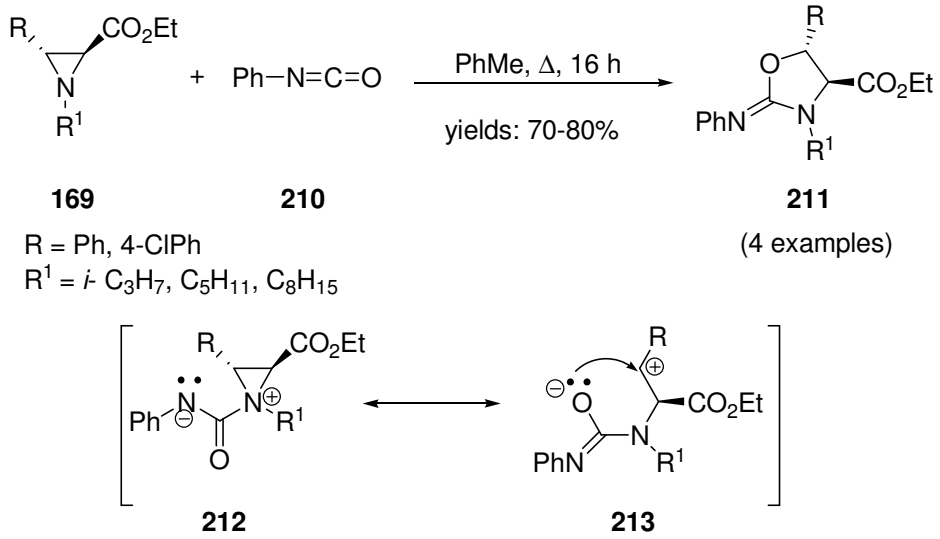


Scheme 62

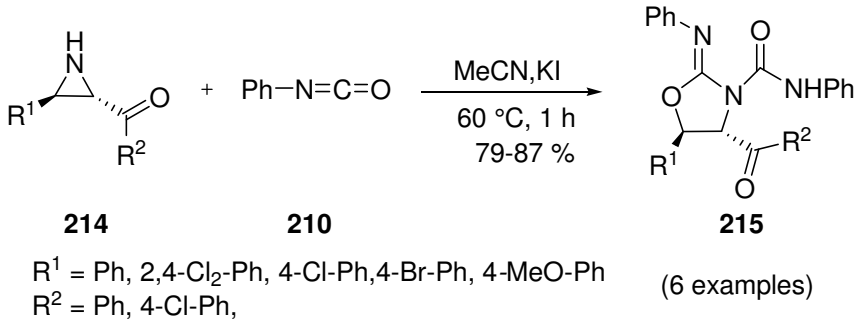
Although the Lewis acid-catalyzed 1,3-dipolar cycloadditions are more common Takeda and coworkers have reported a Lewis base-catalyzed fixation of carbon dioxide with *N*-arylsulfonyl-substituted aziridinofullerenes to synthesize oxazolidinone-fused fullerenes.[87] This group has used 10 mol% of tricyclohexylphosphine as a catalyst. The presence of phenylsulfonyl group gave 85% yield of the product. Introducing a nitro group at C-4 of phenyl ring drastically reduced the yield to 23% whereas a 4-methoxy group on same position yielded 70% of the product. The *N*-methylsulfonyl-substituted aziridinofullerene also afforded the product in 70% yield.

The reaction of *N*-alkyl-3-arylaziridine-2-carboxylates **169** with phenylisocyanate **210** occurs without any catalyst leading to the formation of *trans*-oxazolidin-2-imines **211**.[88] The reaction proceeds by nucleophilic attack of aziridine ring nitrogen on carbonyl carbon of the isocyanate to form an intermediate **212** that cleaves at N-C3 bond of the aziridine ring forming another intermediate **213**. An intramolecular nucleophilic attack by oxygen atom lone pair on enolate leads to cyclization forming the final product (Scheme 63).

The first stereo- and regioselective conversion of keto-aziridines **214** to 2-iminooxazolidines **215** using phenylisocyanate **210** in the presence of potassium iodide is reported (Scheme 64).[115] For the reaction in presence of potassium iodide, authors have proposed that the presence of an aryl moiety on C-3 and a carbamoyl moiety on ring-nitrogen develops a partial positive charge on C-3 making it an appropriate site for nucleophilic attack by iodide ion for ring cleavage. The ring cleavage is followed by an attack of oxygen to the iodide bearing carbon to give the oxazolidine.



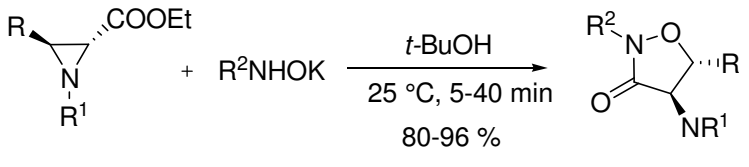
Scheme 63



Scheme 64

4.12 Synthesis of isoxazolidinones

A simple and efficient synthesis of 4-alkylamino isoxazolidin-3-ones is reported by the ring-opening of *N*-alkylaziridine-2-carboxylates by *N*-hydroxylamine anions.[116] The *N*-alkylhydroxylamine salts **216** can act as *N,O*-binucleophile towards ethyl *N*-alkylaziridine-2-carboxylates **169** to form the isoxazolidin-3-ones **217** (Scheme 65). This reaction involved the regio- and stereo-specific nucleophilic ring-opening at the benzylic position by the oxygen atom of the hydroxylamine anion (R-NH-O$^-$) as the first nucleophilic center, accompanied with an inversion of configuration. Then the *O*-alkylated hydroxylamine intermediate formed underwent a spontaneous intramolecular cyclization with the nitrogen atom as the second nucleophilic center, to give functionalized isoxazolidin-3-ones. The reactions of *N*-isopropylaziridine failed with hydroxylamine bearing a benzyl or *tert*-butyl group did not yield the product.



169 **216** **217**

R = Ph, *4*-ClPh; R^2 = Me, Bn, *t*-Bu
R^1 = *i*-Pr, CH-$(CH_3)C_6H_5$, *C*-pent, *C*-oct

Scheme 65

4.13 Synthesis of 2-iminothiazolidines

Craig II and coworkers, in 2014, reported alkyl and aryl isothiocyanates as effective substrates for [3+2]-cycloaddition with 2-substituted *N*-sulfonylaziridines and 2-phenylaziridine for the synthesis of 2-iminothiazolidines.[90] The reaction occurred in chemo-, regio-, and diastereoselective manners. The authors proposed the formation of products through an intimate ion-pair mechanism. The removal of sulfonyl group from the product opens up avenue for their further functionalization. In 2016, two exciting papers have appeared on application of aziridines in synthesis of 2-imonothiazolidines. First, Ghorai and coworkers reported the formation of thiazolidines from activated aziridines by a Lewis-acid catalyzed domino ring-opening and cyclization with aryl- and alkylisothiocyanates[117] and then Punniyamurthy group reported an aluminum-catalyzed enantiospecific [3+2]-cycloaddition of unactivated aziridines **105** with isothiocyanates **218** leading to the formation of 2-iminothiazolidines **219** (Scheme 66).[118] Ghorai and coworkers have studied the reaction of aziridines with different sulfonylaryl groups on nitrogen with alkyl and aryl isothiocyanates in the presence of $BF_3.OEt_2$ to get the products in excellent yields (up to 99%). The reaction with enantiomerically pure disubstituted aziridines yielded the single diastereomer of the corresponding iminothiazolidines with ee up to 99% (Scheme 67). They have proposed similar mechanism as suggested earlier[61,71] that is activation of aziridines by Lewis acid and S_N2-type ring-opening followed by 5-*exo*-dig cyclization with isothiocyanates. Punniyamurthy *et al.* have employed unactivated aziridines using aluminum salen as a catalyst. In this study as well, a stereospecific S_N2-type ring-opening followed by 5-*exo*-dig cyclization is proposed. In both studies, it was observed that the nucleophilic attack took place at benzylic carbon atom of the aziridine ring.

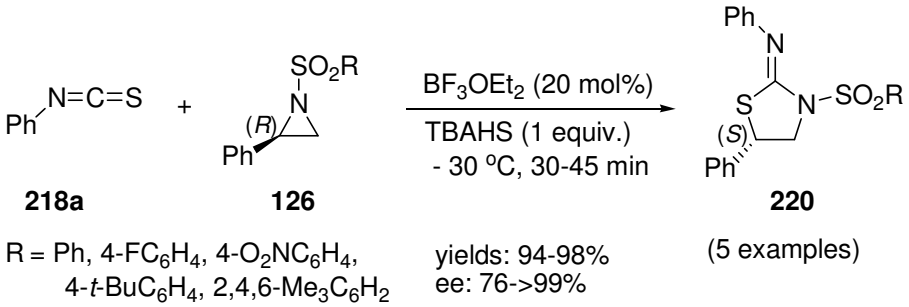
218 **105** **219**

R = aryl; R^1 = alkyl, benzyl
R^2 = Ph

yields: 77-88%
ee: 94-99%

(18 examples)

Scheme 66

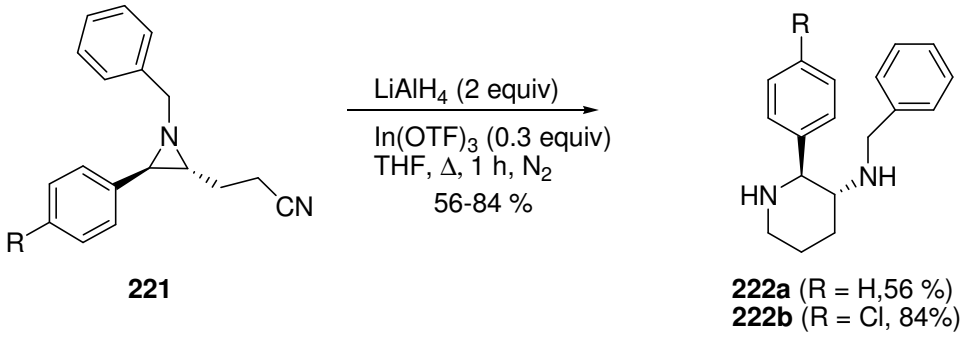


Scheme 67

5. Synthesis of Six-membered Heterocycles

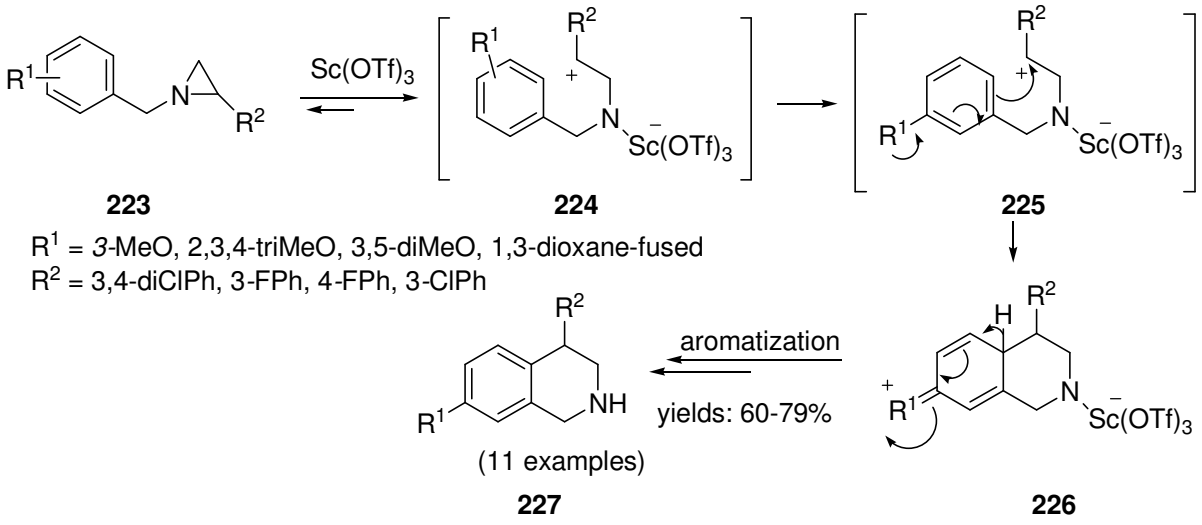
5.1 Synthesis of piperidines and tetrahydroisoquinolines

The formation of piperidines from 2-chloroalkyl-2-trifluoromethylaziridines and from 2-cyanoaziridines has been described earlier in section on pyrrolidines.[13,77] The 2-aryl-3-(2-cyanoethyl)aziridines **221** furnish 3-aminopiperidines **222a** and **222b** through a regioselective ring-opening at the benzylic position due to the resonance stabilization of the developing benzylic carbenium ion at the C-2 position (Scheme 68).[77]



Scheme 68

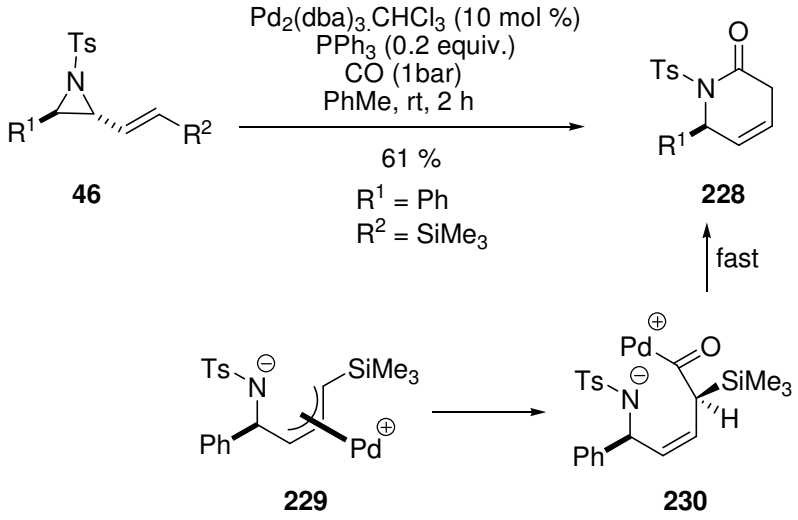
Recently, Tummanapalli reported the first example of an intramolecular ring-expansion of *N*-benzyl-substituted 2-arylaziridines **223** using scandium(III) as a Lewis acid.[119] In this reaction, 4-substituted tetrahydroisoquinolines **227** are obtained by cyclization of carbenium ion **224**, which was generated *in situ* by treatment of *N*-benzyl aziridines **223** with scandium(III) triflate, through intermediates **225** and **226** (Scheme 69). It should be noted that *meta*-alkoxy substitution is essential for the cyclization to occur. It also facilitates the efficient trapping of the carbenium ion leading to the formation of the tetrahydroisoquinoline. The employment of aziridines with other groups afforded 2-aminoalcohols. More recently, Xing and coworkers have reported a Lewis acid ($BF_3.OEt_2$)-catalyzed three-component reaction of arenes, aldehydes, and *N*-tosyl-substituted 2-arylaziridines forming *cis*-1,4-disubstituted tetrahydroisoquinolines in moderate yields.[120] The reaction proceeds through an iminium ion, generated from the reaction of aldehydes with amines [$ArCH(Ar)CH_2NHTs$] that formed after the Lewis-acid catalyzed ring-opening of aziridines.



Scheme 69

5.2 Synthesis of dihydropyridin-2-ones

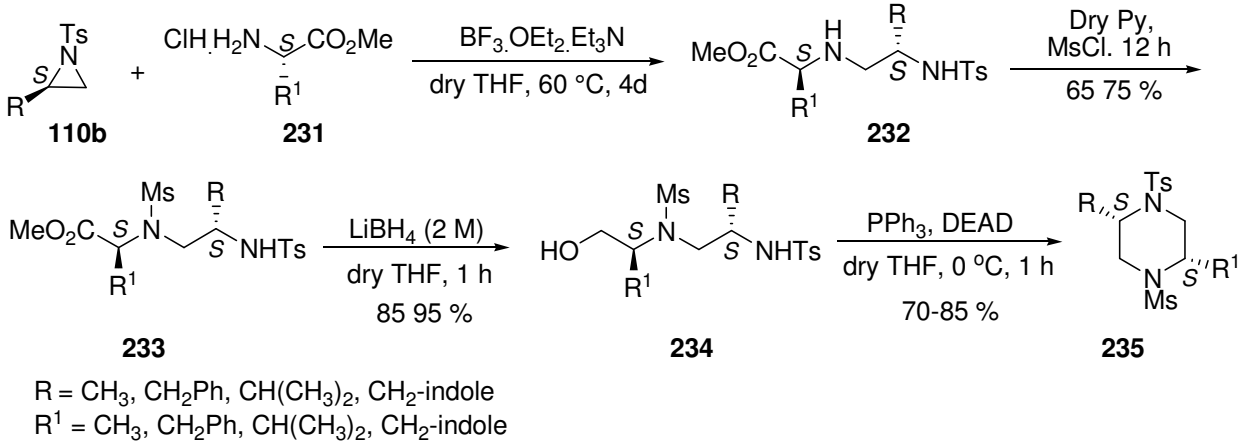
Fontana group has reported that the silyl-substituted aziridines, *trans*-3-phenyl-2-(2'-trimethylsilyl)vinylaziridine **46** underwent palladium-catalyzed carbonylation at 1 bar CO pressure leading to the exclusive formation δ-lactam **228** (Scheme 70).[44] The formation of this product has been explained through an unsymmetrical π-allyl-Pd complex **229**. The preference for carbonylation occurring adjacent to Si may result due to the shorter C-Pd bond length in **229**,[121] leading to the formation of the acyl palladium species **230**. The latter complex may undergo cyclization at a faster rate after photodesilylation. The reaction was observed to depend on the CO concentration which influenced the equilibrium concentration of the acyl palladium species **230.** At higher pressure of CO (50 bar), β-lactam was still the major product (three diastereomers in overall yield of 43%) while the δ-lactam **228** was obtained in only 20% yield.



Scheme 70

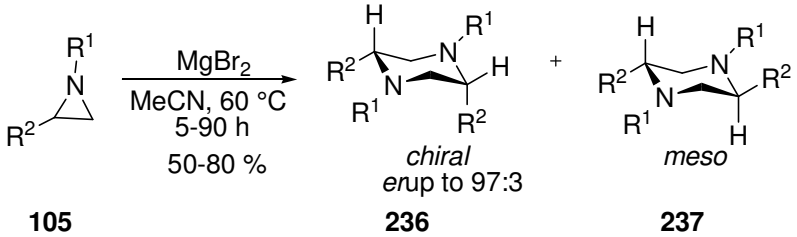
5.3 Synthesis of piperazines

Samanta and coworkers have reported a $BF_3.OEt_2$-mediated highly regioselective ring-opening of less reactive *N*-Ts chiral aziridines **110b** to synthesize piperazines **235**.[122] The *N*-Ts chiral aziridines, derived from α-amino acids, underwent a ring-opening reaction with *S*-phenylalanine methyl ester hydrochlorides **231** to form secondary amines **232**, which were then protected using mesyl chloride. The mesyl protected **233** were treated with $LiBH_4$ to afford carbinols **234**. Finally, the Mitsunobu cyclization of **234** with diethylazodicarboxylate (DEAD) furnished *cis*-2,5-disubstituted chiral piperazines **235** (Scheme 71). This reaction sequence was exploited for the preparation of piperazine core framework of natural product (+)-piperazinomycin.



Scheme 71

Treatment of *N*-alkyl arylaziridines **105** with a catalytic amount of a Lewis acid, magnesium bromide furnished corresponding 2,5-disubstituted *N*,*N*-dialkylpiperazines **236** as a 1 : 1 mixtures of two easily separable diastereoisomers together with the *meso*-product **237** (Scheme 72).[123] Enantioselective version (er >98:2; yield 40 %) of this transformation was also developed, chiral aziridines (*S*) and (*R*) gave the chiral (*S,S*) and (*R,R*) piperazines, respectively, together with *meso*-compounds.

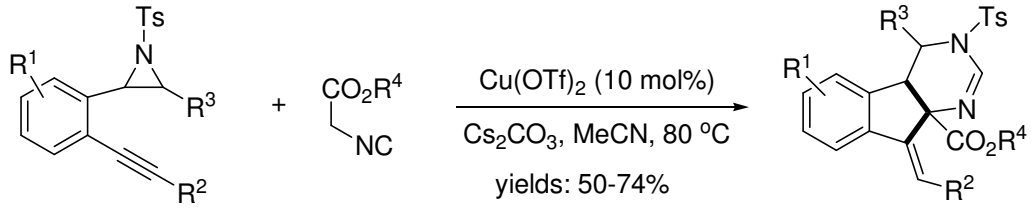


R^1 = alkyl
R^2 = *p*-Cl-Ph, *p*-Br-Ph, 2-Br-Ph, 2-Me-Ph, 2,4,6-$(Me)_3$-Ph, 2-Naphthyl, 3-MeO-Ph, *p*-MeO-Ph, 2-$(CH_2{=}CHCH_2)C_6H_4$, 3-CF_3-Ph, *p*-CF_3-Ph, 2-*n*-Pr-Ph, 2-Me-5-F-Ph

Scheme 72

5.4 Synthesis of pyrimidines

Zheng and Wu have reported a base-promoted tandem reaction of 2-(2-alkynylphenyl)aziridines **238** with 2-isocyanoacetates **239** in the presence of copper(II) triflate (Scheme 73).[124] This reaction led to an entry into tetrahydro-3*H*-indeno[2,1-d]pyrimidine ring system **240** in moderate to good yields. When a 2-(2-alkynylphenyl)aziridines with a *tert*-butyl group attached to the carbon-carbon triple bond was used, the product was obtained in trace amount.



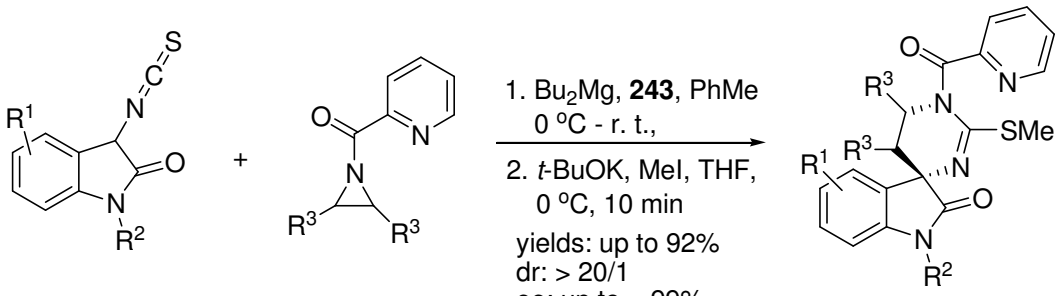
238 **239** **240**

R^1 = H, Me, Cl, F, OR; R^2 = Ph, 4-ClPh, 4-MePh, 4-MeOPh; R^3 = H, Me, Et, *n*-Pr; R^4 = Et, *t*-Bu

(15 examples)

Scheme 73

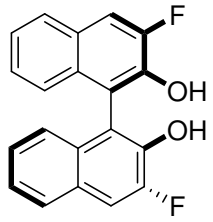
Wang and coworkers have reported a catalytic enantioselective ring-opening followed by formal [3+3]-cycloaddition reaction of 3-isothiocyanato-2-oxindoles **241** with *N*-(2-picolinoyl)aziridines **242** leading to the formation of pyrimidine ring spiro-fused to 2-oxindole ring **244**.[125] The authors have employed a magnesium catalyst generated *in situ* using (*R*)-3,3'-fluorous-BINOL **243** as a chiral ligand to synthesize a series of enantioenriched pyrimidines (Scheme 74). The authors have reported that variation of the ring systems on aziridine was well tolerated as the products were obtained in moderate to good yields but with excellent diastereo- and enantioselectivity.



(14 examples)

241 **242** **244**

R^1 = H, 5-Me; R^2 = Me, Bn, *n*-Pr; R^3 = *C*-hex, *C*-pent, *C*-hexene, tetrahydronaphthale, Me, Et, Ph



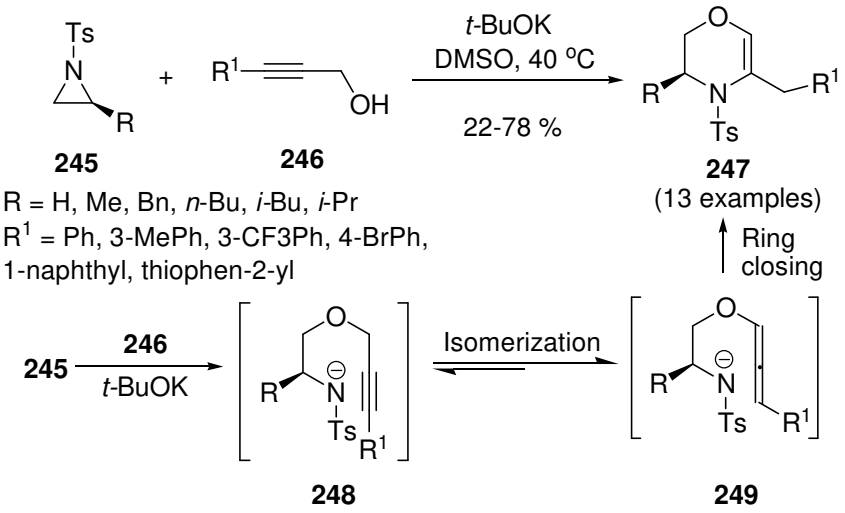
243

Scheme 74

5.5 Synthesis of dihydroxazines

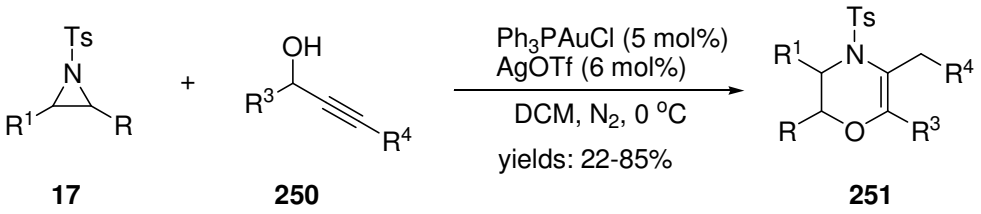
Oxazines are heterocycles with diverse properties useful in material and medicinal chemistry. Some fluorescent dyes such as Nile red and Nile blue possess the aromatic benzphenoxazine structural motif.[126] The 1,3-oxazines possess biological properties such as antifungal,[127,128] antibacterial,[129,130] antitumor,[131] antimalarial[132] and anti-HIV agents.[133] They are also used as monomers for polymer formation and photochromic agents.[134]

The chiral *N*-tosylaziridines **245** undergo a tandem ring-opening/ closing reaction with propargyl alcohols **246** in the presence of potassium *tert*-butoxide in dimethylsulfoxide at 40 °C furnishing 3,4-dihydro-2*H*-1,4-oxazines **247** in reasonable yields (Scheme 75).[135] Various chiral mono *N*-tosylaziridines bearing substituents with different electronic and steric effects were tolerated with the exception of unsubstituted and benzyl substituted *N*-tosylaziridines. Substituent on the aryl propargyl alcohols had no effect on the yield. The most plausible mechanism involves formation of an oxygen nucleophile by deprotonation of aryl propargyl alcohols **246** by potassium *tert*-butoxide. The oxygen nucleophile reacts with the *N*-tosylaziridine **245** to furnish nucleophilic intermediate **248**. Isomerization of intermediate **248** leads to generation of an allene intermediate **249** which then undergoes intramolecular nucleophilic ring-closing reaction to aryl dihydroxazine **247**.[135]



Scheme 75

A gold(I)-catalyzed tandem ring-opening and 6-*exo* dig cyclization/isomerization of aziridines **17** with propargylic alcohols **250** is reported as an efficient entry to functionalized 3,4-dihydro-2*H*-1,4-oxazine ring system **251**.[136] The latter compounds could be easily reduced to corresponding morpholines. The *N*-tosylaziridines with different electronic environments on C-2 and C-3 positions undergo an easy nucleophilic ring-opening by S_N1 mechanism followed by cyclization/isomerization cascade (Scheme 76). The gold(I) catalyst serves as both π acid and σ acid, to activate both the substrates in the reaction. The *N*-benzoylaziridines did not react under these conditions. The symmetric bicyclic aziridines used in study led to the synthesis of corresponding fused-oxazines in reasonable yields at 55 °C.



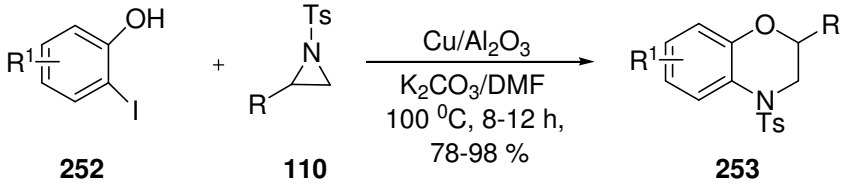
17 **250** **251**

R^1 = H; R = aryl; R^1, R = *C*-pent, *C*-hex (18 examples)
R^3 = H; R^4 = H, alkyl, aryl

Scheme 76

5.6 Synthesis of dihydrobenzoxazines and dihydrobenzothiazines

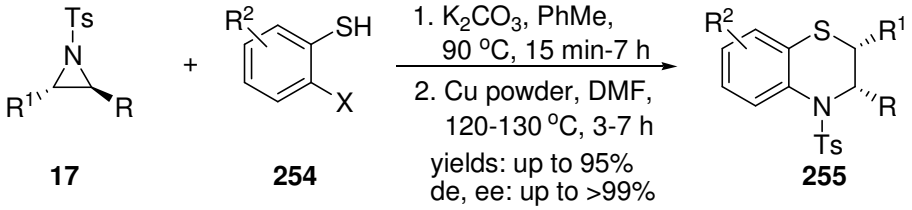
Bhadra and coworkers have reported the synthesis of a series of diversely functionalized 1,4-benzoxazines **253** by Al_2O_3-supported Cu(II)-catalyzed domino aziridine ring-opening of *N*-tosylaziridines **110** with 2-iodophenols **252** followed by cyclization (Scheme 77).[137] The catalytic system was prepared by stirring an aqueous solution of $CuSO_4$-5 H_2O with basic alumina for 2 h at room temperature.[138] The 2,3-dialkylaziridines and cycloalkane-fused aziridines were also employed successfully. The nucelophilic attack occurred regioselectively at benzylic carbon leading to the cleavage of C2-N1 bond only when the catalyst was used. The catalyst could be recovered and reused for seven times without any loss of efficiency. Ghorai and coworkers have reported the synthesis of chiral dihydrobenzothiazines **255** through regio- and stereoselective S_N2-type ring-opening of activated aziridines **17** with 2-halothiophenols **254** followed by copper powder-mediated C-N bond cyclization (Scheme 78).[52]



252 **110** **253**

R^1 = H,Br,I,CHO,CH_3,CO_2Et, Ph
R = Ph, C_6H_{13},C_3H_7, *C*-pent, *C*-hex, *C*-hept, *C*-oct.

Scheme 77

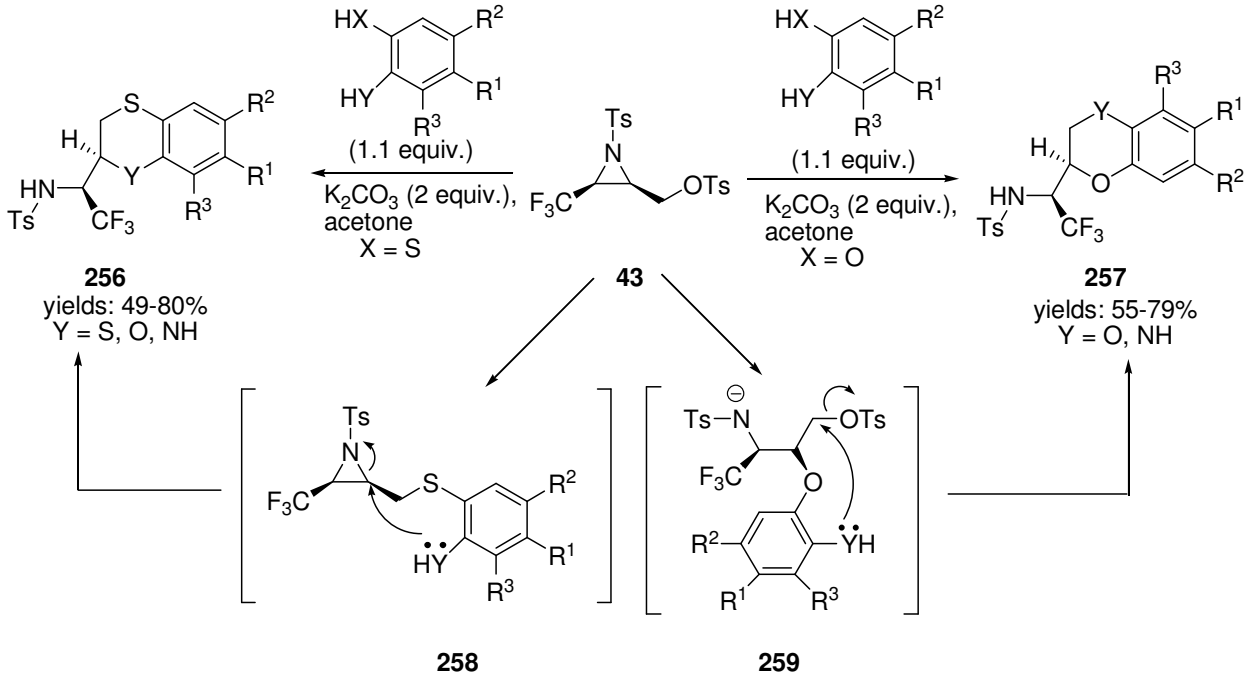


17 **254** **255**

X = Cl, Br; R^2 = Me, F, Cl
R^1 = Ph, 2-ClPh, 3-ClPh, 4-ClPh, 2-BrPh, 4-*t*-BuPh
R = H, Me, n-Pr, *n*-Bu, *i*-Pr, *i*-Bu, *t*-Bu

Scheme 78

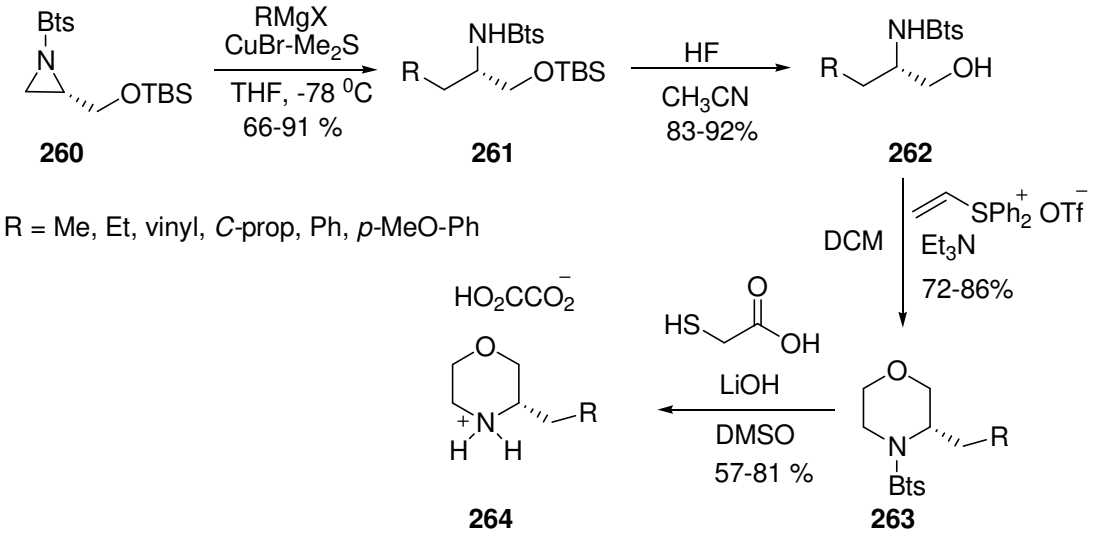
De Kimpe and coworkers have reported the synthesis of dihydrobenzoxazines, dihydrobenzothiazines, dihydrobenzodioxines, dihydrobenzodithiines, and dihydrobenzoxathiines **256** and **257** from *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine **43** (Scheme 79).[38] A regioselective ring-opening occurs either directly forming intermediate **259** or through another aziridine **258** depending on the nucleophile used. The sulfur-nucleophile led to nucleophilic substitution on aziridine followed by ring-opening whereas the oxygen nucleophile led to ring-opening first.



Scheme 79

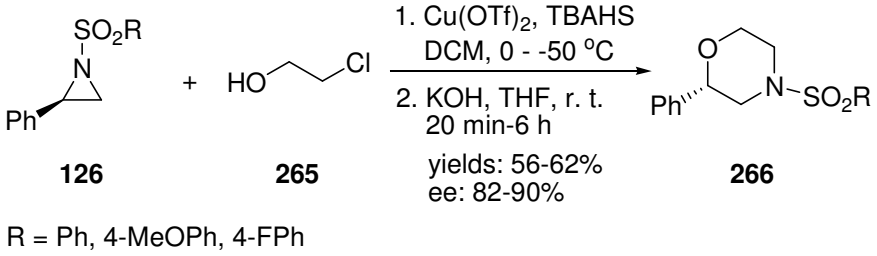
5.7 Synthesis of morpholines and thiomorpholines

The ring-opening of aziridines with different nucleophiles followed by cyclization has been reported to form morpholine derivatives by different group. In 2010, Bornholdt developed a method to access 3-substituted morpholines **264** from *N*-2-benzothiazolesulfonyl (Bts)-activated aziridine **260** (Scheme 80).[139] The reaction involved the Cu-catalyzed ring-opening of aziridine with Grignard reagents forming aminoethers **261** that were converted to alcohols **262**. A subsequent ring-annulation reaction with a vinylsulfonium salt forming morpholines **263** followed by the deprotection of *N*-Bts group under very mild conditions led to the formation of final products.



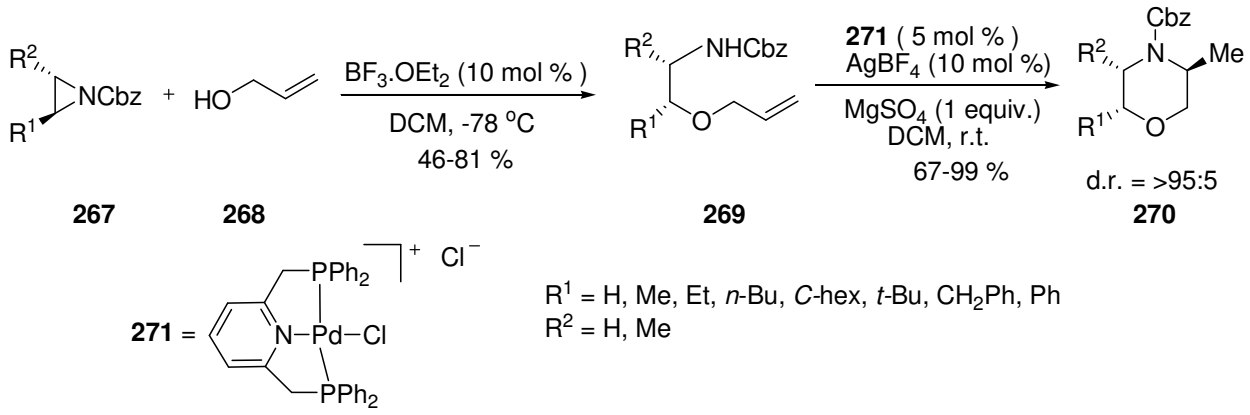
Scheme 80

Ghorai and coworkers have published several papers on Lewis acid-catalyzed ring-opening reaction of activated aziridines.[140,141] A $Cu(OTf)_2$-catalyzed highly regioselective S_N2-type ring-opening of chiral aziridines **126** with 2-chloroethanol **265** followed by cyclization furnishing morpholines **266** is reported (Scheme 81).[142] The partial racemization of the starting aziridine was prevented by using quaternary ammonium salts to get the product with high enantioselectivity (up to 99%) and diastereoselectivity (up to 99%). The highest enantioselectivity of 90% was observed with *N*-tosyl-2-phenylaziridine when the reaction was carried out at -50 ^oC for 6 hours.



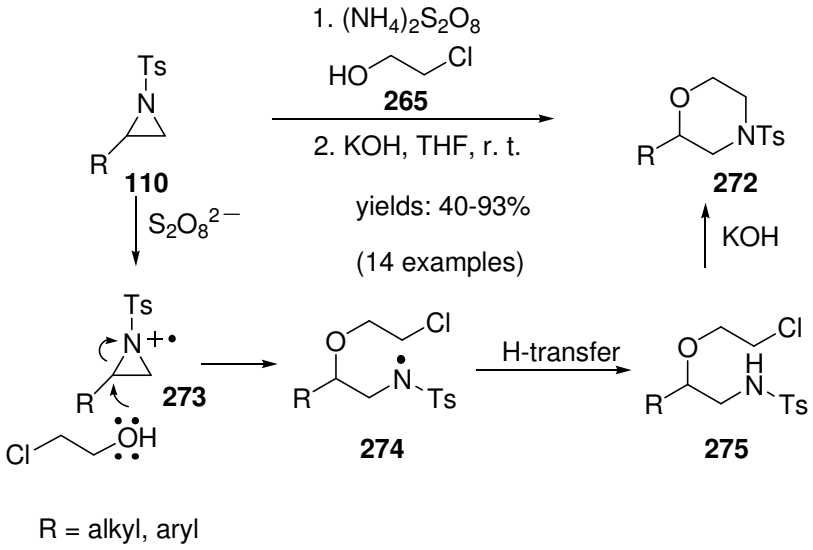
Scheme 81

McGhee has described the synthesis of 2,5-disubstituted and 2,3,5-trisubstituted morpholines **270** from carbamate-protected aziridines **267** in either a two-step sequence (Scheme 82), or a one-pot domino reaction sequence.[143] In the two-step sequence, Lewis acid catalyzed selective attack of allyl alcohol **268** at the more substituted carbon atom of aziridines afforded aminoalkenes **269**, which underwent hydroamination in the presence of palladium catalyst **271** to afford substituted morpholines **270**. They also showed a one-pot ring opening-hydroamination eliminating the need to isolate the amioalkene intermediate procedure using $AgBF_4$ as the latter can also act as a mild Lewis acid.



Scheme 82

Xia and coworkers have reported a metal-free one-pot synthesis of 2-substituted and 2,3-disubstituted morpholines from *N*-tosyl-substituted 2-arylaziridines.[144] This group has used a simple and inexpensive reagent ammonium persulfate as an oxidant for aziridine ring-opening with 2-haloethanols. Use of optically pure aziridines in reactions led to the synthesis of chiral morpholines in 95-99% ee but in low to moderate yields. It is assumed that aziridine participates in single electron transfer (SET) with the persulfate anion to generate the radical cation **273** (Scheme 83). A concerted ring-opening and nucleophilic addition gives an amino radical intermediate **274**. This radical is converted to a haloamine alkoxy intermediate **275** by abstraction of a hydrogen atom from alcohol. Finally, the cyclization in presence of a base gives morpholines.

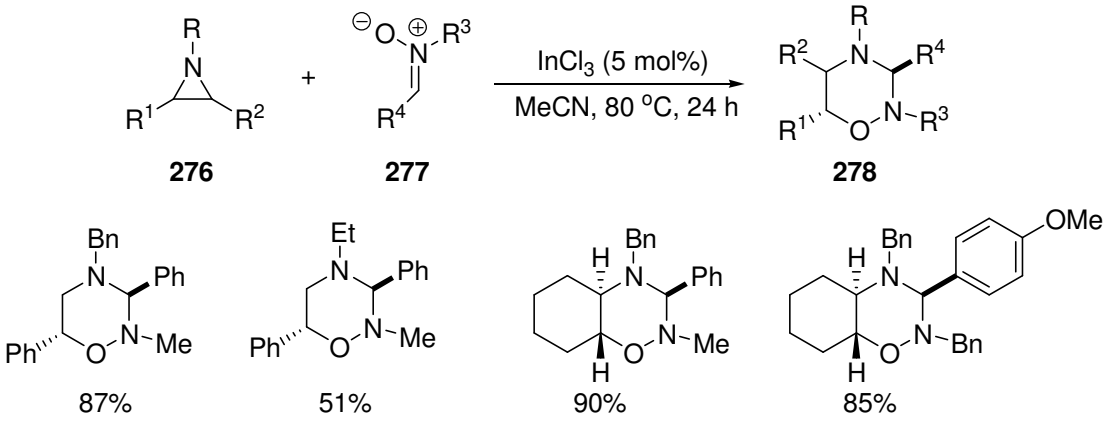


Scheme 83

Samzadeh-Kirmani has reported a single-pot reaction of 2-substituted aziridines, nitromethane, and isothiocyanates forming 1,4-thiomorpholine.[145] The reaction gave the best yield when potassium carbonate was used as base in THF. The reaction occurs at 60 °C in eight hours.

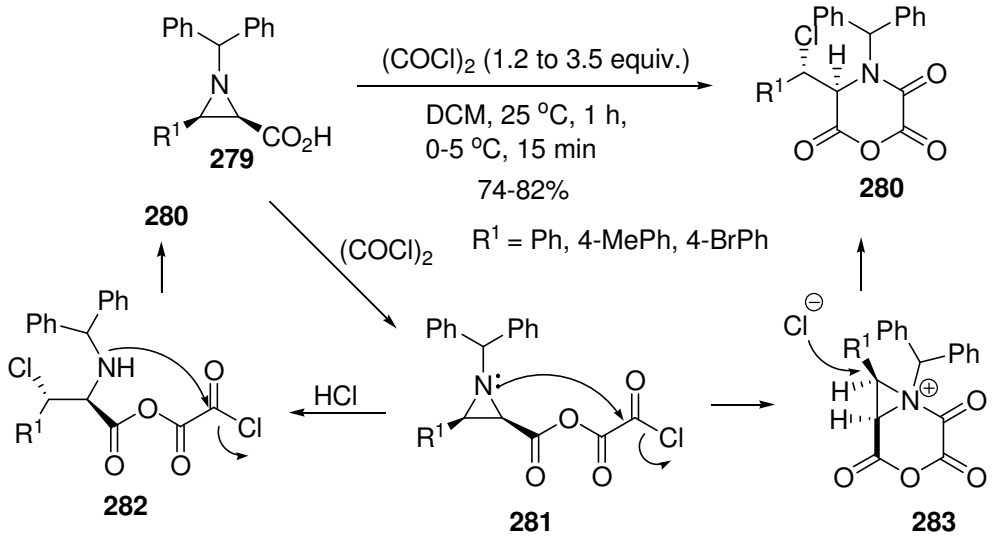
Pathipati and coworkers have reported the expansion of aziridine ring to a six-membered heterocyclic series with three heteroatoms, one oxygen and two nitrogen atoms, in the ring.[146] A series of 1,2,4-oxadiazinanes **278** have been synthesized by reactions of aziridines **276** with nitrones **277** in the presence of

indium(III) chloride as a Lewis acid catalyst (Scheme 84). The *N*-benzylaziridines reacted even without catalyst but furnished low yields. The *N*-ethylaziridine, however, did not react in the absence of a catalyst. Also, *N*-tosylaziridine did not undergo annulation probably due to weak Lewis acid activation or less nucleophilicity of the *N*-tosyl group.



Scheme 84

Wulff and coworkers have reported the formation of morpholine-2,3,6-triones **280** from the reaction of *cis*-1-benzhydryl-3-arylaziridine-2-carboxylic acids **279** with oxalyl chloride (Scheme 85).[45] The authors have suggested two possible mechanisms for the formation of products. The first possibility is an initial ring-opening of the aziridine **281** to give the β-chloramine **282** which may cyclize to morpholine-2,3,6-triones. Alternatively, a nucleophilic addition of the aziridine nitrogen to acyl chloride unit may form an aziridinium ion **283** which can be opened by chloride ion.



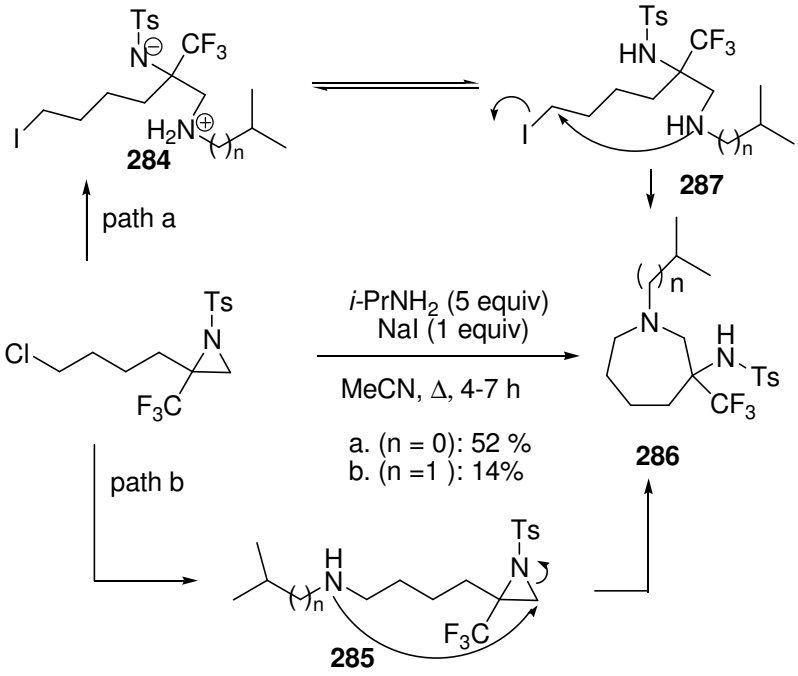
Scheme 85

6. Synthesis of Seven-membered Heterocycles

6.1 Synthesis of azepanes

Azepane motif is present in a number of important heterocyclic compounds and bioactive alkaloids.[147] The functionalized azepanes have flexible ring structures and this conformational diversity is important for their bioactivity. The structural flexibility of azepanes offers potent inhibition against various enzymes.[148]

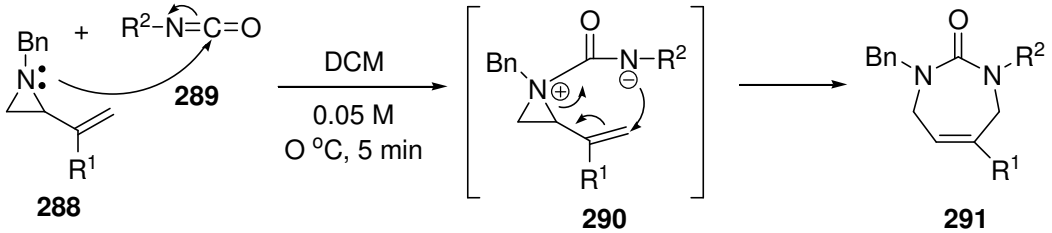
The ring-expansion of aziridines to seven-membered heterocyclic systems is a difficult to achieve goal. De Kimpe and coworkers reported the formation of azepanes through piperidines, obtained in turn, by a ring-expansion of 2-(2-cyano-2-phenylethyl)aziridine.[149] Later on, this group has described the ring-expansion of 2-(4-chlorobutyl)-1-tosyl-2-(trifluoromethyl)aziridine to azepanes (Scheme 86).[13] Of the two possible mechanisms, the first involved an initial cleavage of aziridine ring by alkyl amines at C-3 position followed by substitution of chloride with iodide leading to the formation of an intermediate **284** (path a). The intermediate **284** may cyclize to azepanes **286** via an intermediate **287**. Another possible mechanism involved an initial substitution at alkyl halide side-chain of aziridines by amines furnishing another aziridines **285** which underwent an intramolecular ring-opening (path b).



Scheme 86

6.2 Synthesis of diazepinones

Saito and coworkers have reported a [5+2]-cycloaddition reaction of 1-benzyl-2-vinylaziridines **288** with sulfonyl isocyanates **289** under mild conditions forming cyclic ureas, diazepinones **291** in good yields (Scheme 87).[150] It is worth mentioning that the reaction did not require any catalyst. The reaction was, however, extremely sensitive to solvents. The seven-membered heterocyclic products were obtained in dichloromethane. The change of solvent from dichloromethane to DMF led to the formation of imidazolidin-2-ones. The reaction may proceed through an aziridinium ion **290**, generated by nucleophilic attack of aziridine nitrogen atom on the electrophilic carbon atom of the isocyanate.

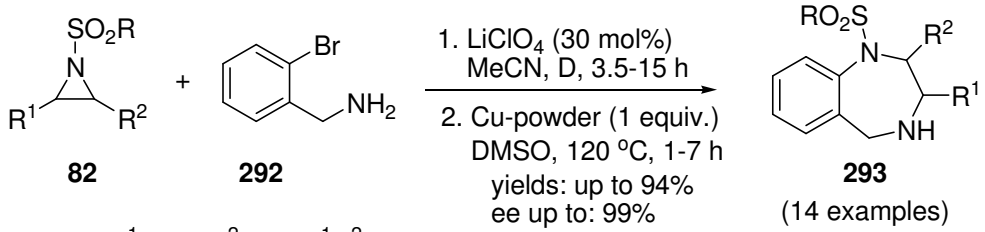


R^1 = Me, R^2 = Ts: 82%; R^1 = Me, R^2 = Ms: 89%;
R^1 = Ph, R^2 = Ts: 90%; R^1 = Ph, R^2 = Ms: 52%;
R^1 = OTBS, R^2 = Ts: 59%; R^1 = OTBS, R^2 = Ms: 48%;

Scheme 87

6.3 Synthesis of benzodiazepines, benzoxazepines and benzothiazepines

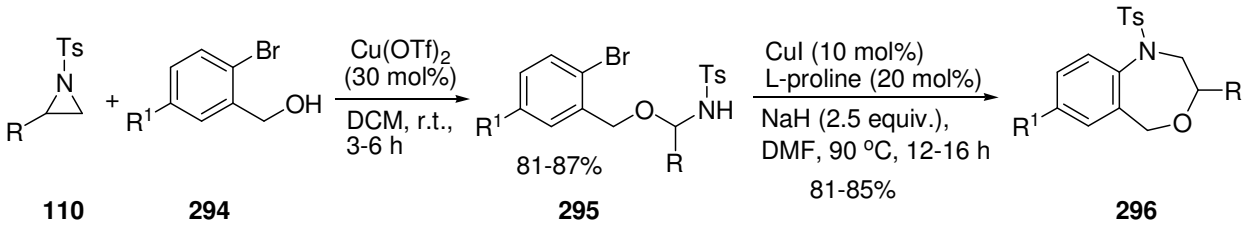
Ghorai and coworkers have reported a simple and stereospecific method for the synthesis of 2,3,4,5-tetrahydrobenzodiazepines **293** from aziridines **82** (Scheme 88).[151] An S_N2-type ring-opening of *N*-activated aziridines with 2-bromobenzylamine **292** followed by an intramolecular cyclization through copper-mediated C-N bond formation led to the formation of products. The scope of the reaction is quite wide as a diverse array of aziridines could be employed successfully to furnish the products in excellent yields (up to 94% yield) with very high enantioselectivity (up to 99% ee).



Ar = aryl; R^1 = Ar; R^2 = H, R^1R^2 = *C*-hex

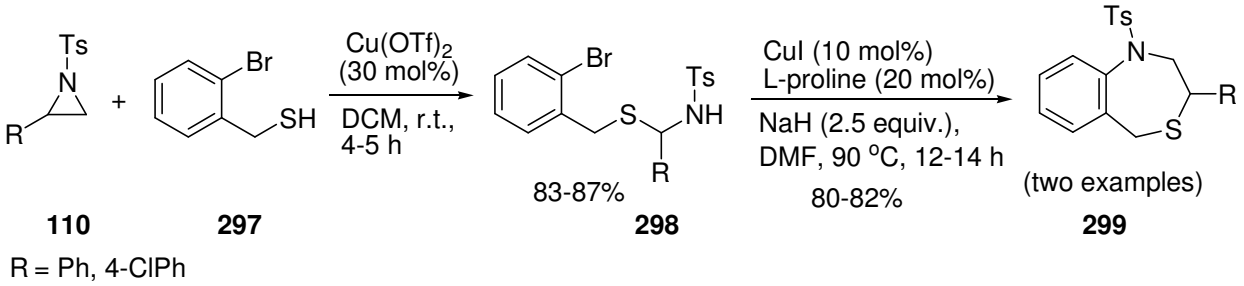
Scheme 88

Ghorai group has also reported similar ring-opening of *N*-activated aziridines **110** with 2-bromobenzylalcohol **294**, and 2-bromobenzylthiol **297** forming ring-opened products **295** and **298**, respectively. The copper-catalyzed cyclization of these products led to synthesis of corresponding tetrahydrobenzoxazepines **296** (Scheme 89) and tetrahydrobenzothiazepines **299** (Scheme 90).[152]



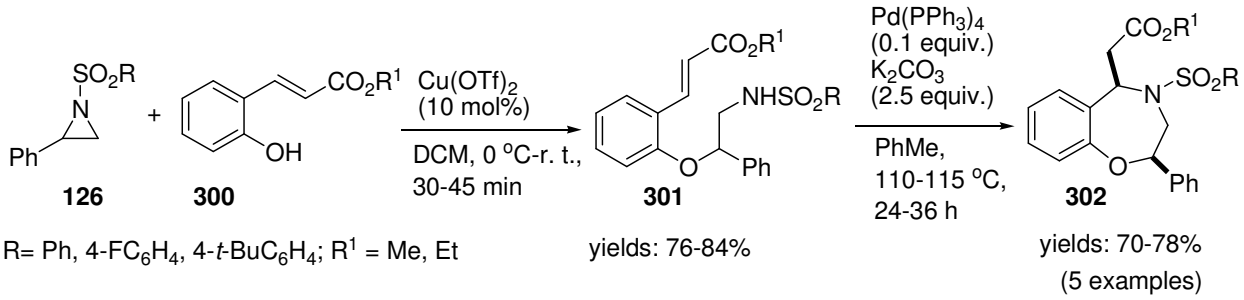
R = Ph, 4-MePh, 4-ClPh, 4-FPh, 4-*t*-BuPh
R^1 = H, F

Scheme 89

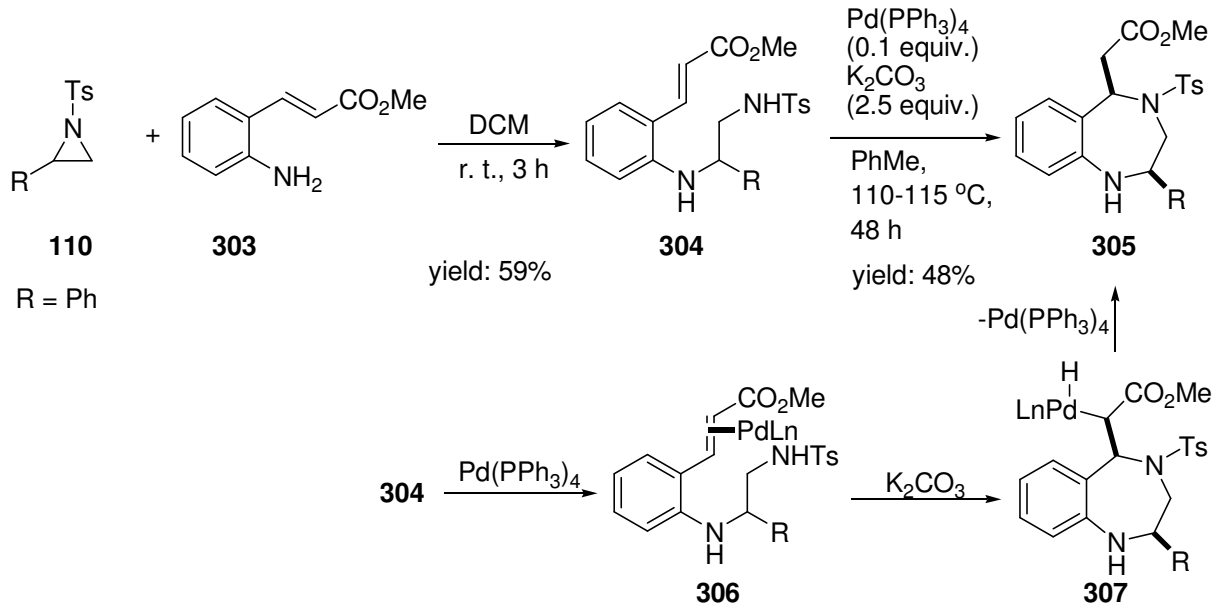


Scheme 90

The aziridine ring opening with hydroxyphenyl acrylates and aminophenyl acrylates followed by intramolecular C-N bond formation through the palladium-catalyzed aza-Michael reaction is reported recently as a straightforward approach for the synthesis of 2,3,4,5-tetrahydrobenzoxazepines **302** (Scheme 91) and 2,3,4,5-tetrahydrobenzodiazepine **305**, respectively (Scheme 92). The products are obtained in high yields (up to 82%) with an excellent enantioselectivity (ee up to 94%).[153] The relative stereochemistry at 2,5-positions was observed as *cis*. The reaction is quite general as a number of activated aziridines with various aryl groups at C-2 position and different arylsulfonyl groups on ring nitrogen have been employed. According to proposed mechanism, the S_N2-type reaction of acrylates occurs at the benzylic carbon of the aziridines leading to ring opening. The ring-opened products **301** and **304** undergo a Wacker-type reaction involving addition of *N*-sulfonylaryl group to the palladium-coordinated olefinic moiety generating the intermediates **306** and **307**. The intermediate **307**, on reductive elimination affords the desired product and the catalyst Pd(0) is regenerated.



Scheme 91



Scheme 92

7. Concluding Remarks

Aziridine ring is undoubtedly a powerful building block for synthesis of diverse types of heterocyclic compounds. Different types of aziridines are easily prepared in laboratory using well-known methods. The investigation on reactivity of aziridine ring with focus on application in synthesis of other heterocyclic compounds has seen resurgence of interest in recent years. Although *N*-sulfonylaziridines and 2-vinylaziridnes appear to be of great interest *N*-alky/aryl-substituted aziridines have also been thoroughly investigated. The review of literature revealed the application of aziridines in synthesis of four- to seven-membered heterocyclic compounds containing one or more heteroatoms in the ring. Many of these heterocyclic motifs are of immense biological importance. The nucleophilic ring-opening of aziridines has led to the synthesis of azetidines. The synthesis of β-lactams is reported by a Pd-catalyzed carbonylation reaction of aziridines, and by reaction of aziridines with oxalyl chloride. The Lewis acid catalyzed nucleophilic ring-opening with different types of nucleophiles followed by [3+2]-cycloaddition with a range of dipolarophiles constitutes a general approach for the synthesis of five-membered heterocycles pyrrolidines, oxazolidines, and thiazolidines. These reactions occur in both intra- and intermolecular fashions. The ring-opening of appropriate C-2 chloroalkyl-substituted aziridines followed by cyclization is known to form four- to seven-membered heterocyclic compounds. The fixation of carbon dioxide by aziridines using a number of catalysts is an important method for the preparation of oxazolidinones. Although the Lewis acid-catalyzed cycloadditions are more common a Lewis base-catalyzed fixation of carbon dioxide with *N*-arylsulfonyl-substituted aziridinofullerenes has been developed to synthesize oxazolidinone-fused fullerenes. Asymmetric synthesis of some five-membered heterocycles is reported as well. The ring-expansion of 2-(2-cyanoethyl)aziridines using $LiAlH_4$, palladium-catalyzed ring-expansion of 2-vinylaziridines, and magnesium bromide-initiated ring-expansion of aziridines serve as useful methods for the syntheses of piperidines, dihydropyridin-2-ones, and piperazines, respectively. A [3+3]-cycloaddition reaction of 3-isothiocyanato-2-oxindoles with *N*-(2-picolinoyl)aziridines leading to the formation of pyrimidine ring spiro-fused to 2-oxindole ring is described. A copper-catalyzed aziridine ring-

opening with various nucleophiles followed by cyclization constitutes an important method for a convenient entry into the five- to seven-membered aza-, oxaza-, and thiazaheterocycles. A bulk of literature in a short span of time indicates continuing interest in the area and more interesting outcome.

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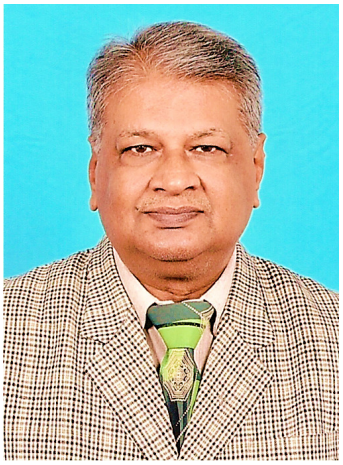
Authors' Biographies



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