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Nucleophilic ring opening of aziridines

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1. Introduction

The aziridine functionality, or alternatively named the azaethylene or ethylenimine unit, represents one of the most valuable three membered ring systems in modern synthetic chemistry, because of its widely recognized versatility as a significant building block for chemical bond elaborations and functional group transformations. Its powerful synthetic utility has been extensively demonstrated by overwhelmingly documented methodologies in aziridine preparation, especially those including asymmetric approaches, and its broad applications to other syntheses.[1–5] The synthetic scope has quickly blossomed in recent years, which is evident in a literature search by a term of 'aziridine reviews', resulting in more than 125 hits of review articles in the last four decades. Among them, 23 reviews were published since year 2000, averaging 5 reviews per year. Because of the emerging interests in nitrogen containing organic compounds and the potential utility of aziridine ring opening chemistry, the intensity in aziridine research is anticipated to increase in the future.

In this review, it is by no means intended to seek a comprehensive overview of aziridine chemistry including chiral aziridines,[6] nor to cover examples of broad applications for the synthesis of amino acids,[7] azasugars,[8–10] chiral ligands,[11,12] biologically active compounds,[13] natural products[8,14] and other synthesis. Instead, the focus of this review is designed to remain in a landscape of presenting only recent noteworthy advances in the development of new methodologies, particularly in nucleophilic ring opening of aziridines, since the review by McCoull and Davis in 2000.[15] Examples of new procedures are presented to highlight reaction conditions, stereo and regio-selectivity, reagent advantages and limitations, so to provide a useful reference tool set of methods handy to satisfy particular reaction needs. The reports of preparative procedures of aziridines and reapplication of existing protocols with little methodological values are excluded from this review to minimize redundancy and exhaustiveness.

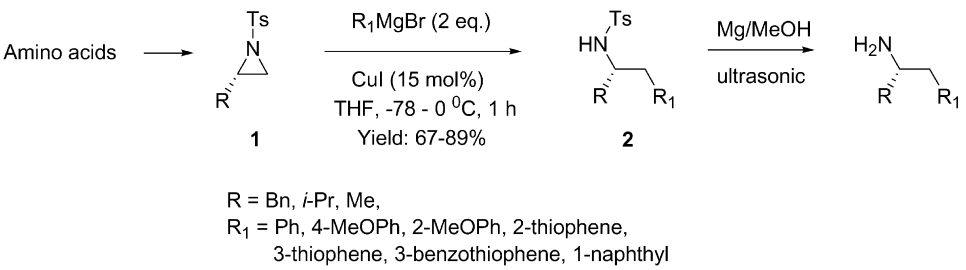
2. Carbon nucleophilic addition

Nucleophilic ring opening of aziridines by organometallic reagents has been known for over three decades.[16] However, the application of the carbanion addition was not significantly accelerated until a more efficient method developed by Eis and Ganem in the opening of non-activated aziridines by organocuprates catalyzed by Lewis acid BF_3 was reported.[17] A subsequent report by Baldwin et al. in the ring opening of N-sulfonated aziridines with requirement of no catalysis further enhanced its broad use.[18] Since then, carbanion nucleophilic addition to aziridines has found its significantly appreciable position in organic synthesis for carbon–carbon bond formation as one of the very prominent methods for organic functional group transformation.

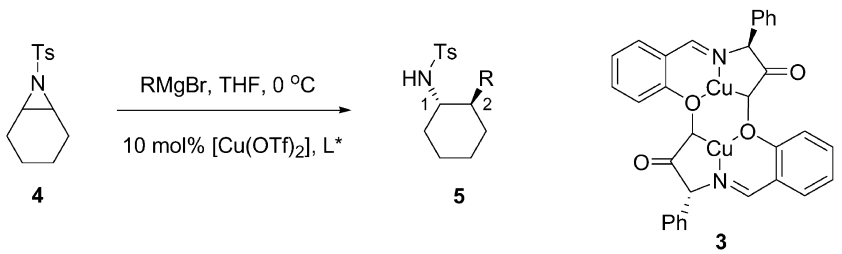
2.1. Alkyl and aryl carbanions

Increasing interest in β-aryl- and β-heteroarylamines due to their pharmacological effects in recent years has triggered considerable attention in asymmetric synthesis of these amines. One representative procedure is outlined in Scheme 1 using *N*-tosyl aziridines **1** derived from optically active amino acids as effective templates to undergo nucleophilic ring opening by aryl and heteroaryl Grignard reagents.[19] The reaction took place in THF in the presence of catalytic CuI premixed with Grignard reagents, and consistent good to high yields of amine derivatives **2** were obtained throughout the cases studied. Regio-chemistry appeared to be specific at the unsubstituted ring carbon in most examples. The tosyl group could be easily removed using magnesium in methanol under ultrasonic conditions, which makes the methodology a very attractive approach to effectively synthesize β-aryl- and β-heteroarylamines.

Recent advances in asymmetric synthesis, especially the development of chiral ligands, led to desymmetrization of *meso*-*N*-sulfonyl aziridines by nucleophilic Grignard addition. Muller and Nury examined a set of chiral ligands



Scheme 1.



Scheme 2.

in ring opening of symmetric aziridines derived from cyclic olefins with Grignard reagents as depicted in Scheme 2 and found Cu complex **3** resulted in the most appreciable asymmetric induction.[20] As shown in the representative examples in Table 1, high asymmetric induction could be achieved in 91% ee with 30 mol% of the chiral ligand under an optimized conditions. Although MeMgBr ring opening gave 55% ee with 10 mol% of the ligand, PhMgBr addition did not provide enantio-selectivity. Increased steric hindrance at the benzene ring as exemplified with (mesityl)MgBr resulted in increased enantio-selectivity, which culminated in 72% ee with **5**. However, acyclic aziridines did not produce desymmetrization products.

Table 1. Cu-catalyzed ring opening of *N*-tosyl aziridine with Grignard reagents

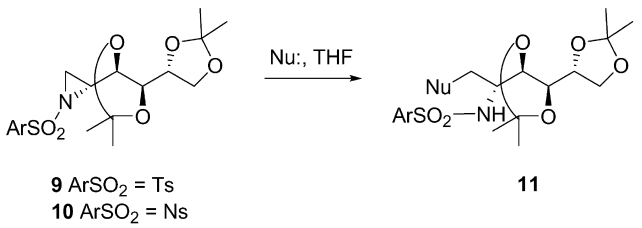
RMgBr	Ligand **3** (mol%)	Time (h)	Yield (%)	ee (%)	Abs. Config.
Me	10	2.0	89	55	(1*S*, 2*S*)
Me	30	1.5	52	91	(1*S*, 2*S*)
I-Pr	10	1.5	71	21	—
Ph	10	2.0	80	0	—
Mes	10	3.0	45	72	—

One of the most useful applications of nucleophilic ring opening of aziridines with carbanions was demonstrated in stereo and regio-controlled synthesis of 3-amino-4-substituted piperidines in our laboratory recently.[21] As shown in Scheme 3, piperidinyl aziridine **6** bearing an *N*-phosphonate activating group was treated with various Grignard reagents/CuI giving the ring opening products (**7** and **8**) mainly derived from C4 addition *trans* to the aziridine ring. The reaction proceeded smoothly with alkyl Grignard reagents in high yields, but hindered *t*-BuMgBr did not add to the aziridine. This was also true for those having sp^2 carbon nucleophiles. In addition, other organometallic reagents such as *n*-BuLi and *n*-BuZnBr gave only complex mixtures (Table 2). The surprising high regio-selectivity in such a simple system was rationalized based on conformational and steric analyses by a computer-assisted modeling approach. The *trans*-3-amino-4-alkyl piperidine derivatives are useful side chains of quinolone antibiotics.

Appropriately activated aziridines could undergo nucleophilic ring opening by various carbanions. The electronic accessibility of the aziridines was demonstrated by Compernolle et al.[22] as shown in Scheme 4 and Table 3. For example, less nucleophilic malonate and sulfonylacetonitrile anions readily attacked either tosyl aziridine **9** or nosyl aziridine **10** to give ring opening products **11** in good to high yields. Stronger carbon nucleophiles of phenyl and 1,3-dithian-2-yl anions reacted with tosyl aziridine in relatively shorter time. Although the nosyl group has been

Table 2. Regio-selective ring opening of aziridine **6** with Grignard reagents

R	Time (h)	Yield (%)	**7**:**8**
MeMgBr	3	86	13:1
EtMgBr	3	78	15:1
n-BuMgBr	5	87	13:1
i-PrMgBr	5	92	22:1
c-PrMgBr	3	78	14:1
c-HexylMgBr	5	82	12:1
t-BuMgBr	5	0	—
CH_2=CHMgBr	24	0	—
PhMgBr	24	0	—
n-BuLi	3	0	—
n-BuZnBr	24	0	—



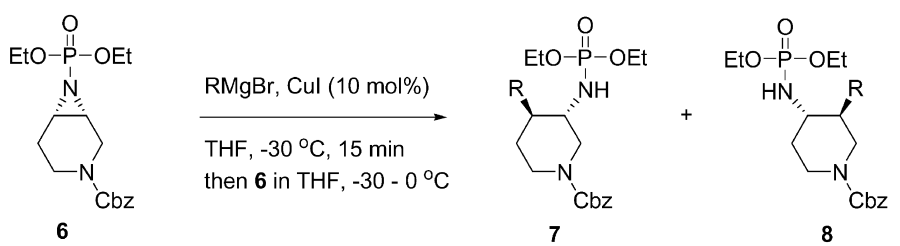
Scheme 4.

Table 3. Nucleophilic ring opening of aziridines

Nu:	Base	Time (h)		Yield (%)	
		Tosyl	Nosyl	Tosyl	Nosyl
$CH(CO_2Me)_2$	NaH	48	4	65	78
$CH(CN)SO_2Ph$	NaH	24	24	87	Mixt.
Ph	PhMgBr/CuI	1	1	75	Mixt.
1,3-Dithian-2-yl	*n*-BuLi	4	—	90	—

widely accepted as an excellent activating group, which can be more readily removed than the tosyl group, it might not be compatible with strong nucleophiles, which may contribute to the complex mixtures of some reactions as illustrated in Table 3.

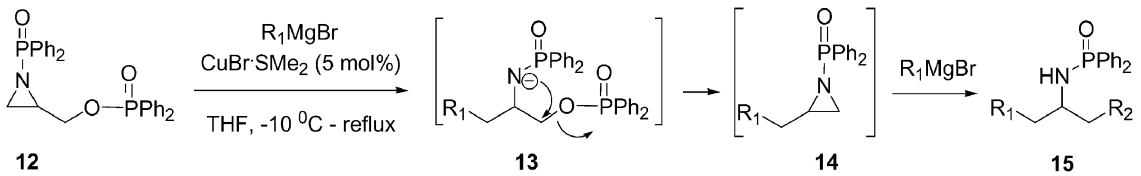
One interesting aziridine containing *N*,*O*-bis(diphenylphsphinyl) (DiDpp) functionality was prepared by Sweeney and Cantrill,[23] which could undergo double nucleophilic addition to give either dialkylated symmetric amines or unsymmetrical amines. The opening of DiDpp aziridine **12** with 5 equiv. of Grignard reagents was facilitated by $CuBr{\cdot}SMe_2$ in reflux THF to produce **15** in good yields. On the other hand, when 1 equiv. of the Grignard reagents was used, mono-alkylated aziridine products **14** were isolated in acceptable yields. Due to two electrophilic carbons present in **12**, the authors attempted to rationalize the addition process by the following assumption. The first



Scheme 3.

Table 4. Reaction of diphenylphosphinyl aziridine with copper(I)-modified Grignard reagents

12→15 R_1=R_2		**12→14**		**14→15** R_1=*i*-Bu	
R_1	Yield (%)	R_1	Yield (%)	R_2	Yield (%)
i-Bu	78	Et	70	Homoallylic	60
Homoallylic	75	*n*-Bu	52	Cyclohexyl	66
Ph	75	*i*-Bu	63	$Ph(CH_2)_3$	72

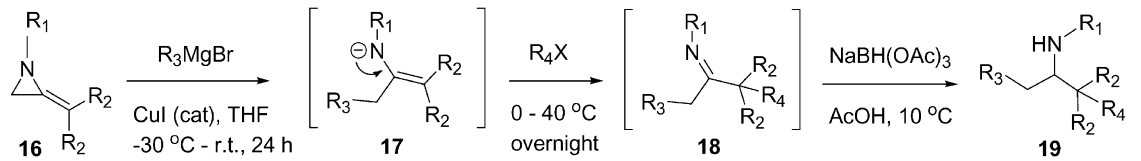


Scheme 5.

addition occurred at the aziridine to give phosphinamide anion **13**, which formed a new aziridine **14**. The second aziridine then underwent the subsequent attack by the Grignard reagents to give the final dialkyl methylamines **15**. The proposed mechanism was experimentally assured by carrying out the addition with the chiral (*R*)-aziridine of **12** and the determination of the reversed chiral center in **14** supported the initial carbanion attack at the aziridine ring carbon, followed by the second addition at the newly formed aziridine intermediate **14** (Table 4, Scheme 5).

Most reported ring opening of aziridines with carbanion nucleophiles required activation of the aziridine ring by incorporating an electron-withdrawing group on the ring nitrogen to facilitate the ring cleavage. However, one example was found in the literature describing the ring opening of aziridines without activation under Grignard nucleophilic addition conditions.[24] As shown in Scheme 6, 2-methylene- and 2-isopropylidene-aziridines **16** having alkyl groups attached to the ring nitrogen reacted with Et or *n*-BuMgBr to give ring cleaved intermediate imines **18** presumably via enamine anion **17**, after being quenched with either MeI or BnBr. Then sequential reduction with $NaBH(OAc)_3$ resulted in secondary amines **19**. This one-pot/three sequential step/multi-component procedure effectively converted aziridines to amines with three new chemical bonds formed in high overall yield (56–73%) shown in Table 5. In addition, when the chiral aziridines bearing *N*-(*S*)-CHMePh chirality were used, optically active amines **19** could be synthesized in excellent diastereoselectivity in the case of 2-isopropylidene **16**. The application of this multi-component method was demonstrated in asymmetric synthesis of 2-substituted piperidines leading to (*S*)-coniine in high enantio-selectivity.[25]

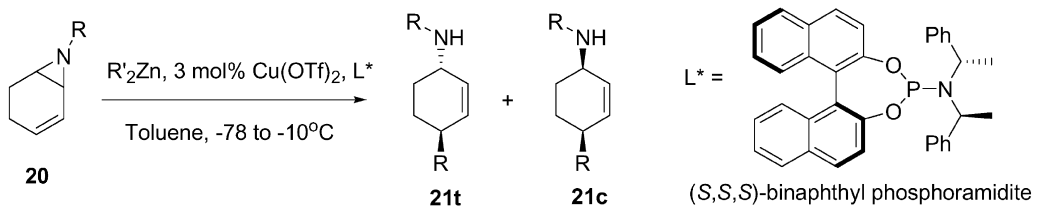
When aziridines possessed a vinyl functionality, the nucleophilic ring opening reaction proceeded with products derived from an alternative pathway involving Sn2′ addition. An effective method was recently developed by Pineschi and co-workers for controlled regio-, stereo- and enantio-selectivity in ring opening of aziridines.[26] The addition of Et_2Zn to *N*-Cbz aziridine **20** in the presence of $Cu(OTf)_2$ occurred smoothly to afford nearly 1:1 ratio of *trans*:*cis* products (**21t** and **21c**, respectively) in 95% conversion. However, a kinetic resolution controlled reaction protocol was used with only 0.55 equiv. of Et_2Zn in the presence of 6 mol% of a chiral ligand, binaphthyl phosphoramidite shown in Scheme 7. Results of 42% conversion of the starting aziridine to the products in 91:9 ratio of the *trans* isomer as a major component was observed with 78% enantio-selectivity. Methyl addition from Me_2Zn proved to be optimal in terms of stereo- and enantio-selectivity. When 1.5 equiv. of Et_2Zn were used in the



Scheme 6.

Table 5. Ring opening of 2-isopropylidene and 2-methylele-aziridines with Grignard reagents

R_1	R_2	R_3	R_4X	Yield (%)	de (%)
(*S*)-CHMePh	Me	Et	MeI	73	≥98
(*S*)-CHMePh	Me	Et	BnBr	56	~100
(*S*)-CHMePh	H	Et	MeI	63	≤25
Cyclohexyl	H	*n*-Bu	BnCl	63	—



Scheme 7.

presence of the chiral ligand, quantitative conversion was obtained with a combined yield of 75% for both stereoisomers, but with diminished enantio-selectivity (8% ee). The presence of the chiral phosphoramidite not only enhanced *anti* stereo-selectivity significantly, but provided a method for kinetic resolution of racemic cyclic 2-alkynyl aziridines. Non-activated *N*-Bn aziridine essentially did not react with organozinc agents under these conditions (Table 6).

Table 6. Regio, stereo and enantio-selective addition of R_2Zn to vinyl aziridines

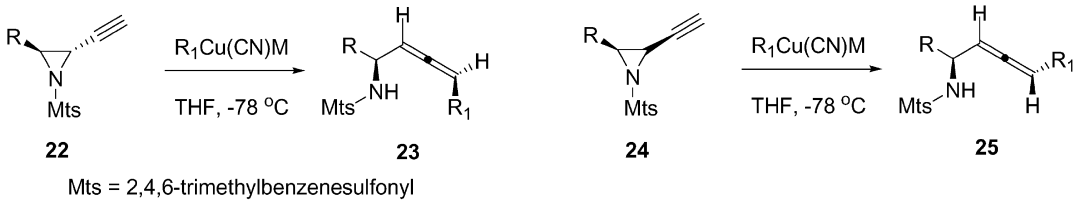
R	R'_2Zn (equiv.)	L* (mol%)	Time (h)	Conv. (%)	**21t**:**21c**	ee (%)
Cbz	Et (1.50)	None	3	>95	48:52	—
Cbz	Et (0.55)	6	2	42	91:9	78
Cbz	Me (0.40)	6	2	48	>95:<5	83
Cbz	Et (1.50)	6	18	100	80:20	8
Bn	Et (1.50)	6	18	<5	—	—

In light of organocopper-mediated ring opening of propargylic epoxides leading to the corresponding hydroxy allenes in a highly regio- and *anti*-Sn2′ selective manner, Ohno et al. also developed regio- and stereo-selective ring opening of chiral ethynylaziridines giving amino allenes.[27] As illustrated in Scheme 8, the *trans* propargylic aziridines **22** could be converted to allene adducts **23** by organocopper reagents in excellent regio- and stereo-specificity under selected reaction conditions in the representative examples in Table 7. In contrast, the *cis* propargylic aziridines **24** resulted in allenes **25** with opposite stereochemistry. The stereochemistry outcome was deduced from the well-established organocyanocuprate-mediated *anti*-Sn2′ pathway, which was further supported by the unambiguous structure assignment of one of the adducts by X-ray analysis.

2.2. Enamines, enolates and olefins

Indoles have been found to be good substrates for ring opening of aziridines under appropriate Lewis acid catalysis conditions. 2-Substituted indole **26** having enamine functionality embedded in the heteroaryl ring readily underwent nucleophilic addition to activated aziridines **27**, when facilitated by $Sc(ClO_4)_3$, to give 2-substituted tryptophan **28** in good yield.[28] This method provided only the adduct derived from the attack at the less hindered aziridine carbon, whereas a mixture of regio-isomers were obtained when catalyzed by $Sc(OTf)_3$. This intermediate was then converted to a fully deprotected α-*C*-mannosyltryptophan, a compound having interesting biological activity. Other Lewis acids such as $BF_3{\cdot}Et_2O$, $Zn(OTf)_2$, $Yb(OTf)_3$, $In(OTf)_3$ and $InCl_3$ were studied, but only $Sc(ClO_4)_3$ was found as a superior catalyst for the ring opening of the aziridine with respect to regio-selectivity and reproducibility (Scheme 9).[29]

N-Tosyl aziridines also reacted with heteroaromatics under catalytic indium(III) chloride ($InCl_3$) conditions.[30] The heteroaromatics including indole, pyrrole, thiophene and furan readily underwent nucleophilic attacks to either

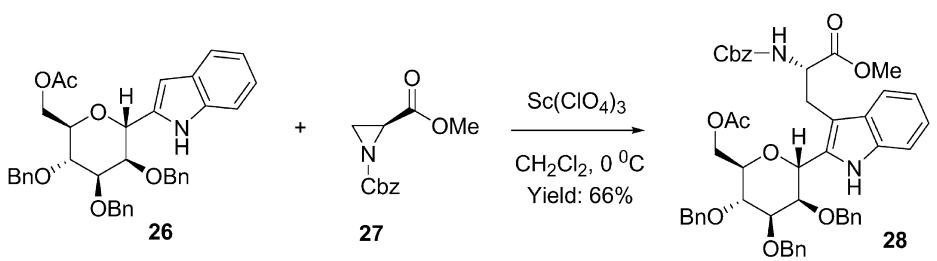


Scheme 8.

Table 7. Ring opening of 2-ethylylaziridines with organocopper reagents

Aziridine	R	$R_1Cu(CN)M$	Time (h)	Yield (%)	Product
22	*i*-Pr	MeCu(CN)Li	3.0	93	**23**
22	*i*-Pr	*i*-PrCu(CN)MgCl	0.5	99	**23**
22	*i*-Pr	*n*-BuCu(CN)Li	0.5	97	**23**
22	*i*-Pr	$Bu_3SnCu(CN)Li$	0.5	90	**23**
24	*i*-Pr	MeCu(CN)Li	0.5	98	**25**
22	Bn	MeCu(CN)Li	2	96	**23**
24	$TBSOCH_2$	MeCu(CN)Li	0.5	98	**25**

symmetric or unsymmetrical aziridines to give the corresponding ring opening products in high yields (Table 8). Indole reacted with cyclopentene and styrene *N*-tosyl aziridines to afford 3-alkylated indole derivatives **29** and **30**, whereas pyrrole gave 2-alkylated derivative **31** as a major isomer along with 3-alkylated isomer **32**. Thiophene and furan added similarly to the aziridines to yield internal adducts. Although this method was claimed to be mild and efficient, low to moderate regio-selectivity was consistently reproduced in unsymmetrical aziridines.



Scheme 9.

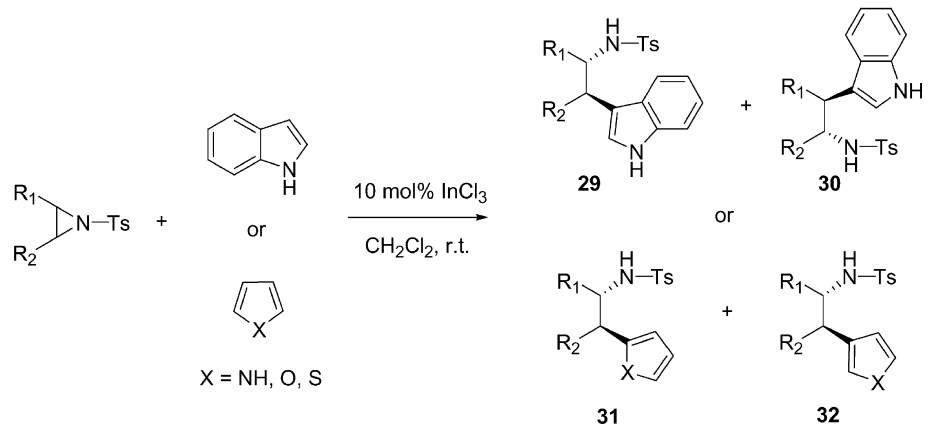
Table 8. $InCl_3$-catalyzed ring opening of aziridines with heteroaromatics

R_1	R_2	Nucleophile	Time (h)	Yield (%)	Isomer ratio
$-(CH_2)_4-$		Indole	12	75	—
$-(CH_2)_4-$		Pyrrole	5.5	72	—
Ph	H	Indole	5.5	85	60:40[a]
Ph	H	Pyrrole	2.5	90	87:13[b]
Ph	H	Thiophene	5.0	87	90:10[a]
Ph	H	Furan	4.0	80	70:30[a]
4-MeO-Bn	H	Pyrrole	4.5	85	75:25[b]
n-C_4H_9	H	Pyrrole	2.5	85	70:30[b]

[a] Ratio of products resulting from internal attack versus external attack of a nucleophile.
[b] Ratio of 2 versus 3-alkylated pyrrole products.

Table 9. Diastereo-selective ring opening of aziridines with lithium enolate

R in aziridine	Yield (%)	(2*R*)/(2*S*)
(*S*)-Ph	88	96/4
(*S*)-Me	89	89/11
(*S*)-*i*-Pr	87	93/7
(*S*)-Bn	93	95/5
(*R*)-Ph	91	75/25
(*R*)-Me	86	85/15
(*R*)-*i*-Pr	90	77/23
(*R*)-Bn	85	70/30



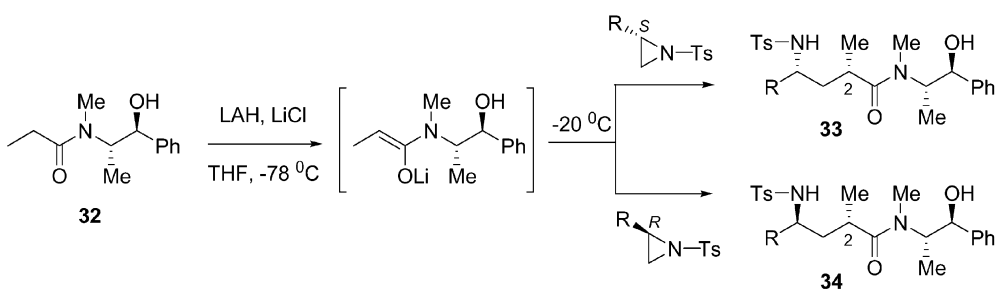
Scheme 10.

Indium(III) tribromide ($InBr_3$) also effectively catalyzed ring opening of aziridines with pyrrole to give products in good yields, but moderate regio-selectivity (Scheme 10).[31]

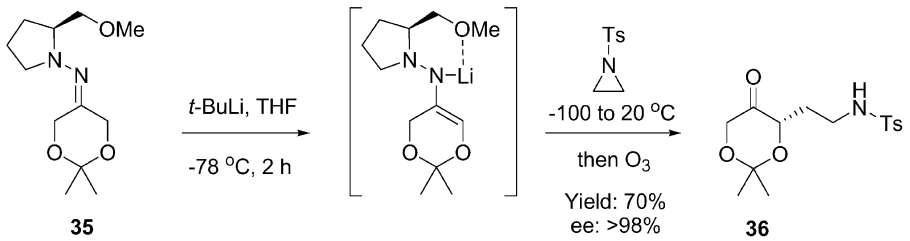
Enolates derived from ketones, esters and amides have been used as effective nucleophiles to undergo addition to aziridines. The application of the enolate addition to aziridines has largely occurred in stereo-selective ring opening to form γ-amino carbonyl difunctionalized derivatives. In a recent report, γ-amino amides were prepared via stereo-controlled addition of a chiral amide enolate to activated optically active aziridines.[32] As shown in Scheme 11, the reaction of amide **32** proceeded at low temperature in THF to give addition products **33** and **34** in high yields and diastereo-selectivity. The diastereo-induction was largely governed by the chiral auxiliary (*S*,*S*)-pseudoephedrine to give (2*R*)-stereoisomers as predominant products. However, the configuration of the starting aziridines had a striking influence on the diastereo-selectivity, in which the (*S*)-aziridines produced high ratio of diastereomers (2*R*)/(2*S*), whereas reduced diastereo-selectivity was the result in the (*R*)-aziridines. The γ-amino amides were readily converted to chiral γ-amino acids and pyrrolidin-2-ones as useful reagents and building blocks for other syntheses (Table 9).

The SAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one represented a valuable chiral equivalent of ketone functionality for asymmetric alkylation with aziridines.[33] The nucleophilic addition of *N*-tosyl aziridine was achieved with the SAMP-hydrazone aza-enolate, generated by deprotonation of **35** with *tert*-BuLi, leading to **36** in good yield (70%) and excellent enantio-selectivity (ee >98%) after the removal of the hydrazone by ozonolysis (Scheme 12).

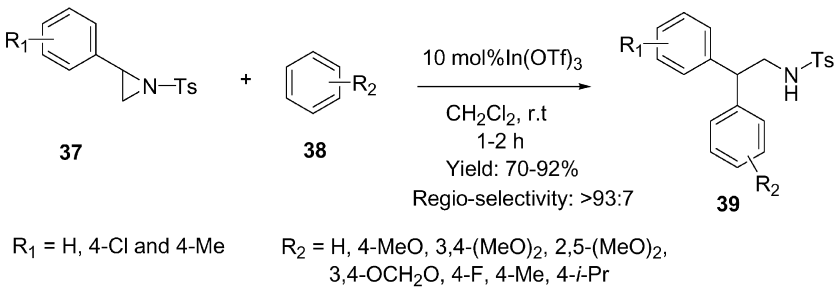
Excellent results were reported by Yadav et al. in their aziridine chemistry research of electron-rich aryl addition to *N*-Ts aziridines.[34] This was the first report regarding arenes **38** to undergo effective nucleophilic ring opening of aziridines in the presence of indium triflate $In(OTf)_3$



Scheme 11.



Scheme 12.

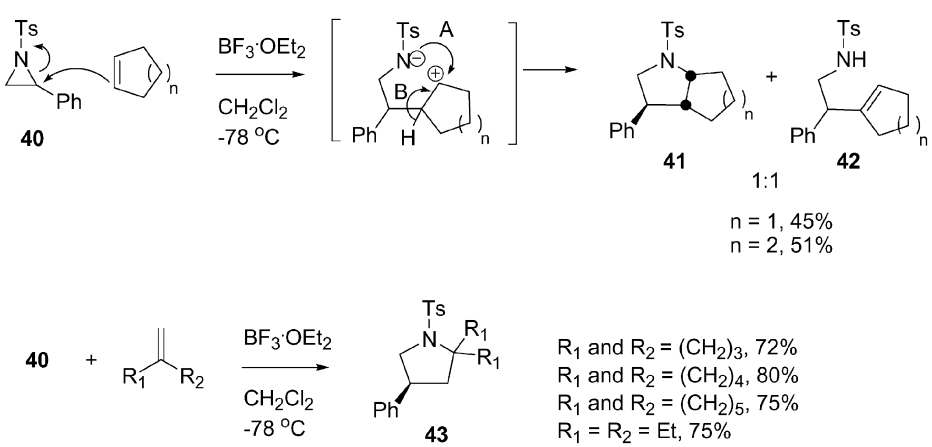


Scheme 13.

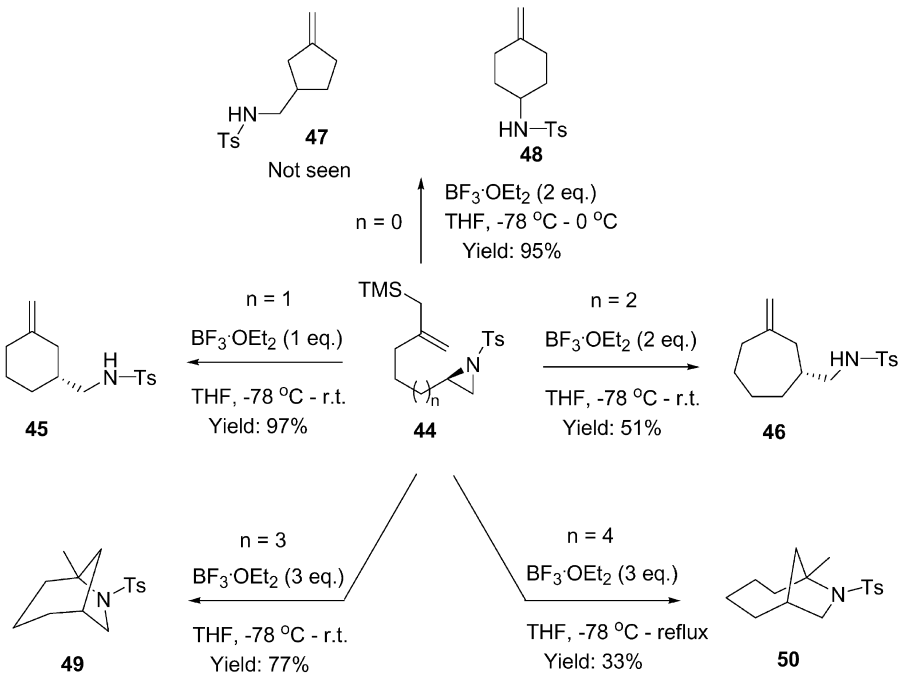
(Scheme 13). Among Lewis acids investigated, $In(OTf)_3$ and $Sc(OTf)_3$ were found to be the most effective catalysts to facilitate the ring cleavage with activated arenes. However, $In(OTf)_3$ was the only catalyst found to trigger C-arylation with non-activated aromatics such as benzene and naphthalene. The arene addition consistently proceeded at the benzylic position of the aziridines **37** leading to 1,2-bisaryl ethylamines **39** in very high regio-selectivity and high chemical yields.

Aziridines have been known for regio-selective ring opening reactions with carbanion nucleophiles, so being considered as useful building blocks for other syntheses. However, aziridines have also been found to undergo ring opening with non-anionic olefin functionality with its potential utility in robust construction of substituted pyrrolidines. This was reported by Mann and co-workers in [3+2] cycloaddition of phenyl aziridine **40** with olefins.[35] As depicted in Scheme 14, cyclopentene reacted with *N*-Ts phenyl aziridine catalyzed by $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at low temperature to give a mixture of bicyclic pyrrolidine **41** and substituted cyclopentene by-product **42** in 1:1 ratio. The designed product was presumably derived from the ring closure of a zwitterionic intermediate via path A, whereas the by-product formed via path B by loss of a β-proton from the intermediate carbocation. Similar results were also observed in the reaction with cyclohexene, which were consistent with those of dihydropyran in their earlier report.[36] The utility of the procedure was further extended to other olefins having methylenecycloalkanes of 4–6 membered rings and 1,1-diethylethylene. The cycloaddition products from these olefins were 2-spiropyrrolidines and 2,2-dialkylpyrrolidine in high yields (72–80%). These non-trivial molecules could be easily built using the cyclo-addition method.

Aziridine-allylsilanes were useful precursors for the synthesis of γ-amino olefin containing C-cycles of various ring sizes. Bergmeier and co-workers[37] found that when requisite aziridine-allylsilane **44** (n=1) was treated with 1 equiv. of $BF_3{\cdot}OEt_2$ in CH_2Cl_2, *exo*-6-membered cyclic olefin **45** was obtained in nearly quantitative yield (Scheme 15). The Lewis acid mediated addition occurred at the C2 position of the aziridine. The consistent addition pattern was

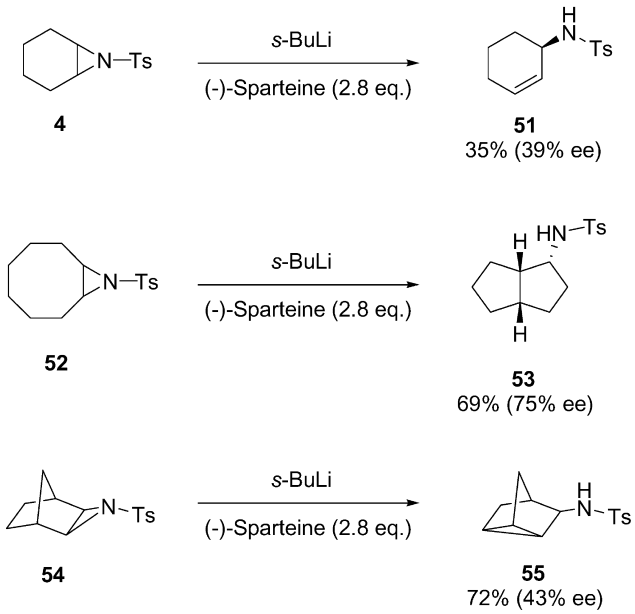


Scheme 14.



Scheme 15.

seen in the case of n=2, but with 2 equiv. of the Lewis acid needed to form *exo*-7-membered cyclic olefin **46** in 51% yield. In contrast, cyclization of aziridine-allylsilane (n=0) did not give C2 addition product **47**, but C1 adduct **48**. Small amount of desilylated azabicyclo[3.2.1]octane **49** was isolated, which was generated from intramolecular cyclo-addition of the sulfonamide to the olefin catalyzed by the Lewis acid. This observation inspired the researchers to convert aziridine-allylsilane precursors directly to an azabicyclic system in one pot. To achieve this sequential cyclization, 3 equiv. of $BF_3{\cdot}OEt_2$ were required and both azabicyclo[3.2.1]octane **49** and azabicyclo[4.2.1]nonane **50** were formed in 77 and 33% yields, respectively.

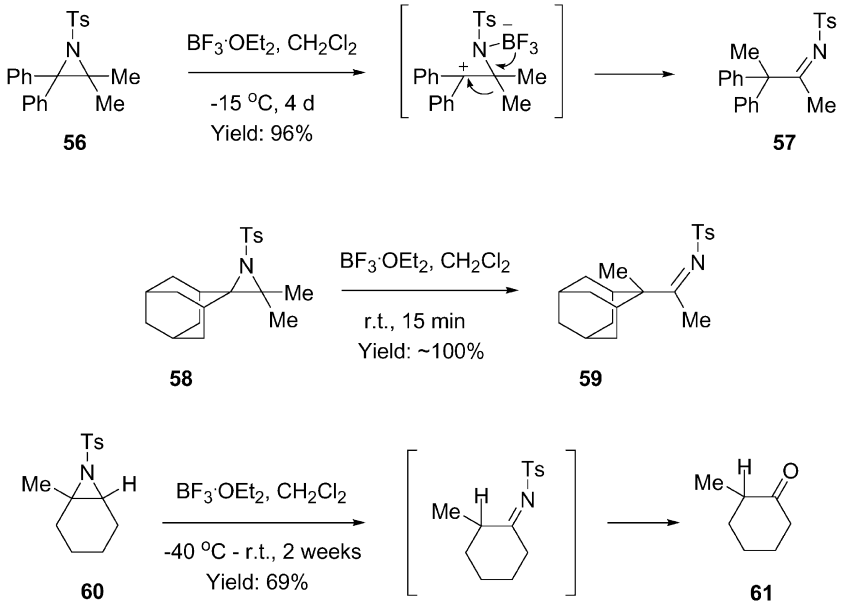


Scheme 16.

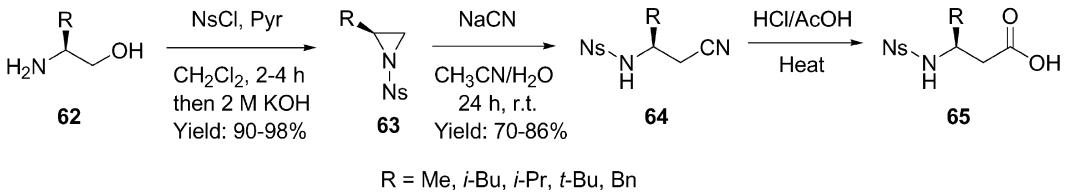
2.3. Rearrangement of aziridines

Muller and Nury further extended their desymmetrization chemistry to rearrangement of *meso*-*N*-tosyl aziridines leading to optically active carbocyclic amines.[20] As exhibited in Scheme 16, when the symmetric aziridine was exposed to *s*-BuLi in the presence of (−)-sparteine, the cyclohexene derived aziridine **4** gave an allylic amine **51** in low yield and low ee. On the other hand, appreciable yield (69%) and enantio-selectivity (75% ee) were seen in the rearrangement of cyclooctene aziridine **52** generating a *cis*-fused bicyclic amine **53**. In addition, bicyclic bridge-headed aziridine **54** underwent rearrangement under the same reaction conditions to afford product **55**. Although the researchers claimed these ring-opening amines were products of intramolecular carbenoid insertion analogous to that in epoxide lithiation, no sufficient experimental data were offered to support the argument. O'Brien et al. disclosed their work quite identical to the work mentioned above.[38] Results of more extensive aziridine rearrangement were captured in another report by Mordini and co-workers. Superbases were used to promote the rearrangement with cyclic and acyclic aziridines[39] and exemplified in the synthesis of α- and β-amino acids.[40]

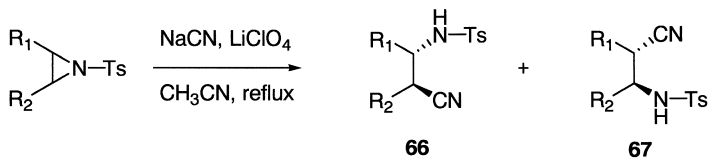
Substituted *N*-tosyl aziridines could undergo another type of rearrangement, namely aza-pinacol rearrangement. Similar to epoxide pinacol rearrangement, $BF_3{\cdot}OEt_2$ was a choice of a robust catalyst to facilitate such a transformation.[41] As exhibited in Scheme 17, tetra-substituted aziridine **56** was treated with the catalyst in CH_2Cl_2 to form *N*-tosyl imine **57**, which was hypothetically derived form a phenyl stabilized carbocation with coordination of the boron reagent to the ring nitrogen, followed by subsequent migration of a methyl group. The same results were obtained in aziridine **58** in quantitative yield. However, tri-substituted aziridine **60** was rearranged to give ketone product **61**, as a result of a



Scheme 17.



Scheme 18.



Scheme 19.

hydrolysed derivative from an imine intermediate. The migration evidently illustrated the preference of a hydrogen atom over an alkyl group.

2.4. Cyanide

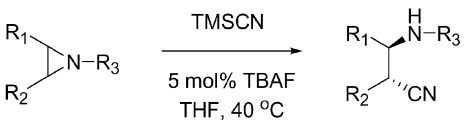
In general, ring opening of non-activated aziridines with a cyanide anion does not proceed without the assistance of Lewis acids, due to low nucleophilicity. However, when appropriate activating groups (such as carbonyl, carboxylate or sulfonamide) are attached to the aziridine nitrogen, the reaction becomes so useful that β-amino acids can be generated as one of its most useful applications. As shown in Scheme 18, aziridines **63** containing *p*-nitrobenzenesulfonyl (Ns) activating element could be derived from 1,2-aminols **62** and readily underwent nucleophilic attack with NaCN to give nitriles **64** in high yields.[42] High regioselectivity was consistently derived from the nitrile addition at the less hindered methylene carbon, except for phenyl aziridine showing a complex mixture. Acid mediated hydrolysis of addition products led to the synthesis of β-amino acids **65**. Because the starting amino alcohols were reduction products of α-amino acids, this method furnishes a complementary procedure for converting α-amino acids to β-amino acids in a straightforward manner.

In a separate report by Yadav and co-workers, no reaction was determined when NaCN was used to open the *N*-Ts aziridine ring.[43] However, they found the reaction took place effectively in the presence of 10 mol% $LiClO_4$ in hot acetonitrile (Scheme 19). Table 10 illustrated nucleophilic addition could be accomplished in less than 10 h to give nitrile products **66** and **67** in high yields. The reaction procedure remained to be simple with clean product profiles, but the regio-selectivity only appeared moderate.

Table 10. $LiClO_4$ catalyzed synthesis of β-azidoamines

R_1	R_2	Time (h)	Yield (%)	**66**:**67**
$-(CH_2)_3-$		7	90	—
$-(CH_2)_4-$		6.5	85	—
Ph	H	5.5	90	92:8
n-C_4H_9	H	8	87	15:85
n-C_8H_{17}	H	9.5	83	10:90

Trimethylsilylcyanide was found to be an efficient nucleophile for ring opening of aziridines under tetrabutylammonium fluoride (TBAF) catalytic conditions as shown in Scheme 20.[44] TBAF was used to release the cyanide anion, which then attacked the activated aziridines at the less hindered site. β-Amino nitrile derivatives **68** were obtained in excellent yields and regio-selectivity. It is noticeable that both phenyl and alkyl aziridines gave the external nitrile regio-isomers, which is in contrast to the regio-selectivity outcome of many other nucleophilic additions resulting in opposite selectivity. The activating group at the aziridine nitrogen seemed to be important to facilitate the addition, in which strong electron-withdrawing groups (Ts and COPh) were needed, except for the *t*-Boc aziridine giving complicated results. Non-activated aziridines did not react with TMSCN. Similar results were also reported by others, when catalysed by lanthanide cyanides [$(Yb(CN)_3$, $Y(CN)_3$ and $Ce(CN)_3$)] (Table 11).[45]



68

Scheme 20.

Table 11. Ring opening of aziridines with TMSCN mediated by TBAF

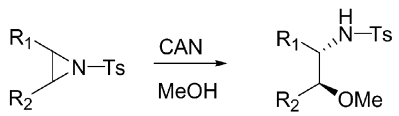
R_1	R_2	R_3	Time (h)	Yield (%)
$-(CH_2)_4-$		Ts	0.5	95
$-(CH_2)_3-$		Ts	5	>99
$-(CH_2)_6-$		Ts	24	0
H	H	Ts	10	91
Ph	H	Ts	0.6	>99
n-C_4H_9	H	Ts	0.3	>99
n-C_6H_{13}	H	Ts	2	82
$-(CH_2)_4-$		COPh	12	88
$-(CH_2)_4-$		H	24	0
$-(CH_2)_4-$		Bn	24	0
$-(CH_2)_4-$		Boc	24	0

3. Oxygen nucleophilic addition

Although structurally identical to epoxides, aziridines, in general, show lower reactivity toward oxygen containing nucleophiles. Therefore, the ring opening of aziridines is largely dependent on the activation at the ring nitrogen either by attaching electron-withdrawing groups and/or on the use of appropriate Lewis acids in oxygen nucleophilic addition. Due to appealing use of bi-functionalized amines in organic synthesis and pharmaceutical research, dramatic progress has been made in recent years in searching for efficient, convenient, low cost and environmentally friendly reagents, as well as simple conditions for ring opening of aziridines.

3.1. Alkyl and aryl alcohols

A powerful aziridine ring opening reagent, ceric ammonium nitrate (CAN) was identified by Chandrasekhar et al. recently to catalyze aziridine ring cleavage to form vicinal amino methyl ethers.[46] The nucleophilic addition of methanol to various tosyl activated aziridines catalyzed by CAN presents a general method for the preparation of amino ethers **69** due to a robust procedure and high yields (Scheme 21). However, the limit remains in the regio-chemistry, when less sterically biased aziridines were used for the ring opening reaction (Table 12).



69

Scheme 21.

Table 12. Ring opening of *N*-tosylaziridines with MeOH

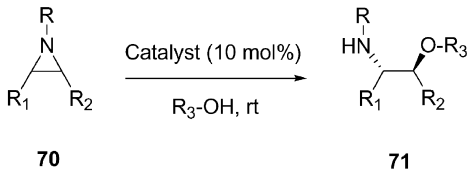
R_1	R_2	Yield (%)	Ratio (internal:external)
$-(CH_2)_4-$		93	—
$-(CH_2)_3-$		94	—
$-(CH_2)_5-$		77	—
H	Ph	90	Internal
n-C_4H_9	H	87	23:77
$MeO_2C(CH_2)_8$	H	85	28:72

A variety of N-substituted aziridines **70** underwent the ring opening reaction with primary alcohols to give vicinal *trans* amino ether **71** in excellent yields, when catalytic amount of $Sn(OTf)_2$ and $BF_3{\cdot}OEt_2$ were used.[47] The tosyl activated aziridine was a good substrate for the ring opening, whereas a non-activated phenyl aziridine worked almost equally well, but with much shorter reaction time needed to complete the addition. On the other hand, the $BF_3{\cdot}OEt_2$ catalyst accelerated the ring opening significantly, particularly in the cases of MeOH and BnOH. This is one of most robust methods reported in the literature for the alcoholysis ring opening of aziridines. It is noticed that regio-selectivity appeared to be poor as reported in mono-substituted aziridines. Similar results were reported using the same catalysts under the microwave conditions.[48] The pronounced advantage for this procedure includes the addition with hindered alcohols that was achieved in microwave in less than 15 min instead of 2 days without microwave irradiation (Table 13, Scheme 22).

Another very interesting regio-selective ring opening of a piperidinyl aziridine with alcohols was disclosed recently from our laboratory.[49] This nucleophilic addition took place with piperidinyl aziridine **6** in the presence of $BF_3{\cdot}OEt_2$ in alcoholic solvents. We found the size of the alcohols played

Table 13. Cleavage of aziridines with alcohols catalyzed by $Sn(OTf)_2$ and $BF_3{\cdot}OEt_2$

R	R_1	R_2	R_3	$Sn(OTf)_2$		$BF_3{\cdot}OEt_2$	
				Time	Yield (%)	Time	Yield (%)
Ts	$-(CH_2)_4-$		Me	1 h	99	20 min	99
	$-(CH_2)_4-$		Allyl	1 h	99	1 h	92
	$-(CH_2)_4-$		Bn	20 h	90	2 h	94
	H	Ph	MeOH	30 min	98	15 min	99
	C_5H_{11}	H	MeOH	30 h	76	4 h	96
Ph	$-(CH_2)_4-$		Me	10 min	76	10 min	92
	$-(CH_2)_4-$		Allyl	15 min	86	5 min	91
	$-(CH_2)_4-$		Bn	24 h	66	2 h	86



Scheme 22.

a role in the rate of the addition: longer reaction time for hindered *t*-BuOH to complete the conversion. In all the cases studied, the nucleophilic addition occurred at the *para* position to the piperidine nitrogen in >20:1 ratio in favor of the designed products **72** (Table 14). The consistent high yields with remarkably high regio-selectivity in such a simple system were a gift to our research program. The regio-selectivity was rationalized based on a plausible argument in which a nucleophile accessed the C4 carbon more readily than the C3 carbon, due to the bottom face shielding by the carboxylate-boron complex (Scheme 23). The more pronounced selectivity in the Lewis acid catalyzed ring open of the aziridine is consistent with that in carbanion addition discussed in Section 2.1.

Table 14. Ring opening of aziridine with alcohols catalyzed by $BF_3{\cdot}OEt_2$

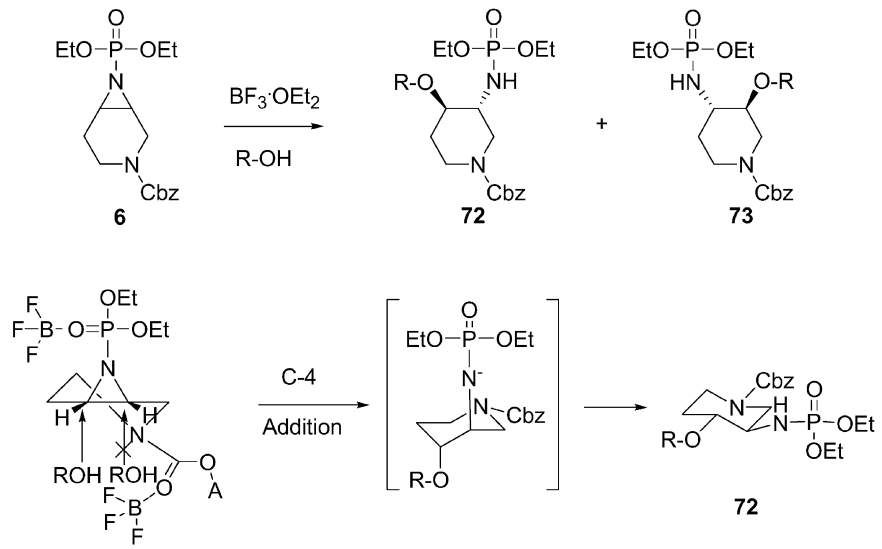
R-OH	Temperature	Time (h)	Yield (%) of **72** (%)	**72**:**73**
MeOH	0 °C	2	72	>20/1
EtOH	0 °C	2	83	>20/1
i-PrOH	0 °C–rt	5	84	>20/1
t-BuOH	rt	16	87	>20/1
BnOH (CH_2Cl_2)	rt	6	81	>20/1
PhOH(CH_2Cl_2)	rt	6	78	>20/1

Table 15. KSF clay catalyzed ring opening of aziridines with alcohols

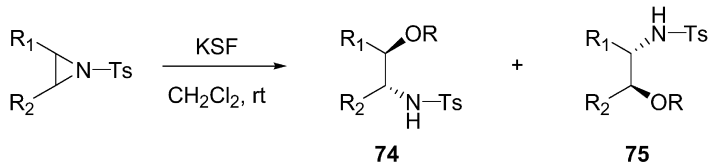
R_1	R_2	R	Time (h)	Yield (%)	**74**:**75**
$-(CH_2)_4-$		Allyl	5.0	89	—
$-(CH_2)_4-$		Propargyl	6.5	90	—
$-(CH_2)_3-$		Allyl	6.0	85	—
Ph	H	Et	3.5	90	96:4
p-Tolyl	H	Allyl	3.0	88	97:3
p-Tolyl	H	Benzyl	4.0	89	92:8
Cyclohexyl	H	Et	6.0	81	7:93
n-Bu	H	Allyl	8.5	87	12:88

The advances in organic chemistry in searching for effective solid acidic catalysts such as clays, ion-exchange resins and zeolites have led to discovery of montmorillonite KSF catalysis for the cleavage of aziridines with alcohols.[50] The low cost and environmentally compatible catalyst triggered the ring opening of tosyl aziridines with various alcohols (Scheme 24). The procedure not only presented a convenient method in operation, but gave the products in high yields as seen in Table 15. More significantly, the clay catalysis resulted in the nucleophilic addition to alkyl substituted aziridines with higher regio-selectivity than that in other protic or Lewis acid catalytic conditions.

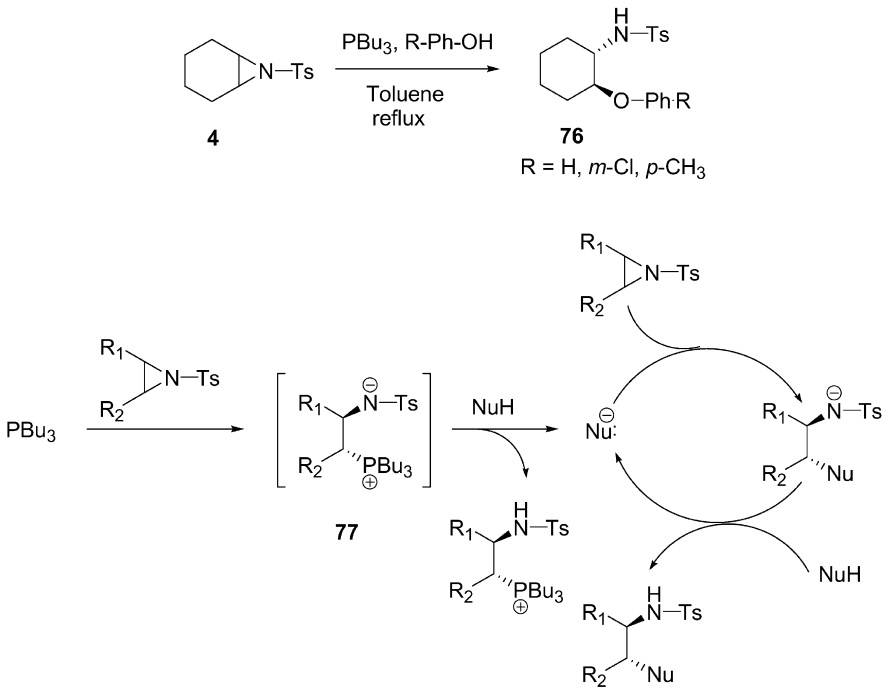
It has been noticed that phosphine reagents are weaker bases, but stronger nucleophiles than amines. This unique feature was captured by Dai and co-workers in ring opening of aziridines promoted by tributylphosphines.[51] When *N*-tosyl cyclohexyl aziridine **4** and phenol was treated with 10 mol% of PBu_3 in refluxing toluene, good to excellent yields of aziridine ring opening products were obtained with *trans* stereochemistry. Under the same conditions, no ring opening products were obtained in the



Scheme 23.



Scheme 24.



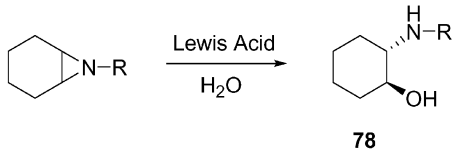
Scheme 25.

absence of PBu_3, which suggested that the phosphine reagent was involved in the catalysis. This was further supported by a mechanistic study of the ring opening reaction, in which a crystalline perchlorate salt of phosphonium **77** was isolated and characterized by ^1H and ^{31}P NMR spectroscopies. A possible pathway was proposed as shown in Scheme 25, where the organophosphine acts as a nucleophilic trigger to produce **77**, which then serves as a base to deprotonate the nucleophile. The aryloxy anion then attacks the aziridine to complete the catalytic cycle. However, the application of this procedure remains limited only to aryl alcohols and regio-selectivity was not discussed.

3.2. Hydroxyl anion

The ring opening of both activated and non-activated aziridines with a water molecule can be achieved similarly to that with alcohols. Reaction conditions have been developed mainly under protic or Lewis acid catalyzed conditions. The stereochemical outcome of the addition is controlled by an *anti* attack in general and the regio-chemistry is largely dependent on the reaction conditions chosen. Steric effects and effects from the functional group present in substrates also play roles in governing the site of the addition.

The ring opening of activated aziridines with the water nucleophile has long been recognized under the conditions of mineral acids[52] and recently Lewis acids, such as $BF_3{\cdot}OEt_2$ and $Sn(OTf)_2$, were reported in the literature to promote the ring opening reaction.[53] As shown in Scheme 26, the water molecule attacked the cyclohexyl ring *anti* to the aziridine nitrogen to give *trans* aminols **78**. Both activated and non-activated aziridines proved substrates for the opening reaction. Although other Lewis acids, such as $Cu(OTf)_2$, $CuCl_2$, $SnCl_2$, $AlCl_3$, $FeCl_3$ and $LiClO_4$, were also explored to catalyze the ring opening reaction, only inefficient functional group transformation was observed with essentially impractical chemical yields (Table 16).



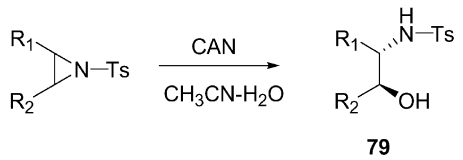
Scheme 26.

Table 16. Ring opening of cyclohexylimines with water catalyzed by $BF_3{\cdot}OEt_2$ and $Sn(OTf)_2$

R, Lewis acid	*p*-Tosyl			Ph		
	Solvent	Time (h)	Yield (%)	Solvent	Time (min)	Yield (%)
$BF_3{\cdot}OEt_2$	CH_3CN	5	90	THF	20	90
$Sn(OTf)_2$	CH_3CN	15	89	THF	20	92

Ceric ammonium nitrate (CAN) again demonstrated high utility in catalyzing ring opening of aziridines leading to the synthesis of vicinal amino alcohols as seen in vicinal amino ether formation.[46] Tosyl activated aziridines underwent the ring opening smoothly and consistent high chemical yields for aminols **79** were obtained in all cases reported. Again, the same limitation for the poor regio-chemistry was seen in water addition as that in alcohol addition mentioned above (Scheme 27), except for that in aryl aziridines (Table 17).[54]

High regio-selective aziridine ring opening was demonstrated by Concellon and Riego[55] in the case of non-activated amino aziridines. The water molecule attacked the amino aziridines at either C3 or C2 depending on the reaction conditions employed. When the dibenzylamino



79

Scheme 27.

Table 17. Ring opening of *N*-tosylaziridines

R_1	R_2	Yield (%)	Ratio (internal:external)
$-(CH_2)_4-$		95	—
$-(CH_2)_3-$		90	—
$-(CH_2)_5-$		75	—
H	Ph	92	Internal
C_4H_9	H	90	70:30
$MeO_2C(CH_2)_8$	H	75	68:32

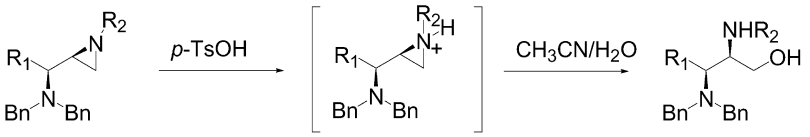
aziridines **80** was treated with 1 equiv. of *p*-TsOH in a mixed solvent CH_3CN/H_2O (Scheme 28), the addition occurred at the less hindered methylene via a protonated aziridinium intermediate, leading to 2,3-diaminoalkan-1-ols **81** as a result of the C3 addition in good to high yields, as shown in Table 18. This is consistent with the observation reported earlier by Davis and co-worker[56] with regio- and stereo-selectivity of the addition to an arylaziridine under protic conditions. The reaction proceeded faster at higher temperature (80 °C) with limited effects on the reaction yield and purity. However, higher regio-selectivity (19:1 ratio) was observed at 20 °C.

Alternatively, the same group developed another set of reaction conditions, which allowed the C3 addition as a predominant ring opening site.[55] $BF_3{\cdot}OEt_2$ was used to promote the addition at the more hindered carbon. In this case, the reaction was carried out in CH_3CN on heating and amino alcohols **82** were obtained in low to good yields. Total regio- and stereo-selective ring opening was characterized by NMR spectroscopy. Addition at the C2 position was rationalized by neighboring group participation of the dibenzylamine resulting in a highly activated aziridinium salt form as shown in Scheme 29, which underwent water attack to give the C2 addition products. The double inversion at the C2 center led to the retained stereochemistry (Table 19).

Table 19. C-2 Ring opening of aziridine **80**

R_1	Me	Me	*i*-Bu	Bn	$TBSOCH_2$
R_2	Bn	Pr	Bn	Bn	Bn
Yield (%)	40	38	81	74	76

Aziridinyl carboxylates are of particular interests in nucleophilic addition, due to the importance of addition products as useful amino acid congeners. Under protic conditions, the ring opening preferentially proceeded at the β-position to give serine-type amino acid analogs. In connection with work on pyrrolidine-containing HIV protease inhibitors, Iqbal's group developed an efficient synthetic pathway to construct tripeptide derivatives by using regio- and stereo-selective ring opening of aziridine peptide (Scheme 30).[57] *p*-TsOH promoted addition of water



80 81

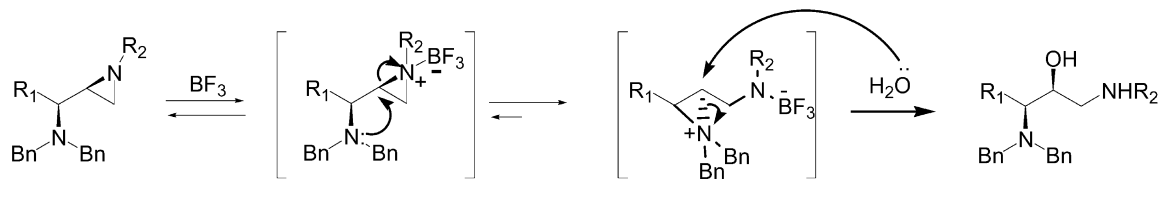
Scheme 28.

Table 18. C-3 Ring opening of aziridine **80**

R_1	R_2	Temperature (°C)	Time (h)	Yield (%)
Me	Bn	80	1	72
Me	Bn	20	24	90
Me	Pr	80	1	76
i-Bu	Bn	80	0.5	78
Bn	Bn	80	0.5	74

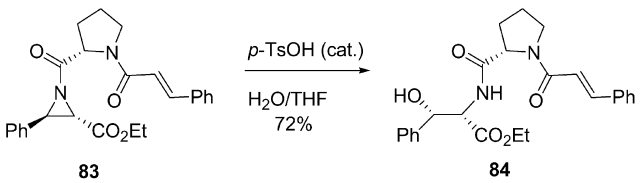
to the aziridine **83** occurred at the β-position in an *anti* attack fashion to give β-hydroxy phenylanaline analog **84** in 72% yield as a single stereo-isomer.

Alternatively, an indirect α-addition to an aziridine to result in an α-ring opening product was presented by Cardillo and co-workers[58–60] An acyl activated aziridinyl amide **85** was catalyzed by $BF_3{\cdot}OEt_2$ to initially produce a rearrangement oxazoline **86**, which was then hydrolyzed to give an isoserine product **87**, an equivalent of β-adduct. The stereo center at the α-position was inverted during this



80 82

Scheme 29.



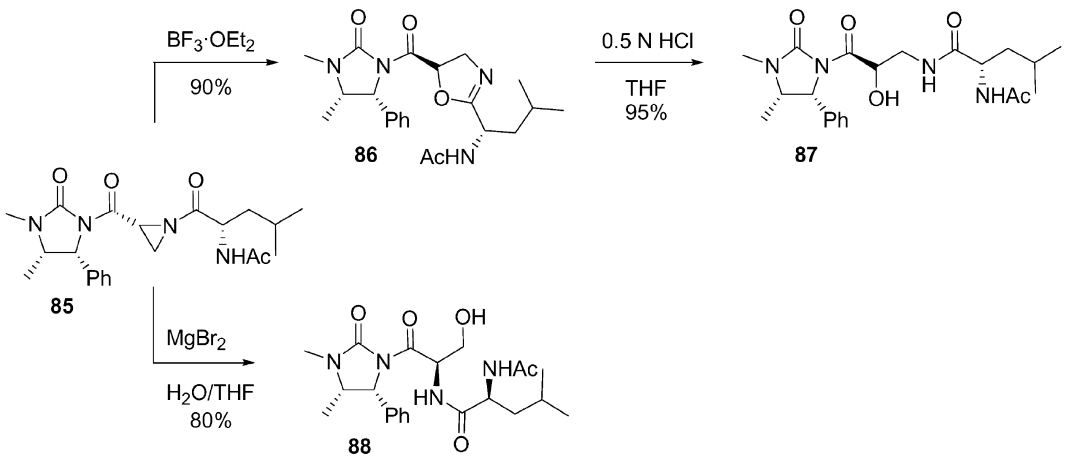
Scheme 30.

transformation by *anti* attack. In addition, the β-attack could also be achieved using a different set of ring opening conditions involving Lewis acid $MgBr_2$ and only 1.1 equiv. of the water molecule needed to give D-serine product **88** (Scheme 31).

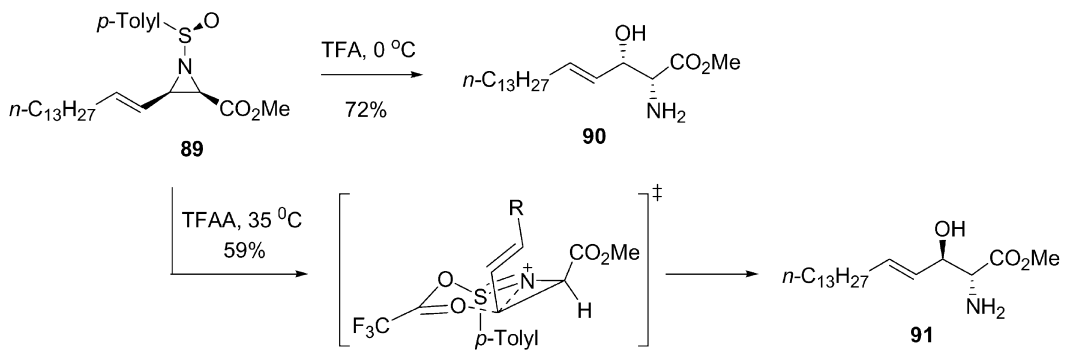
Other reaction conditions were also explored in the aziridine ring opening to form a hydroxy amine difunctionality, including trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA).[61] In both cases, the same regio-chemistry, β to the carboxylate of aziridine **89**, was observed. One notable difference was observed with opposite chirality between adducts **90** and **91**. This was rationalized via an intramolecular transition state as shown in Scheme 32. A complementary procedure was also reported using an acyl or a carbamate as an activating group, which was involved in the ring opening reaction to form an oxazolidinone.[62,63] After hydrolysis, a hydroxy amine was obtained for further functionalization (Scheme 33).

Most of aziridine ring openings to form amino alcohols were achieved under either protic or Lewis acid conditions. However, Besbes[64] reported the ring opening could also be achieved using a neutral protocol, but the addition occurred specifically at the more substituted carbon of acyl aziridines **92**. The formation of a tertiary carbocation for the confirmed regio-specificity was excluded by the author, whereas a mechanism involving the formation of a hydrogen bond with the acyl group at the aziridine nitrogen was proposed to support the observation. The second water molecule came to break the weakened bond in the transition state to yield the tertiary alcohols **93** in 76–91%.

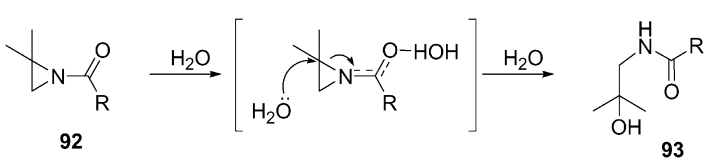
Scarce examples were found in the literature describing



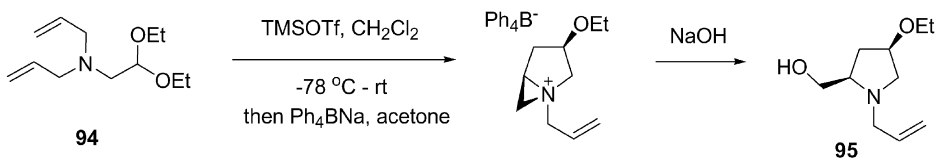
Scheme 31.



Scheme 32.

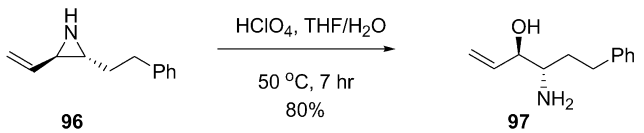


Scheme 33.

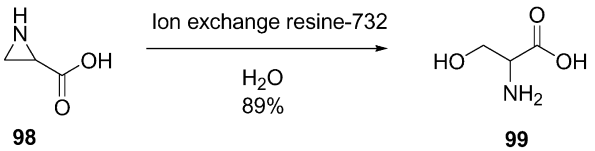


Scheme 34.

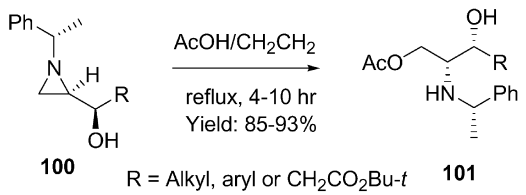
nucleophilic aziridine ring opening to form aminols under basic conditions, which has been believed largely due to insufficient activation of the aziridine ring. Exceptions were found in a report by Rayner and co-workers[65] in which a highly activated aziridinium intermediate was generated from diallylamine **94** and underwent attack by a hydroxy group to give pyrrolidinyl methanol **95** in 67%. Steric control governed the site of the addition at the less hindered carbon leading to the primary alcohol (Scheme 34). This tandem cationic cyclization-aziridinium ion formation-nucleophilic ring opening procedure provided a useful methodology for the stereo-controlled synthesis of substituted pyrrolidines from an acyclic precursor.



Scheme 35.



Scheme 36.



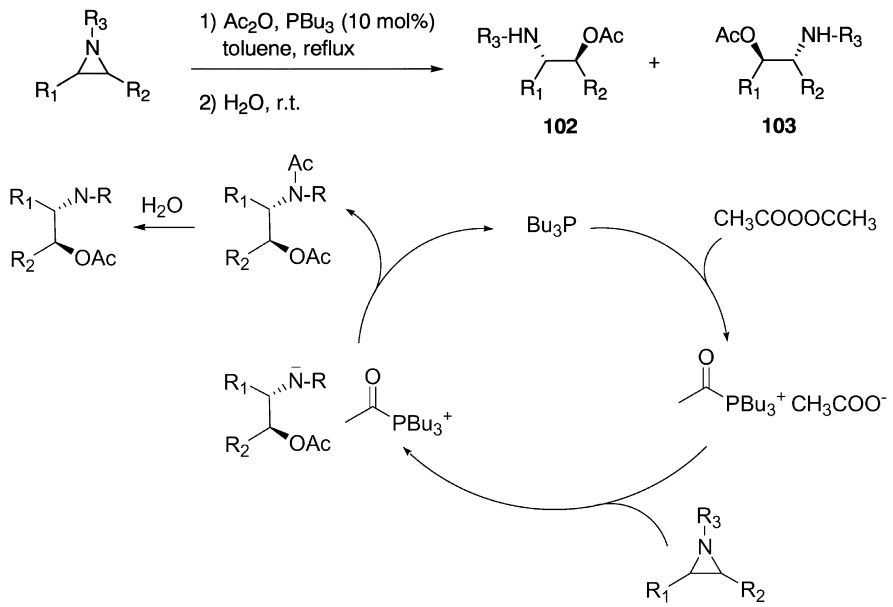
Scheme 37.

The majority of aziridine hydrolysis leading to amino alcohol derivatives took place with fully substituted aziridine ring nitrogen for sufficient activation to undergo nucleophilic attacks. However, it should be noted that hydrolysis of *N*-H aziridines can also be achieved under protic conditions, such as $HClO_4$ (Scheme 35)[66] ion exchange resin (Scheme 36)[67] with high regio-selectivity and stereo-selectivity.

3.3. Carboxylate anion

Regio-selective ring opening of activated or non-activated aziridines in the presence of carboxylic acids proceeds in a similar steric controlled fashion to that of the alcohols and the water molecule. The carboxylates of the addition products usually resided at the less congested carbons. The work reported by Ha and co-workers[68,69] is a recent example of the regio-selective ring opening of aziridines **100** with carboxylic acids to give amino alcohol **101**. It is widely believed that the acid used catalyzes the addition by activating the ring nitrogen and then the second acid molecule attacks the less hindered ring carbon to give amino carboxylates (Scheme 37).[70]

The ring opening of aziridines catalyzed by tributylphophine with acetic anhydride is a complementary procedure to prepare amino esters. Based on previous observation of

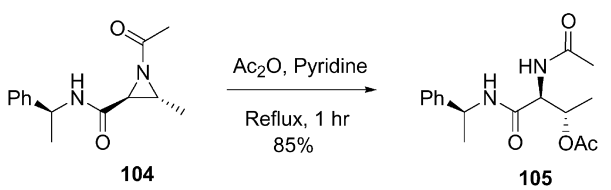


Scheme 38.

an organophosphine promoted ring opening reaction of aziridines and epoxides, Fan and Hou[71] found that activation of anhydrides with a catalytic amount of the organophosphine facilitated the aziridine ring opening under neutral conditions with high chemical yields (Scheme 38). In general, the reaction products (**102** and **103**) were obtained in good yields with excellent regio-selectivity, but regio-chemistry suffered in the phenyl aziridine case (Table 20). The steric argument may explain the results due to the increasing bulkiness of the activated tributylphosphine-anhydride complex, leading to the attack at the less crowded ring carbon. A plausible mechanism was proposed based on ^{31}P NMR spectral evidence. Tributylphosphine activated the anhydride by forming $Bu_3P^+OAc{\cdot}AcO^-$, which underwent attack to the aziridine to yield the ring opening product with recycling of the phosphine catalyst.

Table 20. The tributylphosphine catalyzed ring opening of aziridines with acetic anhydride

R_1	R_2	R_3	Time (h)	Yield (%)	**102**:**103**
$-(CH_2)_4-$		Tosyl	24	85	—
Ph	H	Tosyl	12	76	65:35
$-(CH_2)_4-$		-COPh	24	72	—
$-(CH_2)_4-$		Boc	48	81	—
n-Bu	H	Tosyl	24	89	>95:5



Scheme 39.

Table 21. $In(OTf)_3$-catalyzed ring opening of aziridines with carboxylic acids

R_1	R_2	Acid	Time (h)	Yield (%)	**107**:**108**
$-(CH_2)_3-$		Acetic acid	3.5	89	—
$-(CH_2)_3-$		Crotonic acid	2.5	92	—
Ph	H	Phenylacetic acid	3.0	90	92:8
Ph	H	Acetic acid	2.5	92	96:4
c-Hex	H	Acetic acid	4.0	89	7:93
n-Bu	H	Acetic acid	4.5	87	12:88

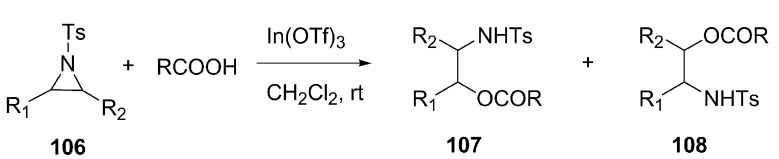
This method is equally applicable to epoxide ring opening with even higher chemical yields.

A similar procedure was used by Cardillo and co-workers to convert acyl aziridines to enantio-pure L-allo-threonine analogs.[72] The activated aziridine ester **104** was treated with acetic anhydride in the presence of pyridine. The ring opening reaction was conducted in refluxing pyridine with high regio- and stereo-selectivity in product **105** as shown in Scheme 39. It was believed that the catalytic cycle for the aziridine ring opening with Ac_2O-Pyr should likely proceed in an identical fashion to that with Ac_2O-PBu_3 as mentioned previously.

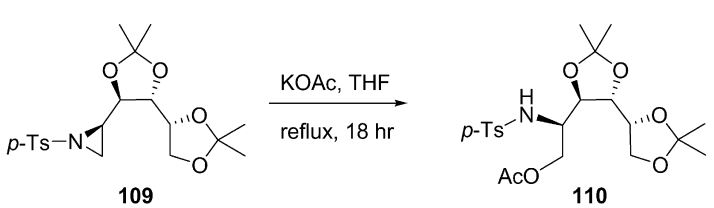
A general procedure was recently developed in the laboratory of Yadav,[73] in which indium triflate was found to effectively catalyze the ring opening of aziridine **106** under mild reaction conditions leading to β-amino acetates and benzoates in high yields and high regio-selectivity. Both phenyl-and alkyl-*N*-tosyl aziridines underwent cleavage by acids to form the products **107** and **108** in decent, but opposite, regio-selectivity as seen in other nucleophilic addition to aziridines. However, the authors did not mention potential application of this method for alcohol nucleophiles, which could be indicative of the limitation of the method only to the acids, not general to other types of nucleophiles (Table 21, Scheme 40).

An alternative method for the ring opening of an *N*-tosyl aziridine was reported by the laboratory of Compernolle[74] describing conversion of aziridine **109** to the corresponding amino acetate **110** using potassium acetate as a nucleophile. The tosyl aziridine was heated with KOAc in THF for 18 h to afford the product in 90% (Scheme 41). Excess nucleophile must be used to prevent dimeric by-product formation. The product generated was a precursor to an aminoglucital leading to the synthesis of analogs of 1-deoxymannojirimycin, inhibitors of mannosidases. The experiment represented an example of the aziridine ring opening under neutral conditions without a catalyst (Scheme 41).

Rearrangement of acyl aziridines into oxazolines has been well documented in the literature. The most widely used method would be the ring opening of aziridine catalyzed by $BF_3{\cdot}OEt_2$. One very recent representative sample included



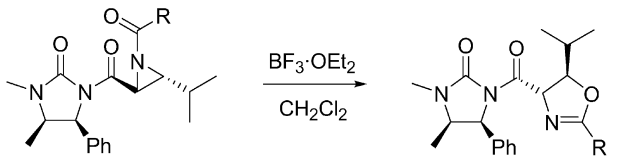
Scheme 40.



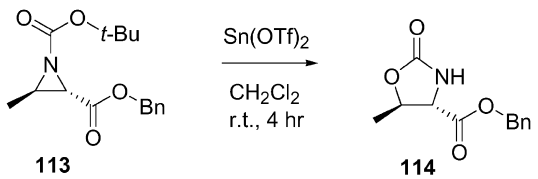
Scheme 41.

the report from Cardillo's group in an effort toward synthesis of 5-isopropyl-oxazoline-4-imide as *syn*-hydroxyleucine precursor.[75] The ring expansion to the corresponding *trans*-oxazolines occurred under complete regio- and stereo-control, by treatment with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (Scheme 42). The reaction of both alkyl and aryl amides **111** provided high chemical yields. The mechanistic aspects of this reaction were discussed by Hori[76] and Lectka,[77] in which an S_N1 pathway was suggested to explain the observed stereochemistry. A number of isomerization methods have been developed to facilitate this transformation, including mineral acid H_2SO_4,[78] azaphilic metal salts $Cu(OTf)_2$, $Sn(OTf)_2$, $Zn(OTf)_2$,[79,80] $MgBr_2$, $Zn(O_2CCF_3)_2$,[81] and halide salt NaI.[82] These methods are complementary to that by $BF_3{\cdot}OEt_2$ catalysis for the improvement of reaction conditions, regio- and stereo-selectivity. The formed oxazolines **112** can be hydrolyzed to vicinal amino alcohols, useful functionalized intermediates as building blocks for other syntheses (see Section 3.2).

Aziridine ring expansion has been further extended to another subclass of oxazolidines under Lewis acid conditions. One recent report by Lucarini and Tomasini[83] showed that the optically active aziridine ester **113** containing a *t*-Boc group was converted to the corresponding oxazolidin-2-one **114** in quantitative yield with complete regio- and stereo-selectivity (Scheme 43). The retention of the stereochemistry at the carbon of the bonding breaking and forming process can be rationalized in the same fashion as that discussed earlier.



Scheme 42.



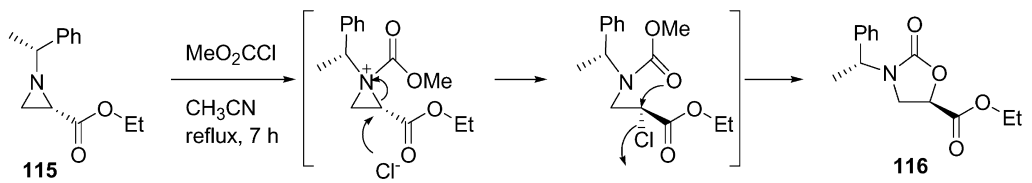
Scheme 43.

Due to sufficient nucleophilicity of the aziridine nitrogen, the ring opening could be initiated by the formation of the aziridinium ion intermediates when treated with chloroformates, which then underwent double nucleophilic addition to form oxazolidines. This work was reported by Lee and co-workers[84] in the enantio-selective synthesis of 5-functionalized oxazolidin-2-ones **116**. Because of double nucleophilic additions at the chiral center of aziridines **115**, retention of the configuration was the result with high chemical yields. In contrast to other Lewis acid catalysed aziridine ring expansion to form oxazolidin-2-ones, the regio-chemistry occurred at the α-position of the aziridine carboxylates, with the chloride attacking the chiral carbon to give a ring opening intermediate followed by ring closure to form an oxazolidinone ring as depicted in Scheme 44. Methyl and allyl chloroformates were good substrates for the ring expansion, whereas benzyl chloroformate caused a dramatic decrease in the reaction rate.

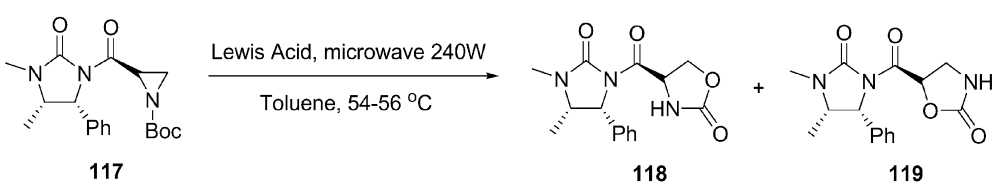
Microwave-assisted rearrangement of *N*-Boc-chiral aziridine-2-imides and esters to oxazolidin-2-ones in the presence of different Lewis acids was reported by Cardillo's laboratory.[85] The regio-selectivity of the reaction strongly depends upon the Lewis acids selected and the reaction conditions. As shown in Scheme 45 and Table 22, the treatment of aziridine **117** with 1 equiv. of the Lewis acid, $Cu(OTf)_2$, gave nearly 100% yield, but low ratio of regio-isomers, in favor of 4-substituted oxazolin-2-one **118** over isomer **119**, whereas $Zn(OTf)_2$ resulted in lower yield, but excellent regio-selectivity. In contrast, $BF_3{\cdot}OEt_2$ catalyzed the ring expansion with both excellent yield and

Table 22. Lewis acid assisted aziridine ring opening

Lewis acid	Reagent concentration (M)	Yield (%)	**118**:**119**
$Cu(OTf)_2$	0.028	>99%	64:36
$Zn(OTf)_2$	0.028	65	>99:1
$BF_3{\cdot}OEt_2$	0.056	>99	72:28
$BF_3{\cdot}OEt_2$	0.028	>99	>99:1
$MgBr_2{\cdot}OEt_2$	0.028	0	—
$BF_3{\cdot}OEt_2$	0	65	85:15



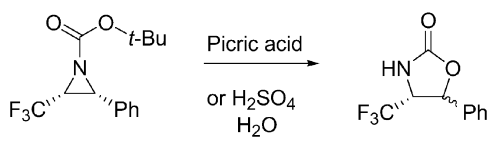
Scheme 44.



Scheme 45.

regio-selectivity at only 0.028 M concentration, but reduced ratio of regio-isomers at a higher concentration. $MgBr_2 \cdot OEt_2$ was found ineffective to the ring expansion under the microwave conditions with only recovered starting aziridine. The same reaction conditions were used to initiate the rearrangement catalyzed by $BF_3 \cdot OEt_2$ in 0.028 M concentration without microwave assistance, the products were observed in 65% yield, but 85:15 ratio of regio-isomers. This suggested that the ring expansion is activated by microwave irradiation (Table 22).

In contrast, a racemization outcome of stereochemistry is a result of selection of protic acids as catalysts in the ring expansion of aziridines to oxazolidin-2-ones. Two representative examples were found in the literature using H_2SO_4 and picric acid (Scheme 46),[86] in which stereo-selectivity suffered so much that the synthetic potential is greatly diminished in comparison to the aforementioned mild and selective methods.



picric acid: 2,4,6-trinitrophenol

Scheme 46.

3.4. Miscellaneous

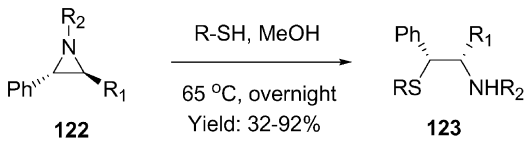
Other oxygen containing acids such as *p*-tolyl solfonic acid[87] and phosphoric acid[88] were also reported as effective nucleophiles to undergo ring opening of aziridines. A particular notion should be made to Sommerdijk's[89] work on autocatalytic ring opening of *N*-acylaziridines with complete control of regio-selectivity (Scheme 47). The researchers deliberately incorporated fatty acid chains and phenoxy groups to the aziridine **120** to increase their lipophilicity, which then acted as an interface orientation pointer under the reaction conditions of an organic-aqueous medium. Therefore, the unsubstituted aziridine carbon atom was exposed to the aqueous layer leading to the attack by phosphoric acid, which resulted in exclusive regio-selectivity (**121**).

4. Sulfur nucleophilic addition

The ring opening reaction of aziridines by thiols can readily proceed in either an activated or a non-activated form. The aziridine ring nitrogen in the non-activated form can served as a base to abstract a proton from the thiophinols or alkyl thiols to form an aziridinium intermediate, which is a very labile species. The nucleophiles of the deprotonated thiol anion then attack the aziridine ring carbon. The orientation of the attack generally occurs at a less hindered site to provide 2-amino sulfide products. On the other hand, activated aziridines, lacking basic nitrogen, often require a Lewis acid for further activation; thiol nucleophiles approach the less hindered site to open the ring. Consistently high chemical yields and high regio-selectivity have been observed in many reports.

4.1. Alkyl and arylsulfide anion

Thiophenols and aliphatic mercaptans are nucleophiles sufficient to induce ring opening of aziridines without assistance of catalysts or bases. A recent report by Leeuwen and co-workers[90] described such conditions in regio-selective addition of various sulfur nucleophiles to aziridines **122** derived from norephedrine. The reaction required heating in methanol overnight to complete the addition (Scheme 48). The optically active vicinal amino disulfide products **123** were efficient catalytic ligands for asymmetrical transfer hydrogenation of unsymmetrical ketones. Similar results were also reported by others in thiophenol addition to non-activated aziridines to give regio-selective β-amino sulfides in good yield.[91,92]



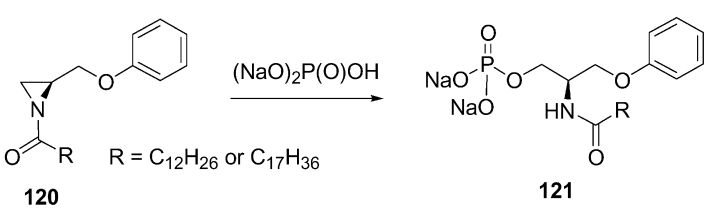
122 123

R = Ph, Bn, *i*-Pr; R_1 = Me or Ph; R_2 = H or Me;

Scheme 48.

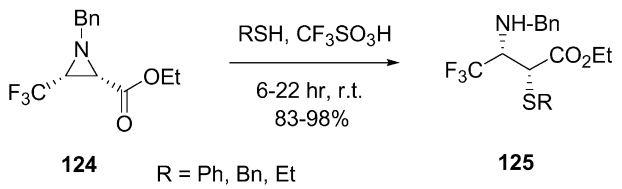
Alternatively, the ring opening reaction proceeded more readily with thiols in the presence of a strong acid (CF_3SO_3H).[93] In this case, the reaction was carried out at room temperature and completed in less than 16 h with alkyl thiols, but 22 h with thiophenol. The ring opening of **124** was highly regio-selective with the thiol addition at the α-carbon of the carboxylate and stereo-selective with the *anti* attack to the ring to give the corresponding adducts **125** in high chemical yields (Scheme 49).

It was found that the use of Lewis acids significantly accelerated the ring opening of aziridines when attacked by thiophenols and other thiols.[94] For example, (2*S*,3*S*)-*N*-benzyl-2,3-diphenylaziridine **126** underwent nucleophilic addition with thiophenol to give only 8% of the corresponding adduct **127** in 24 h at room temperature. However, in the presence of $ZnCl_2$ (10 mol%), the same ring opening reaction was complete within 5 min at room temperature in 85% yield (Scheme 50). The Lewis acid could catalyze

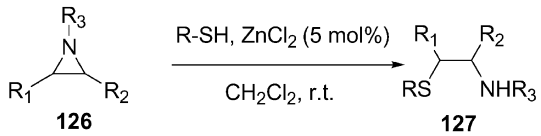


120 121

Scheme 47.



Scheme 49.



Scheme 50.

the ring opening of the activated and non-activated aziridines in good to excellent yields (Table 23). The addition occurred at the less hindered ring carbon with high regio-selectivity. Other Lewis acid catalysts were also found to effectively promoted the ring opening of aziridines, including $Zn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$.

Table 23. Ring opening of aziridines with thiols catalyzed by $ZnCl_2$

R_1	R_2	R_3	R	Yield (%)
H	Ph	H	*p*-Cl-Ph	61
H	Ph	Bn	Ph	81
H	Ph	Bn	Bn	71
H	Ph	Bn	*n*-Bu	79
$-(CH_2)_4-$		PhCO	Ph	72
$-(CH_2)_4-$		Boc	Ph	81
$-(CH_2)_4-$		Ts	Ph	67
H	*n*-Bu	Bn	*p*-*t*-Bu-Ph	95

Boron trifluoride-diethyl etherate has been widely used in catalytic ring opening of aziridines under nucleophilic conditions using thiophenols and other thiols. However, at least a stoichiometric amount of $BF_3{\cdot}OEt_2$ and excess thiol were needed to achieve practical chemical results. As shown below, phenyl aziridine carboxylate **128** underwent the ring opening with 3 equiv. of *p*-$MeOPhCH_2SH$ under catalytic conditions of 1.5 equiv. of $BF_3{\cdot}OEt_2$ to provide (2*R*,3*S*)-Boc protected β-phenylcysteine derivative **129** in 67% yield (Scheme 51).[95]

Aqueous organophosphine-mediated ring opening of aziridines was developed by Fan and Hou.[96] In the presence of catalytic amount of tributylphosphine, the ring opening proceeded smoothly with various nucleophiles including thiophenols and aliphatic mercaptans in water as a solvent as shown in Scheme 52. In a control reaction, it was found no reaction took place in the absence of the organophosphine agent. The screening of several organophosphines resulted in the identification of tributylphosphine as the best catalyst to promote the ring opening reaction. A plausible mechanism was proposed: the phosphine attacked the aziridine **130** to form a salt, which acted as a base to abstract a proton from the nucleophile to generate the sulfur anion. Then the anion attacked the activated aziridine as depicted in Section 3.1. This method exhibits potential of being both economical and environmentally benign (Table 24).

Table 24. Ring-opening reaction of aziridines in water catalyzed by PBu_3

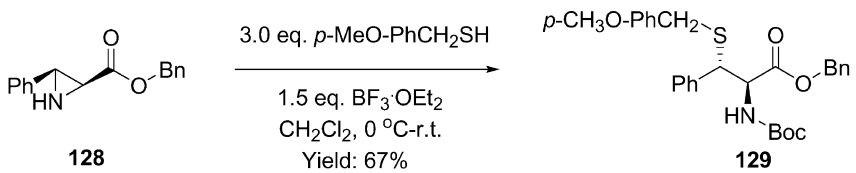
R_1	R_2	R_3	R	Yield (%)	**131**:**132**
$-(CH_2)_4-$		Tosyl	Ph	98	—
$-(CH_2)_4-$		Tosyl	4-Me-$PhCH_2$	99	—
$-(CH_2)_4-$		Bn	Ph	62	—
$-(CH_2)_4-$		Tosyl	*t*-Bu	88	—
Ph	H	Tosyl	Ph	98	50:50

4.2. Thioacyl acids

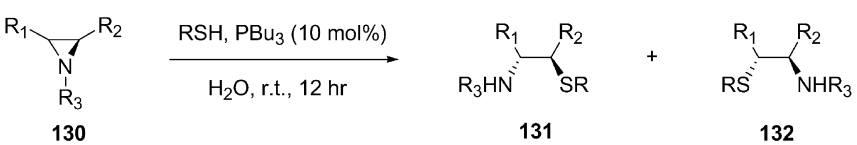
Only limited reports were found in the literature describing addition of thioacyl acids to aziridines in recent years. It was believed that the proton transfer from thio acids to aziridines to form aziridinium cation was the rate determining step. Therefore, in a study of the acidity influence of thio acids to aziridines was carried out by Lee and co-workers,[92] and found that the aziridine ring opening (**133**) was significantly fast with thioacetic acid: at −78 °C, the reaction finished within 3 min and gave the corresponding product **134** in 87% yield (Scheme 53), whereas thiophenols and other thiols took longer time at room temperature to complete the reaction as discussed earlier.

4.3. Miscellaneous

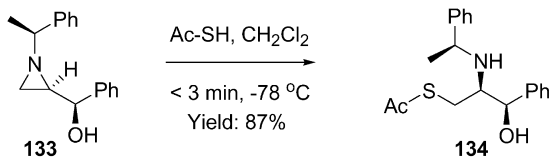
A recent report described a new and expeditious asymmetric



Scheme 51.



Scheme 52.



Scheme 53.

synthesis of 2-amino alkanesulfonic acids from chiral aziridines.[97] As shown in Scheme 54, the unsubstituted aziridines **135** could undergo ring opening with sodium bisulfite ($NaHSO_3$). The reaction proceeded in high regio-selectivity, in which the bisulfite anion attacked the aziridines at the less hindered site. 2-Amino alkanesulfonic acids **136** are mimics of amino acids and potentially useful for the study of the physiological processes of some compounds found in many mammalian tissues.

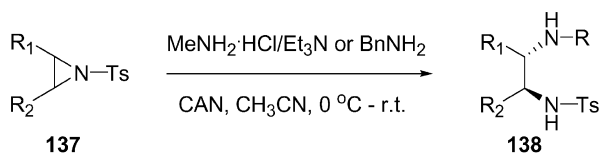
Scheme 54.

5. Nitrogen nucleophilic addition

Ring opening of aziridines with nitrogen nucleophiles including amines and azides still attracts significant attention of organic community due to increasing interests in diamine compounds in synthetic and medicinal chemistry. Amines are strong nucleophilic agents attacking either activated or non-activated aziridines without assistance of catalysts. However, recent advances in aziridine chemistry have led to the development of a number of efficient and useful methods under catalytic conditions representing high yields, high regio-selectivity and ease of experimental operation, complementary to those already reported in the literature.

5.1. Amines

Activated aziridines could be converted to ring opening products when alkylamines were used to attack the aziridines in the absence of assistance of Lewis acids to yield the corresponding 1,2-diamino derivatives.[98] As shown in Scheme 55, both $MeNH_2{\cdot}HCl$ salt/Et_3N or $BnNH_2$ could open the aziridine ring in **137** containing a tosyl group at the ring nitrogen. As shown in Table 25, both methyl- and benzylamines attacked the phenyl substituted aziridines at the benzylic carbon, whereas no reaction was seen with $BnNH_2$ in the case of mono-substituted phenyl aziridine at room temperature. In contrast, methylamine did not react with cyclohexyl- and cylcopentylaziridines, but



Scheme 55.

Table 25. Ring opening of *N*-tosylaziridines with amines in CH_3CN

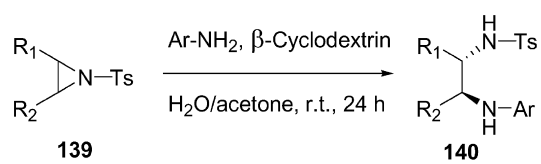
R_1	R_2	R	Time (h)	Yield (%)
Ph	H	Me	12	81
Ph	H	Bn	12	No reaction
Ph	CH_2OBn	Me	10	82
Ph	CH_2OBn	Bn	8	94
	$-(CH_2)_3-$	Me	12	No reaction
	$-(CH_2)_3-$	Bn	7	87
	$-(CH_2)_4-$	Me	12	No reaction
	$-(CH_2)_4-$	Bn	3 (at 55 °C)	93

benzylamine did. In general, the reaction occurred at room temperature with complete regio- and stereo-selectivity for **138**. However, heating could potentially compromise regio-selectivity. Similar results with amine nucleophilic addition to aziridines were also reported by others with regio- and stereo-selectivity (Table 26).[99]

Table 26. β-Cyclodextrin catalyzed aziridine opening with aniline nucleophiles

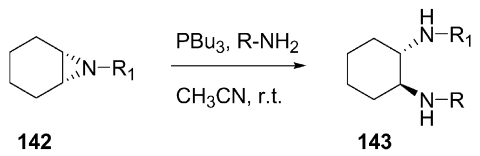
R_1	R_2	Ar	Yield (%)
	$-(CH_2)_4-$	Ph	89
	$-(CH_2)_4-$	*p*-MeOPh	92
n-C_4H_9	H	*o*-MeOPh	89
H	Ph	*o*-MeOPh	79

In contrast to ring opening of aziridines with azides catalyzed by Lewis acids (Section 5.3), there have been fewer methods developed for Lewis acid catalysis of amine addition to aziridines. This is largely due to incompatibility of many Lewis acids with basic amines under reaction conditions. One elegant procedure was recently developed using non-Lewis acid catalytic conditions, β-cyclodextrin, to facilitate ring opening of aziridines.[100] The reaction was carried out by dissolving β-cyclodextrin, a cyclic oligo-saccharide, in water followed by addition of various aziridines **139** and nucleophiles. The optimum ratio of the catalyst was found to be 0.25 mol% of the substrate and it could be recovered for recycling. The alkyl aziridine gave the adducts **140** from the attack at the less hindered carbon; in contrast, the phenyl aziridine afforded the products from attack at the benzylic carbon, all with high regio-selectivity (Scheme 56).



Scheme 56.

Similar to the examples discussed earlier in Section 3.1, tributylphosphine also demonstrated its potential in promoting the nucleophilic addition of free amines to aziridines. As shown in Scheme 57, the conversion of aziridines **142** to diamines was carried out smoothly with aniline and alkylamines in the presence of catalytic tributylphosphine (10 mol%) at room temperature to give good to high yields of addition products **143**. This method not only allowed the ring opening of activated aziridines,



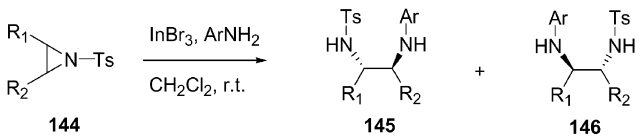
Scheme 57.

but non-activated ones as well in good yields. It was found that only low yields of products were obtained in the absence of the catalyst in the *N*-tosyl aziridine, whereas traces of products were detected in *N*-Boc and *N*-Bn aziridines. Regio-selectivity was not discussed in this case, but assumed to be less pronounced, similar to that in the ring opening of aziridines with alcohols (Table 27).

Table 27. Ring opening of aziridines with amines catalyzed by *n*-Bu_3P

R_1	R	Yield (%) (10 mol% catalyst)	Yield (%) (no catalyst)
Ts	Ph	89	55
Ts	Bn	85	50
Ts	*i*-Pr	80	50
Boc	Ph	70	Trace
Bn	Ph	62	Trace

Among Lewis acids studied for catalytic ring opening of aziridines, indium tribromide ($InBr_3$) has recently been identified as an alternative Lewis acid catalyst to effectively activate the aziridine ring for nucleophilic addition.[101] A mild reaction procedure was developed which required only 10 mol% of the $InBr_3$ catalyst to facilitate the addition of aziridines **144** (Scheme 58). This catalyst was compared with $YbCl_3$ and higher chemical yields were obtained throughout the cases examined (Table 28). In addition, good to high regio-selectivity was seen, especially in the case of the alkyl substituted aziridine (up to 95:5). The limitation of this procedure remains in the use of aryl amines as nucleophiles, and no examples of alkylamine nucleophiles were reported in the publication.



Scheme 58.

In recent years, the laboratory of Yadav has been actively involved in the development of effective catalysts facilitating ring opening of aziridines with various nucleophiles. One of his new findings included lithium perchlorate-catalyzed analine addition to aziridines as depicted in Scheme 59 below.[102] When aziridines were treated with aromatic amines in the presence of catalytic $LiClO_4$ in acetonitrile, 1,2-diamine derivatives **147** and **148** were formed in high yields (82–95%). Styrene-*N*-tosyl imine underwent cleavage in a regio-selective manner with preferential attack at the benzylic carbon as shown in Table 29, whereas external attack was seen in the alkyl aziridine. Higher regio-selectivity was seen in the latter case. However, a limitation existed in the choice of nucleophiles, in which only aromatic amines produced the ring opening to give the diamine products, but aliphatic amines failed to react with aziridines under the conditions described.

Table 29. $LiClO_4$ catalyzed ring opening of aziridines with arylamines

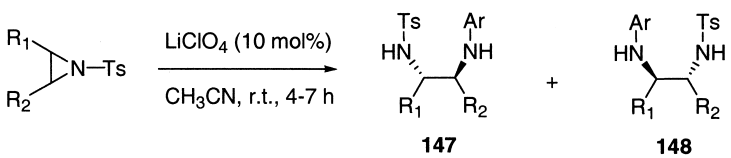
R_1	R_2	Ar	Time (h)	Yield (%)	**147**:**148**
$-(CH_2)_4-$		Ph	5.5	90	—
$-(CH_2)_4-$		4-MeO-Ph	5.0	95	—
H	Ph	Ph	4.0	90	78:22
H	Ph	4-MeO-Ph	4.0	91	87:13
Vinyl	Ph	Ph	6.5	82	75:25
n-C_5H_{11}	H	Ph	5.0	90	95:5
n-C_5H_{11}	H	4-MeO-Ph	7.5	85	92:8

A method using $LiClO_4$ to facilitate the ring opening of aziridines was described by another group as a complimentary procedure to that of Yadav's demonstrated above.[103] As shown in Scheme 60, the reaction took place with non-activated aziridines in refluxing acetonitrile in the presence of $LiClO_4$ and resulted in ring opening products **149** in good to high yields. In this case, aliphatic amines were used as nucleophiles to attack the aziridines. However, the chiral amine addition led to a mixture of diastereomers with no diastereo-selectivity, although *trans* addition was consistent throughout the study.

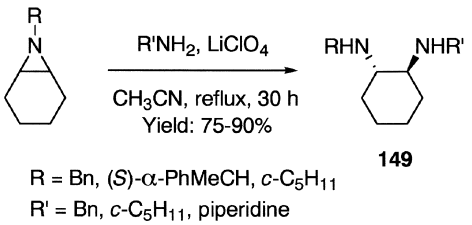
Bismuth trichloride represented one of the mildest and most efficient methods for ring opening of aziridines with amines.[104] The addition reaction of either activated or non-activated aziridines was carried out with anilines in the

Table 28. Indium tribromide catalyzed aminolysis of aziridines with aryl amines

R_1	R_2	Ar	10% $InBr_3$ time (h)	Yield (%)	Ratio (**145**:**146**)	10% $YbCl_3$ time (h)	Yield (%)
$-(CH_2)_3-$		Ph	6	92	—	7.5	81
$-(CH_2)_4-$		Ph	5.5	90	—	7.0	82
$-(CH_2)_4-$		2,5-$(MeO)_2$Ph	7.5	78	—	9.0	69
H	Ph	Ph	4	90	78:22	6.0	83
H	*n*-Bu	Ph	7	85	95:5	9.0	71

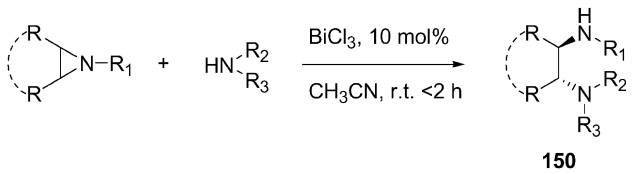


Scheme 59.



Scheme 60.

presence of $BiCl_3$ to give nearly quantitative yields of 1,2-diamines **150** (Scheme 61 and Table 30). Although the convenient procedure was attractive, neither regio-selectivity was discussed in the report, nor the generality of amine nucleophiles for aliphatic amines. In addition, the nucleophiles were limited to only aniline type amines.



Scheme 61.

Table 30. $BiCl_3$ catalyzed aziridines opening with amines

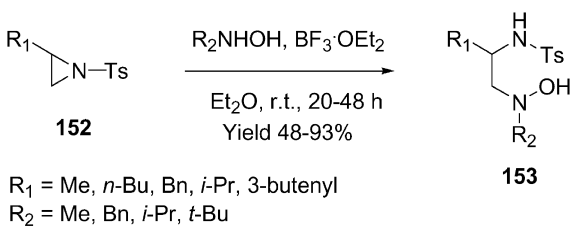
R–R	R_1	Amine	Time (h)	Yield (%)
$-(CH_2)_4-$	Ts	$PhNH_2$	1.5	96
$-(CH_2)_4-$	4-MeOPh	$PhNH_2$	2	94
$-(CH_2)_4-$	Ph	4-$MeOPhNH_2$	2	93
$-(CH_2)_3-$	Ph	$PhNH_2$	1.5	95
Me, Me	Bn	PhNHMe	2	93

Although BF_3 Lewis acid has been widely used in catalytic ring opening of aziridines with a number of nucleophiles, including alcohols, thiols, azides, nitrile, there has been limited success in ring opening of aziridines with amines. This is suspected to be largely due to deactivation of the amine nucleophile by the catalyst toward reaction with the aziridine. To circumvent this detrimental effect, Yudin and Watson recently developed a method using tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] as an effective Lewis acid to promote the ring opening successfully with amines.[105] The addition reaction to non-activated aziridine took place with amines in the presence of 10 mol% $B(C_6F_5)_3$ in refluxing CH_3CN to give diamine products **151** in nearly quantitative yields (Table 31). It was found that at least 2 equiv. of water were needed to facilitate the opening reaction, which was proven by elucidation of ^1H, ^{19}F NMR spectra and X-ray crystal structure. As shown in Scheme 62, an intermediate was proposed, in which a water molecule was involved in the catalytic process leading to the ring opening product. Although (*S*)-methyl benzylamine amine added to the aziridine in excellent yield, it failed to provide diastereoselectivity. This method also worked for the *N*-tosyl activated aziridines as effective as non-activated ones. The diamine product formed an adduct complex with $B(C_6F_5)_3$, which was inseparable by chromatography and basic extraction. However, the diamine product could be separated by the solid resin Amberlyst A-21.

Table 31. Ring opening of non-activated aziridines catalyzed by $B(C_6F_5)_3$

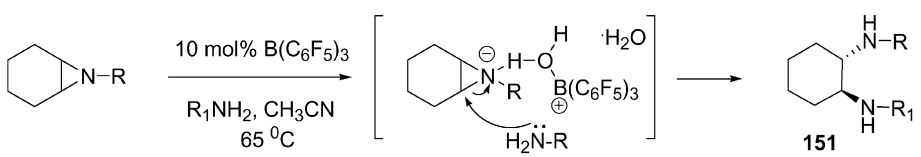
R	R_1	Equiv. of amine	Time (h)	Yield (%)
Bn	Bn	1.0	16	98
Bn	Ph	1.2	24	99
Bn	(*S*)-MeCHPh	1.2	24	98 (1:1)
$(CH_2)_3OH$	Bn	2.0	48	97
Ts	Bn	1.2	12	99

BF_3, in general, was not an effective catalyst for ring opening of aziridines as mentioned above, but proved to be the mediator of choice to facilitate hydroxylamine addition to aziridines. O'Neil et al. demonstrated that BF_3 smoothly catalyzed ring cleavage of mono-substituted *N*-tosylated aziridines **152** with hydroxylamines at the less hindered site to afford the hydroxylamine adduct **153** in reasonable to high yields (Scheme 63).[106] The β-*N*-tosylaminohydroxylamine products are differentially functionalized 1,2-diamine precursors, useful for other synthesis.

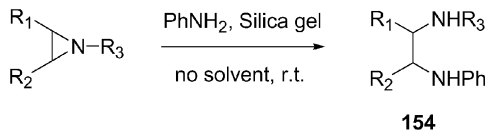


Scheme 63.

In distinction to other methods reported for catalytic ring opening of aziridines, Singh et al. took a different approach by opening non-activated aziridine rings with aryl amines without Lewis acids.[107] The reaction took place on the surface of silica gel resulting in diamines **154**. The great feature of this procedure included a solvent free condition, and addition products were easily obtained by eluting the silica gel on a column with solvents (Scheme 64). Reaction yields varied depending on the substituents of the aziridines and aniline nucleophiles as shown in Table 32. Aliphatic amines were found inactive under these conditions and the finding can be potentially useful for selective ring opening.



Scheme 62.

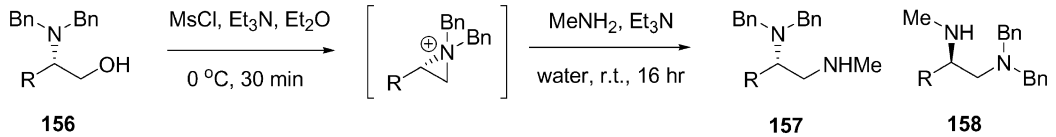


Scheme 64.

Table 32. Silica gel assisted ring opening of aziridines with amines

R_1	R_2	R_3	Time (h)	Yield (%)
$-(CH_2)_4-$		Ph	1	91
$-(CH_2)_4-$		Bn	2	91
Me	Me	Bn	24	45
H	Ph	*n*-Bu	48	89
n-$C_{10}H_{21}$	H	*t*-Bu	10	35

1,2-Diamines, especially chiral 1,2-diamines, are of considerable synthetic interests due to their synthetic and pharmaceutical value. One recent approach involved intermediate aziridinium ions as activated species to undergo nucleophilic ring opening by amines.[108] This intermediate could be directly derived from chiral amino alcohols as shown in Scheme 65. The study on the regio-selectivity of methylamine addition to the aziridinium ions indicated that methyl substituted aziridinium ion gave low regio-selectivity. However, benzyl and isopropyl substituted amino alcohols gave excellent selectivity. In contrast, phenyl aziridinium salt produced the corresponding diamine in nearly exclusive opposite regio-selectivity. In this case, no Lewis acids or bases were needed to facilitate the ring opening reaction. An identical work was reported by Lowden and Mendoza in parallel synthesis of 1,2-phenethyldiamines from ring opening of aziridines via an aziridinium ion (Table 33).[109]



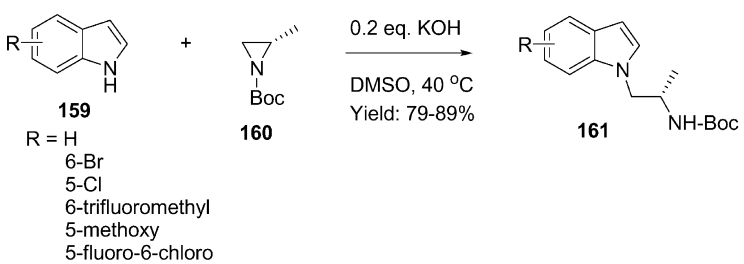
Scheme 65.

Table 33. Study of regio-selectivity of ring opening of aziridinium ions

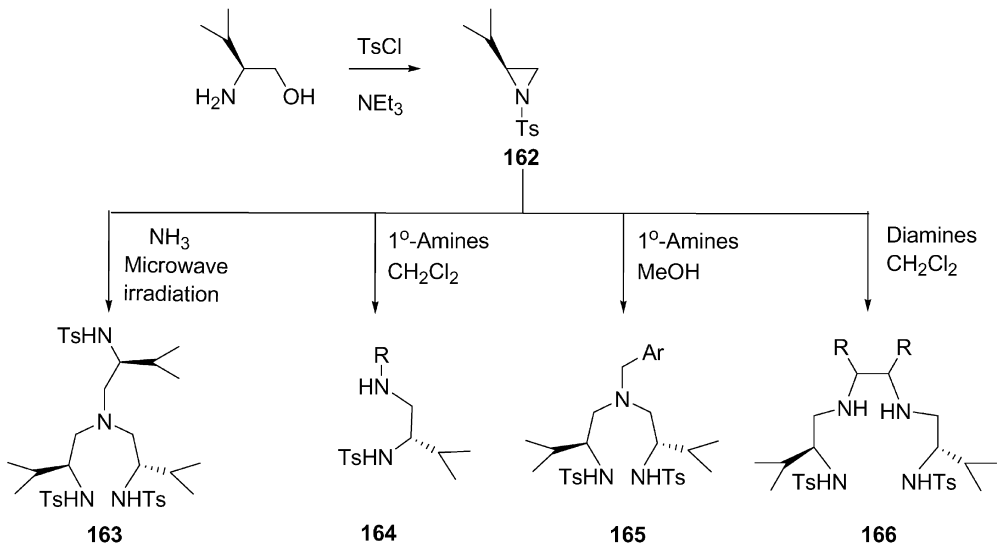
R	Yield (%) (isolated)	**157**:**158**
Me	98 (78)	70:30
Bn	94 (70)	94:6
i-Pr	81 (62)	93:7
Ph	78 (—)	2:98

As discussed earlier in Section 2.2, indoles can undergo nucleophilic addition to aziridines to give ring opening products derived from the C3 attack of the indoles. However, the indole nitrogen cac also conduct the ring opening of aziridines under a different set of reaction conditions. A method published very recently as an improved process for the N-alkylation of indoles **159** using chiral 2-methylaziridine **160** with activation.[110] The reaction was carried out in a catalytic KOH solution in DMSO as an optimal procedure with a high degree of conversion to products **161** (79–89% yield) and simple precipitation for purification as shown in Scheme 66.

The development and application of new monochiral ligands in asymmetric catalysis continues to be an area of enormous interests and activity, since the approach represents one of the most efficient means of obtaining enantiopure chiral compounds. Ring opening of aziridines by nucleophilic addition of amines represented an attractive method for synthesis of monochiral ligands. Moberg and co-workers[111] presented their results by altering the mole amount of aziridines relative to amines used to optimize the formation of desired products. As shown in Scheme 67, the *N*-Ts aziridine **162** was prepared from (*S*)-alaninol and then underwent alkylation with various amine nucleophiles. Under microwave conditions with ammonia, a C3-symmetric tripodal tris(sulfonamide) **163** was obtained in 88% yield. It was found that a ratio of 4.5:1 of the aziridine:NH_3 was optimal with no detectable mono- and di-adducts (Table 34). Alkylation could be stopped at mono-addition (**164**) with a large access of amines (3.0 equiv.). On the other hand, when 3.0 equiv. of the aziridine was used, di-alkylation products **165** were the predominant adducts as C2-symmetric dipodal bis(sulfonamide). Alternatively, when C2-symmetric primary diamines were taken as nucleophiles to add to 2.1 equiv. of the aziridine, tetradentate ligands **166** were obtained in good to high yields. The important aspect of these symmetric ligands was their potential utility in asymmetric induction, such as diethylzinc addition to benzaldehyde mediated by Ti(O*i*-Pr)$_4$. Solvent effects of single and double ring opening of *N*-tosyl chiral aziridines with $BnNH_2$ was also reported by others,[112] in which chemo-selectivity favored the single ring opening



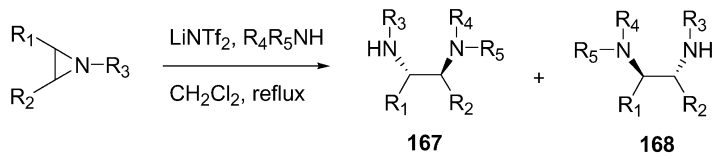
Scheme 66.



Scheme 67.

Table 34. Ring opening of aziridine **162** with ammonia, benzylamines and diamines

Amine	**162** (equiv.)	Solvent	Time	Temperature	Yield (%)	Product
NH_3	4.5	MeOH	45 min (MW)	160 °C	88	**163**
$BnNH_2$	0.33	CH_2Cl_2	21 h	0 °C –rt	75	**164**
Ph_3CNH_2	0.33	CH_2Cl_2	21 h	0 °C–rt	100	**164**
t-$BuNH_2$	0.33	CH_2Cl_2	21 h	0 °C–rt	66	**164**
$BnNH_2$	3.0	MeOH	35 h	45–55 °C	63	**165**
$Ph(CH_3)CHNH_2$ (*R*)	3.0	CH_2Cl_2	2–3 d	rt	83	**165**
Ph_2CHNH_2	3.0	CH_2Cl_2	2–3 d	rt	82	**165**
R=Ph (*R,R*)	2.1	CH_2Cl_2	2–3 d	rt	84	**166**
R=$(CH_2)_4$ (*R,R*)	2.1	CH_2Cl_2	2–3 days	rt	64	**166**
R=binaphthyl (*R*)	2.1	CH_2Cl_2	2–3 days	rt	58	**166**



Scheme 68.

in acetonitrile exclusively, whilst the double ring opening took place in methanol. In a similar fashion, double adduct bis(sulfonamide) **165** was converted to chiral 1,4,7-triazacyclononanes, useful metal-chelating agents (Table 34).[113]

Table 35. Reaction of amines with aziridines

R_1	R_2	R_3	R_4	R_5	Time (h)	Yield (%)	**167**:**168**
$-(CH_2)_4-$		Bn	Bn	H	48	83	—
$-(CH_2)_4-$		Bn	Et	Et	48	45	—
$-(CH_2)_4-$		Ts	$Ph(CH_2)_2$	H	72	87	—
$-(CH_2)_4-$		Ts	Et	Et	48	0[a]	—
$-(CH_2)_4-$		Ts	Et	Et	48	60	—
$-(CH_2)_4-$		Boc	$Ph(CH_2)_2$	H	48	73	—
H	Ph	Ts	$Ph(CH_2)_2$	H	72	73	70:30

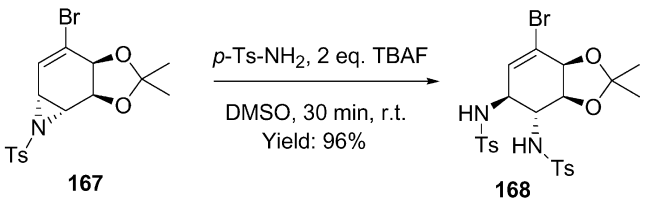
[a] In the absence of $LiNTf_2$.

When lithium bistrifluoromethanesulfonimide ($LiNTf_2$) was used as a promoter, either activated or non-activated aziridines could be converted to the corresponding ring opening diamine products.[114] As shown in Scheme 68 and Table 35, 0.2 equiv. of the catalyst was used to accelerate the ring opening reaction at reflux CH_2Cl_2. $LiNTf_2$ not only catalyzed the *N*-tosyl aziridines to open the ring by amine attack, but so did *N*-benzyl aziridine as well. Primary amine nucleophiles resulted in high yield of products **167** (or **168**), whereas diethylamine and diallylamine gave the products with only reduced yields. A Boc group was also a suitable activating substituent for the aziridines, when catalyzed by $LiNTf_2$. However, regio-selectivity is less appealing when

unsymmetrical aziridines were studied, in comparison to other alternatives.

5.2. Amides

There have been only sparse reports describing amide nucleophilic addition to aziridines in recently years. One related work was found in the literature by Hudlicky and co-workers[115] showing that vinyl aziridine **169** opening could be accomplished with *p*-toluenesulfonamide as the nucleophile by employing TBAF as a catalyst. 1,2-*trans*-Diamino relationship for the synthesis of 3,4-diamino-3,4-dideoxyl-L-*chiro*-inositol was established. The addition occurred under such mild reaction conditions (Scheme 69) that excellent chemical yield (95%) for **170** was achieved coupled with high regio- and stereo-selectivity.



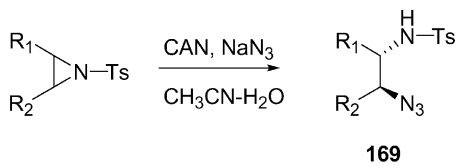
Scheme 69.

5.3. Azides

There have been tremendously increasing activities in method development for ring opening of aziridines with azides in recent years. Most of these activities have remained in searching for catalysts, which promote the nucleophilic addition with either metal azide salts or trimethylsilylazide. Most of the reported methodologies are practically useful, but complementary in various perspectives including high chemical yield, high regio-selectivity, easy operation (mild reaction condition, short reaction time, quick work up and non-anhydrous conditions), low cost of reagents and non-hazardous chemicals. All these provide multiple options of methods with consideration of substrate and product criteria.

Ceric ammonium nitrate (CAN) has demonstrated its utility in hydrolysis and alcoholysis of aziridines to form vicinal amino alcohols and amino ethers (see Section 2.1 and 2.2). In addition, its application has been extended to synthesis of vicinal azidoamines by azide addition to aziridines.[46] Due to the mild reaction conditions used, high chemical yields were obtained in most of cases reported. But moderate regio-selectivity was observed when alkyl substituted aziridines were subjected to the ring opening reaction conditions (Scheme 70 and Table 36).

Although activated aziridines were commonly used as electrophiles to undergo ring opening by the azide attack,

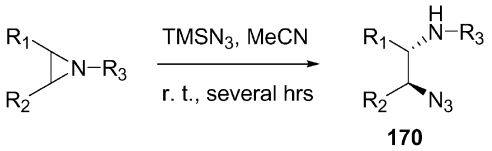


Scheme 70.

Table 36. Ring opening of *N*-tosylaziridines

R_1	R_2	Yield (%)	Ratio (internal:external)
$-(CH_2)_3-$		92	—
$-(CH_2)_4-$		95	—
$-(CH_2)_5-$		70	—
H	Ph	93	internal
C_4H_9	H	83	25:75
$MeO_2C(CH_2)_8$	H	82	18:82

non-activated aziridines were also precursors to produce the ring opening smoothly with trimethylsilylazide.[116] When *N*-benzyl cyclohexylaziridine was treated with $TMSN_3$ in CH_2Cl_2, a quantitative yield of the azido adduct **170** was obtained (Scheme 71). The optimal solvents were found to be CH_2Cl_2 and MeCN, but high tolerance to various solvents was observed when $Sn(OTf)_2$ was added as a catalyst. The addition appeared to be regio-selective when unsymmetrical aziridines were used (Table 37). It was assumed that the non-activated aziridines formed an aziridinium complex with TMS, and then the activated species underwent nucleophilic addition by the azide to give the ring opening products.[117] This assumption was supported by the evidence that *N*-Ts aziridine reacted slowly with $TMSN_3$ in 20 days to complete the reaction.

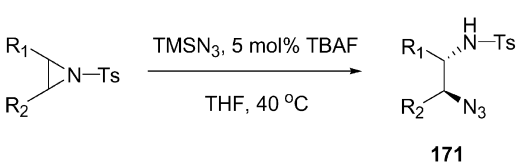


Scheme 71.

Table 37. Cleavage of N-substituted aziridines with TMS azide in MeCN at room temperature

R_1	R_2	R_3	Time (h)	Yield (%)
$-(CH_2)_4-$		Bn	2.5	99
$-(CH_2)_4-$		Ph	4	98
H	Ph	Bn	2	83
n-C_7H_{15}	H	Bn	1	93
n-C_9H_{19}	H	*t*-Bu	1	82
$-(CH_2)_4-$		Ts	20 d	70

Although activated aziridines were not good substrates for the ring opening with $TMSN_3$ alone, the reaction could be facilitated in the presence of tetrabutylammonium fluoride in excellent yields.[44] The reaction occurred under mild conditions and was complete within several hours dependent on the substrates (Scheme 72). However, poor regio-selectivity was seen in the case of a phenyl substituted aziridine, excellent regio-selectivity was obtained in the alkyl substituted aziridines as shown in Table 38. Activating groups were sensitive to the reaction conditions and *N*-tosyl



Scheme 72.

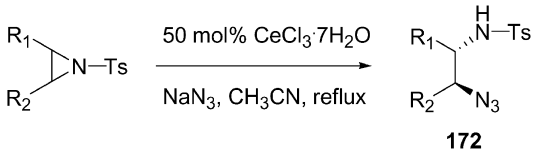
Table 38. Ring opening of *N*-tosylaziridines with $TMSN_3$

R_1	R_2	Time (h)	Yield (%)
$-(CH_2)_3-$		12	83
$-(CH_2)_4-$		4	99
H	Ph	4	90 (36:64)[a]
n-C_4H_9	H	6	97
n-C_6H_{13}	H	4	99

[a] Ratio of internal adduct versus external adduct.

was identified to be the most suitable group for the ring opening reaction.

With *N*-sulfonamide activation, aziridines could also be attacked by sodium azide in the presence of Lewis acid cerium(III) chloride to give ring opening products. This was a convenient and efficient method developed by Yavad and co-workers for the synthesis of 1,2-azidoamines.[118] Various *N*-Ts aziridines were treated with NaN_3 and 50 mol% $CeCl_3{\cdot}7H_2O$ in acetonitrile and water mixed solvent at reflux temperature for 3–6 h to give the corresponding azidoamines derivatives **172** in high yields. The regio-selectivity was very high in all examples studied in which the addition proceeded at the internal site with aryl aziridines and at the external site with alkyl aziridines as shown in Scheme 73 and Table 39. Identical results were also reported by the same group using $TMSN_3$ catalyzed by a different Lewis acid to promote the ring opening of aziridines.[119]



Scheme 73.

Table 39. Regio-selective ring opening of aziridines using $CeCl_3{\cdot}7H_2O/NaN_3$

R_1	R_2	Time (h)	Yield (%)
$-(CH_2)_4-$		3	97
H	Ph	3	94 (3)[a]
H	4-Me-Ph	3	90 (5)[a]
n-C_4H_9	H	6	90
n-C_8H_{17}	H	6	95

[a] Yield for the other regio-isomer.

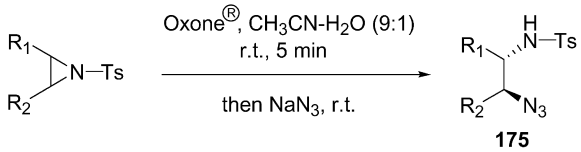
Along with emerging application of lithium perchlorate as an effective promoter for various organic transformations, this mild Lewis acid also found its utility in catalyzing ring opening of aziridines with sodium azide.[120] As shown in Scheme 74 and Table 40, the nucleophilic addition of the azide to aziridines containing an *N*-Tosyl group resulted in

Table 40. $LiClO_4$ catalyzed synthesis of β-azidoamines

R_1	R_2	Time (h)	Yield (%)	**173**:**174**
$-(CH_2)_3-$		6	90	—
$-(CH_2)_4-$		5.5	85	—
Ph	H	4	90	8:92
4-Me-Ph	H	3.5	92	5:95
n-C_4H_9	H	6	90	13:87
n-C_8H_{17}	H	6	85	12:88

the ring opening products **173** and **174** in high chemical yields and acceptable regio-selectivity. The efficacy of other Lewis acids, such as $InCl_3$, Ycl_3 and $YbCl_3$, was also studied for this transformation and $LiClO_4$ was found to be the most effective catalyst. These conditions were claimed to display mild and clean reaction profiles, simplicity in operation and low cost in the catalyst.

Analogous to ring opening of epoxides, Oxone® ($2KHSO_5$, $KHSO_4$, K_2SO_4) could also convert the aziridines to 1,2-azidoamine derivatives under very mild reaction conditions.[121] This inexpensive, safe and readily available oxidizing agent appeared to be more powerful than many other Lewis acid catalysts in ring opening of aziridines, due to its extraordinarily mild conditions and high yields coupled with high regio-selectivity (Scheme 75 and Table 41).



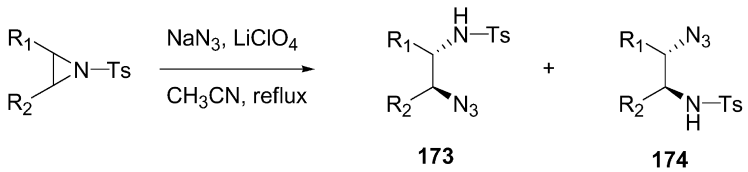
Scheme 75.

Table 41. Regio-selective ring opening of aziridines with NaN_3 in the presence of Oxone®

R_1	R_2	Time (h)	Yield (%)
$-(CH_2)_3-$		1	94
$-(CH_2)_4-$		1	98
$-(CH_2)_6-$		1	96
H	Ph	1.5	93 (5)[a]
H	4-Me-Ph	1.5	89 (6)[a]
Cyclohexyl	H	1.5	96
n-C_4H_9	H	3	89 (2)[a]
n-C_8H_{17}	H	3	94 (3)[a]

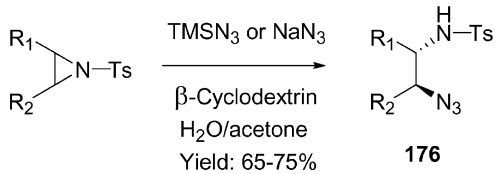
[a] Yield for the other regio-isomer.

Like ring opening of aziridines with amines, β-cyclodextrin equivalently catalyzed the ring opening of aziridines with either sodium azide or trimethylsilylazide to form azido-amines.[100] Unlike many other ring opening reactions mentioned previously, this reaction required aqueous conditions in a mixed solvent of water and acetone. The



Scheme 74.

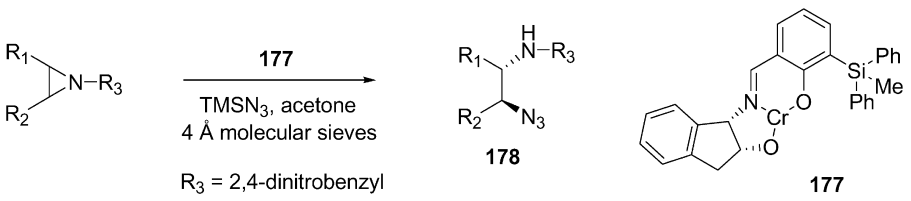
reaction took place at room temperature and good chemical yields were commonly obtained with various substituted *N*-Ts aziridine substrates (Scheme 76). With unsymmetrical aziridines, the reaction was highly regio-selective with the formation of only one product **176**, which was due to attack of the nucleophile at the less hindered terminal carbon atom.



R_1, R_2 = $(CH_2)_4$; R_1 = *n*-Bu, R_2 = H; R_1 = H, R_2 = Ph

Scheme 76.

Asymmetric nucleophilic ring opening of aziridines with azides has been of significant interest, but only limited success had been achieved with regard to scope and efficacy, although asymmetric ring opening of epoxides with $TMSN_3$ has demonstrated great success with the emergence of (salen)Cr(III) complexes. Recently, Jacobsen and co-workers discovered new and effective chromium(III) complexes containing tridentate Schiff bases to catalyze the ring opening of *meso* aziridines.[122] After examining a number of complexes of metals and chiral ligands, Cr(III) tridentate complex **177** as shown in Scheme 77 was identified to be one of the most optimal catalysts resulting in nucleophilic addition of the azide to symmetric aziridines. The reaction was carried out in acetone in the presence of 4 Å molecular sieves at −15 or −30 °C with only 5–10 mol% of the catalyst required. A high degree of conversion of the aziridines to azidoamines **178** and a high level of enantio-selectivity were obtained as summarized in Table 42. However, the ring opening reaction appeared to be very slow, and the application of this method for kinetic ring opening of other aziridines remains to be explored for its potential utility.



Scheme 77.

Table 42. Enantio-selective ring opening of *meso* aziridines catalyzed by chiral chromium(III) complexes

R_1	R_2	Time (h)	Temperature (°C)	Yield (%)	ee (%)
$-(CH_2)_4-$		48	−30	95	94
$CH_2CH{=}CHCH_2$		100	−30	75	88
$-(CH_2)_3-$		72	−30	87	87
CH_2OCH_2		90	−15	73	90
Me	Me	96	−30	80	83

5.4. Miscellaneous

Imidazolines could also be derived from aziridines as a ring expansion reaction. This was reported by Moretti and collegues in aziridine ring expansion reaction.[123] When an acyl activated aziridine **179** was treated with $BF_3{\cdot}OEt_2$ in CH_3CN, the solvent attacked the less substituted ring carbon to give an intermediate shown in Scheme 78, which underwent ring closure to form *N*-acetyl-imidazole **180** with complete stereo retention. The imidazoline then could be hydrolyzed in 10% HCl to afford optically active 2,3-diaminopropanoic acid **181**, a recognized useful building block for other synthesis.

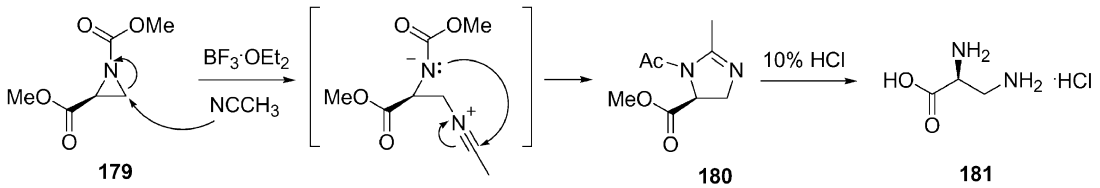
6. Halogen nucleophilic addition

Since a review describing metal halide opening of aziridine rings by Tighi and Bonini,[124] development of new methods for halogen nucleophilic ring opening of aziridines continues to occur in recent years, concerning improving reaction conditions, chemical yields and selectivity by applying more efficient catalysts. As results, the new procedures are either complementary or superior to other known methods in the literature.

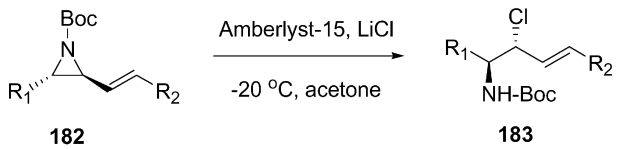
6.1. Chloride

Amberlyst-15 catalyzes aziridine alcoholysis (see Section 3.1). It is also an effective catalyst in halogen addition to aziridine rings. Righi and co-workers found that the reaction of *N*-Boc-alkenyl aziridines **182** with lithium chloride in the presence of Amberlyst 15 afforded the regio- and stereo-selective ring opening products in high yields (Scheme 79).[125] The regio-selectivity was examined with various substituents (R_1) and only single regio-isomers **183** were detected in the reaction and assigned to be anti addition allylic chloro derivatives (Table 43). However, regio-selectivity suffered when the carboxylate group was replaced with a methyl group.

Hydrogen chloride itself is a source of a proton for activation and of a chloride anion for the ring opening of aziridines. One representative example demonstrated that a non-activated aziridine **184** could undergo halogenolysis in dry HCl-ether solution to give a chloro amine product **185** in excellent yield and exclusive regio-selectivity (Scheme 80).[93] Another example illustrated the use of an aqueous HCl solution in the ring opening reaction of non-activated aziridines. Regio-isomer **186** was isolated with quantitative yields (Scheme 81).[126] A similar result was found in the literature in the case of bicyclic aziridine **187** with regio-selective formation of product **188** (Scheme 82).[127] Under



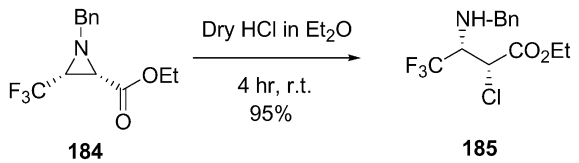
Scheme 78.



Scheme 79.

Table 43. Ring opening of alkenyl aziridines by Amberlyst-15/LiCl

R_1	R_2	Yield (%)
n-Propyl	CO_2Et	84
Cyclohexyl	CO_2Et	86
t-butyl	CO_2Et	82
R	Methyl	Mixture of regio-isomers



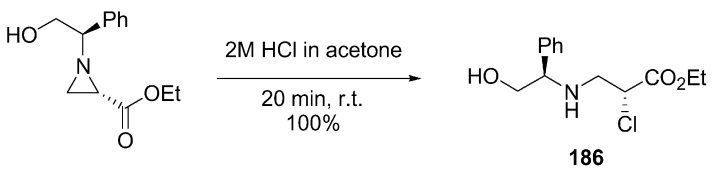
Scheme 80.

Table 44. Regio-selective ring opening of aziridines using cerium(III) chloride

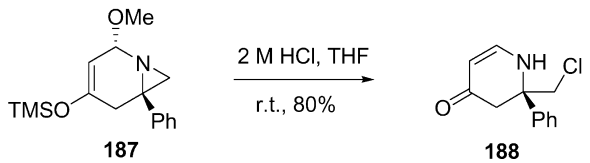
R_1	R_2	Product	Yield (%)
Ph	H	**190**	92
4-Chloro-Ph	H	**190**	91
$-(CH_2)_4-$		—	92
$-(CH_2)_6-$		—	90
Et	H	**191**	95
n-Octyl	H	**191**	90

aqueous HCl conditions, the β-methoxy TMS vinyl either was decomposed to give a substituted 2,3-di-hydro-1*H*-pyridin-4-one **189** in 80% yield. The common feature in the examples demonstrated that non-activated aziridines can undergo highly regio-selective ring opening halogenolysis to give vicinal chloroamines in high yields.

Cerium(III) chloride, an inexpensive, non-toxic and ready available inorganic salt, has found its application in the ring opening reaction of aziridines to form β-chloroamines.[128] The reaction was performed under very mild conditions with short reaction time and excellent chemical yield. In addition, very high regio-selectivity was observed with aryl aziridines giving internal adducts **190**, and with alkyl



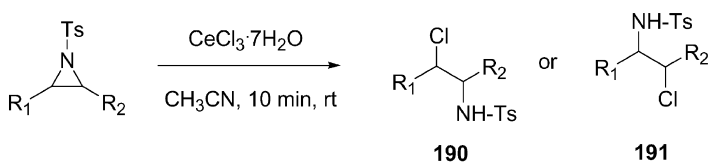
Scheme 81.



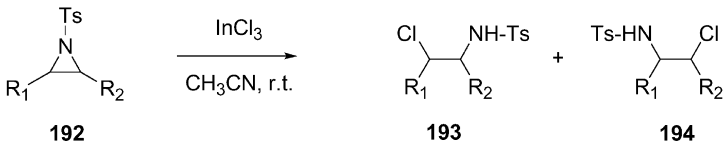
Scheme 82.

aziridines giving only external adducts **191** (Scheme 83 and Table 44). This procedure represents one of the most efficient conversions of aziridines to chloroamines to date.

Indium trichloride also demonstrated its utility in the ring opening of aziridines with high conversion and selectivity (Scheme 84).[129] The reaction results of the substituted aziridines **192** having tosyl activation with indium tricholide



Scheme 83.

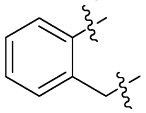


192 193 194

Scheme 84.

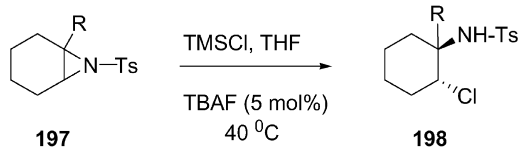
in acetonitrile were summarized in Table 45 below. In the cases of cyclohexyl and cyclopentyl aziridines, *trans* stereoisomers were obtained in 98:2 ratio. In aryl substituted aziridines, the internal addition products **192** were isolated as major regio-isomers. However, the external regio-isomers **193** were obtained predominantly in alkyl substituted aziridines. Although regio-selectivity in the ring opening of unsymmetrical aziridines is not as compatible as in the methods aforementioned, the method itself represents a useful procedure of simple operation, high chemical yield and use of non-toxic and water-tolerant indium reagent.

Table 45. Regio-selective ring opening of aziridines with indium trichloride

R_1	R_2	Time (h)	Yield (%)	**193**:**194**
$-(CH_2)_4-$		8.5	78	—
$-(CH_2)_3-$		9.0	80	—
		7.0	83	92:8 (internal:external)
Ph	H	5.0	90	80:20
i-butyl	H	7.5	77	10:90
n-Butyl	H	9.0	75	17:83
n-Octyl	H	8.5	80	5:95

Another source of the chloride anion is generated from phosgene, with which oxazolidin-2-ones were formed from enantiomerically pure aziridine 2(*R*)-methanol.[130] The other important feature of phosgene is the activation of the aziridine by forming an oxazolidinonium salt, which underwent rapid ring opening at low temperature (Scheme 85). The conversion of the aziridines **195** to oxazolidinone rings **196** was achieved in the presence of a base (NaH) to facilitate oxazolidinone ring closure. A bicyclic aziridinium salt was proposed as a reaction intermediate, which then underwent nucleophilic chloride addition at the less hindered aziridine carbon. Consistent high chemical yields were obtained in all cases (Table 46), even those with sterically hindered alcohols. This method appears to be general for the direct conversion of aziridinyl alcohols to oxazolidinonyl methylchlorides.

The ring opening of aziridines with a chloride nucleophile can also be achieved by trimethylsilyl chloride. The reaction proceeded with TMSCl in THF in the presence of a tetrabutylammonium fluoride (TBAF) trigger.[131] The addition occurred *anti* to the aziridine ring in cyclohexyl aziridines **197** with the regio-selectivity at the less hindered ring carbon. The ring opening took place very fast (<10 min) with unsubstituted bicyclic aziridines, but much more slowly with a methyl substituent (6 h). High yields and high regio-selectivity for **198** were observed in TMSCl/TBAF addition to the aziridines (Scheme 86 and Table 47). The TBAF was proposed to release the chloride anion, which underwent nucleophilic attack to the aziridines to give the chloro adducts.

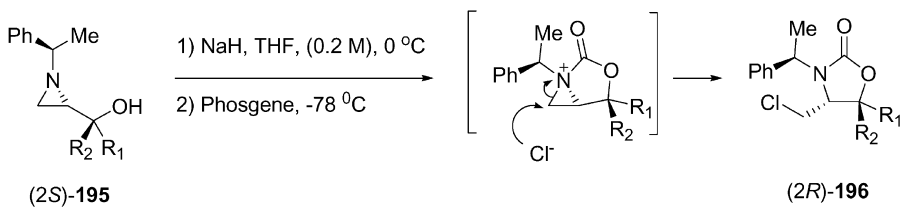


197 198

Scheme 86.

Table 47. Ring opening of *N*-tosylaziridines

n	R	Time (h)	Yield (%)
1	H	0.1	97
0	H	0.1	94
1	Me	12	99



(2*S*)-**195** (2*R*)-**196**

Scheme 85.

Table 46. Conversion of aziridines to oxazolidinones

	196										
	a	b	c	d	e	f	g	h	i	j	k
R_1	H	Me	Ph	H	H	H	H	H	H	H	Vinyl
R_2	H	Ph	Ph	Me	*n*-Bu	*t*-Bu	Ph	*p*-F-Ph	*m*-totyl	Vinyl	H
Yield (%)	89	92	83	91	84	90	88	85	90	89	80

6.2. Bromide

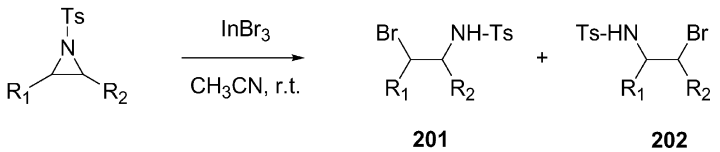
Highly regio-selective ring opening of *N*-Boc-2,3-aziridino alcohol derivatives **199** with $MgBr_2$ was successfully achieved by Righi and co-workers.[132] Instead of a commonly used tosyl amide as an activating functionality for the ring opening, interestingly, they found *N*-Boc amide could serve the same purpose in activating and directing the nucleophilic addition (Scheme 87). In addition, this reaction gave excellent regio-selectivity with great ease of deprotection at the nitrogen. In all examples presented in the ring opening reaction, a bulky *t*-butyldimethyl silyl (TBDMS) group might also play role in directing the site of the addition by the halide (Table 48). Because of the excellent regio-selectivity in the ring opening with $MgBr_2$, the bromoamine products **200** could be reduced to give the corresponding amino alcohols with high chemo-selectivity and high chemical yields.

Scheme 87.

Table 48. Regio-selective ring opening of *N*-Boc-aziridines with $MgBr_2$

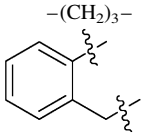
R	Methyl	*n*-Propyl	Cyclohexyl	Ph
Ratio (C3/C2)	>99:1	>99:1	>99:1	>99:1

Indium tribromide was also used as a nucleophile to undergo the ring opening of aziridines similarly to that of indium trichloride as discussed in Section 6.1. In the same report, Yadav and co-workers[129] found that the bromide reagent effectively converted tosyl aziridines to β-bromo amino adducts **201** and **202** in high chemical yields (Scheme 88), but reduced regio-selectivity as seen in Table 49, when compared to indium trichloride. However, the orientation of the addition remained the same.

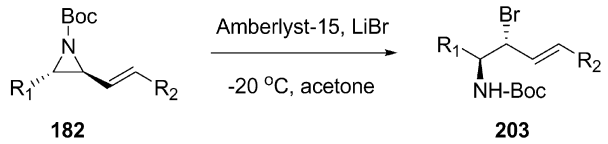


Scheme 88.

Table 49. Regio-selective ring opening of aziridines with indium tribromide

R_1	R_2	Time (h)	Yield (%)	**201**:**202**
$-(CH_2)_4-$		6.5	83	—
$-(CH_2)_3-$		7.5	84	—
		5.5	85	88:12 (internal:external)
Ph	H	4.5	87	76:24
i-butyl	H	6.0	85	15:85
n-Butyl	H	8.0	83	12:88
n-Octyl	H	6.0	85	8:92

Another ring opening reaction of aziridines with bromide was reported using Amberlyst-15/LiBr conditions.[125] The reaction took place in acetone at low temperature to give vicinal bromo amine derivatives **203** in high chemical yields and excellent regio-selectivity (Scheme 89 and Table 50). These results were identical to those seen in the Amerlyst-15/LiCl conditions in Section 6.1.



Scheme 89.

Table 50. Ring opening of alkenyl aziridines by Amberlyst-15/LiBr

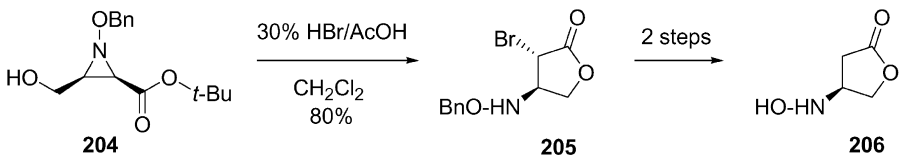
R_1	R_2	Yield (%)
n-Propyl	CO_2Et	94
Cyclohexyl	CO_2Et	94
t-butyl	CO_2Et	87

Hydrogen bromide has been a widely used agent for ring opening of aziridines to form vicinal bromo amines for a long time. The advantages of HBr conditions include no need for activation on the aziridine nitrogen to promote the ring opening and high regio- and stereo-selectivity. Recently, Hanessian et al. successfully applied the HBr nucleophilic addition to aziridine **204** in the synthesis of enantiomerically pure hydroxylamino lactone derivatives **206** as a useful building block (Scheme 90).[133]

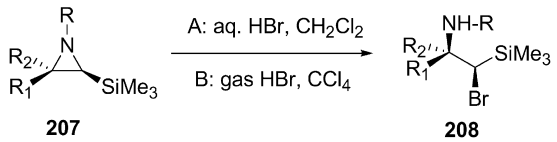
Trialkylsilyl groups played an important role in strongly directing the site of the nucleophilic ring opening of aziridines (Scheme 91). Such results were reported by Taylor and co-workers[134] in the ring opening reaction of 2-trialkylsilylaziridines **207**. Activation or non-activation at the aziridine nitrogen did not seem to affect the addition reaction (Table 51). Apparently, the protic acid served as an activating factor and the bromide attacked the weakened N–C bond adjacent to the silyl group. The addition gave bromoamines in moderate to good yields with regio-specificity, using either gaseous or aqeous HBr.

6.3. Fluoride

In contrast to other halide nucleophilic addition to aziridines, there have been fewer reports documented in



Scheme 90.

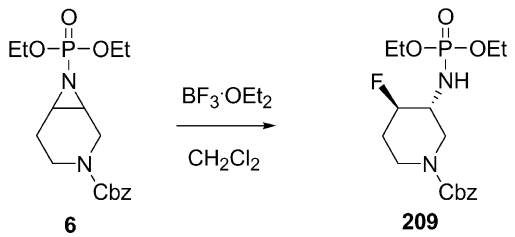


Scheme 91.

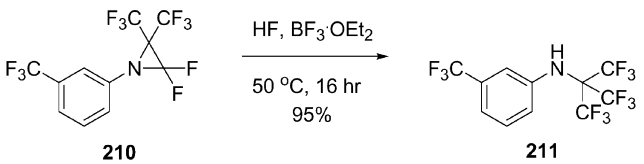
Table 51. Addition of HBr to a range of trimethylsilyl aziridines

R	R_1	R_2	Method	Yield (%)
n-Propyl	Ph	H	A	83
n-Propyl	Ph	H	B	72
Ph	Ph	H	B	76
H	Ph	*n*-Butyl	B	65
CO_2Et	H	H	B	52

the literature recently describing methods for the ring opening of aziridine with a fluoride anion. In our recent effort toward the $BF_3{\cdot}OEt_2$ catalyzed ring opening of a piperidine aziridine with various alcohols (see Section 2.2.1), an intriguing finding of a by-product containing fluoro atom led to a regio- and stereo-selective conversion of the aziridine **6** to 3-amino-4-substituted piperidine derivative **209**.[49] The reaction was carried out in dry CH_2Cl_2 in the presence of 2 equiv. of $BF_3{\cdot}OEt_2$, and the fluoro adduct was isolated in 66% yield (Scheme 92). This is one of the most convenient methods reported for the conversion of aziridines to vicinal fluoro amine adducts.



Scheme 92.



Scheme 93.

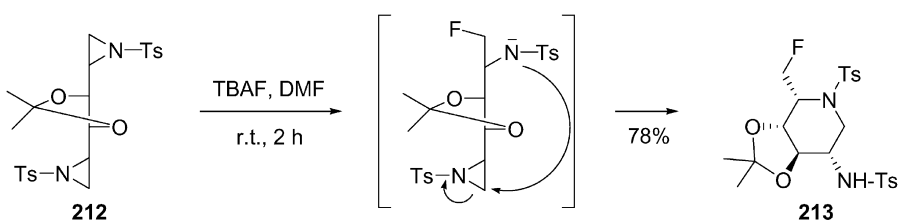
Due to the weak acidity of hydrogen fluoride, the ring opening of aziridines required a Lewis acid to facilitate the nucleophilic addition. This work was demonstrated by Petrov[135] in the synthesis of poly-fluoronated amines **211** from aziridine **210** as shown in Scheme 93. Excellent yield and regio-selectivity were seen in this particular case in the presence of $BF_3{\cdot}OEt_2$. When other halogen substituted aryl aziridines were used to undergo the ring opening reaction, complicated results were obtained.

Other fluorinating agents include tetrabutylammonium fluoride (TBAF) in the ring opening of bis-aziridines **212** in the synthesis of enantiomerically pure piperidine derivatives.[136] The bis-aziridine derived from D-mannitol was treated with this highly nucleophilic fluorinating agent in DMF to give mono-addition aziridine ring opening intermediate, which then underwent rapid ring closure to form piperidine **213** (Scheme 94). The regio-selectivity was derived from the addition at the less hindered terminal aziridine carbon. In the same report, it was found that $LiBF_4$ was much less effective in the ring opening reaction.

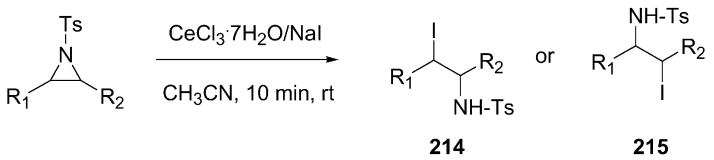
6.4. Iodide

As reviewed in Section 2.5.1, cerium(III) chloride reacted with the tosyl aziridines to give highly regio-selective chloro amine derivatives. Interestingly, when the same conditions were used to undergo the ring opening of aziridines in the presence of 1 equiv. of sodium iodide, the products isolated were β-iodo sulfonamides with complete iodo-chloro exchange (Scheme 95).[128] As shown in Table 52, the reaction gave excellent yields and excellent regio-selectivity in all cases. The orientation of the iodo addition proceeded in the same fashion as that of the chloro addition: internal addition with the aryl aziridines to give **214**, and external addition with the alkyl aziridines to give **215**.

Similar results were obtained in the ring opening of aziridines with indium(III) iodide as those with $InCl_3$ and $InBr_3$ as discussed in Section 5.1.[129] In this reaction β-iodo amino adducts were synthesized in high chemical yields (Scheme 96), but reduced regio-selectivity as seen in



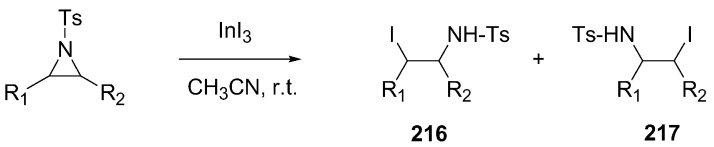
Scheme 94.



Scheme 95.

Table 52. Regio-selective ring opening of aziridines using cerium (III) iodide

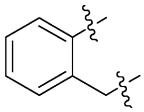
R_1	R_2	Product	Yield (%)
Ph	H	A	99
4-Chloro-Ph	H	A	95
$-(CH_2)_4-$		—	96
$-(CH_2)_6-$		—	92
Et	H	B	97
n-Octyl	H	B	91



Scheme 96.

$InBr_3$ when compared with indium trichloride as seen in Table 53. Again, the orientation of the addition remained to be the same: internal addition for the aryl aziridines to give **216**, but external for the alkyl aziridine to give **217**.

Table 53. Regio-selective ring opening of aziridines with indium triiodide

R_1	R_2	Time (h)	Yield (%)	**216**:**217**
$-(CH_2)_4-$		5.5	87	—
$-(CH_2)_3-$		5.5	88	—
		4.0	88	85:15 (internal:external)
Ph	H	3.5	92	70:30
n-Butyl	H	5.0	90	17:83

Amberlyst-15 can not only catalyze the ring opening of aziridines by nucleophilic attacks of chloride and bromide from lithium halides, but also can catalyze the same reaction with LiI.[125] The reaction proceeded at very mild conditions as described before, but somehow reduced chemical yields were seen with iodo adduct **218** (Scheme 97 and Table 54). These results were identical to those seen in the Amerlyst-15/LiCl conditions in Section 6.1. The low yields were due to the activity of the iodide anion as a leaving group to form oxazolidinones **219**.

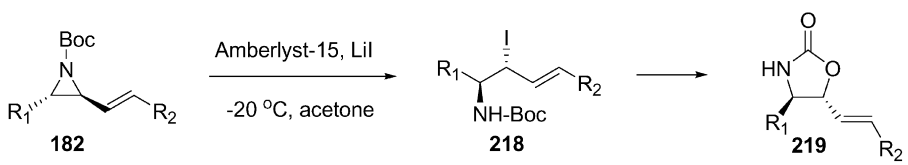
Table 54. Ring opening of alkenyl aziridines by Amberlyst-15/LiBr

R_1	R_2	Yield (%)
n-Propyl	CO_2Et	70
Cyclohexyl	CO_2Et	72
t-butyl	CO_2Et	67

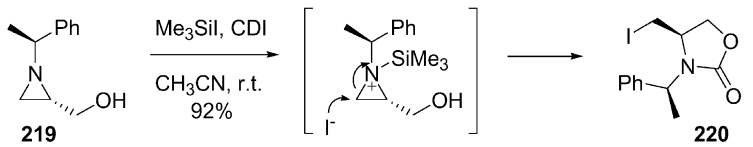
The ring opening of aziridines when treated with trimethylsilyl iodide (TMSI) led to iodo amine compounds, which were a useful building block for tryptophanol synthesis.[137] TMSI nucleophilic addition could take place on non-activated aziridine **219**. The silyl reagent was assumed to initially activate the ring nitrogen and then the released iodo anion acted as a nucleophile to attack the less hindered ring carbon to give an iodo imide anion (Scheme 98). In the presence of carbodiimidazole, an iodomethyl-2-oxazolidinone **220** was obtained in high yield and high regio-selectivity.

7. Hydrogen nucleophilic addition

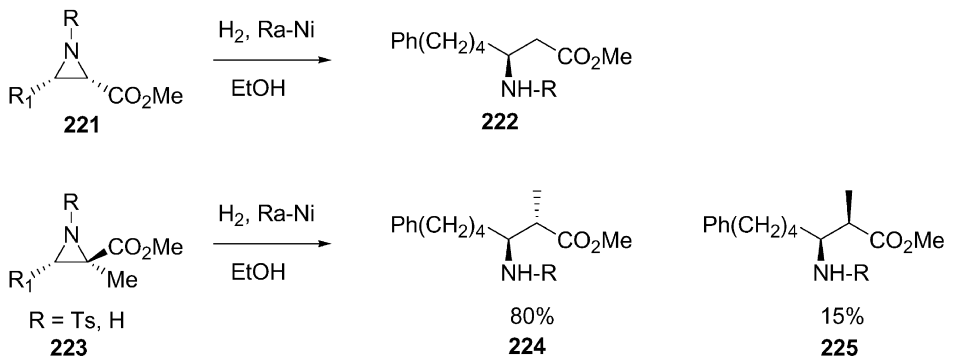
Although hydrogen is not characterized as a nucleophile, it serves the purpose of cleaving the aziridine ring. Catalytic hydrogenation of both activated and non-activated aziridines produces amines as useful building blocks for other synthesis and synthon for the synthesis of biologically active products. Hydrides are common nucleophiles analogous to those mentioned above to undergo ring opening of aziridines. However, hydride reduction requires activation of aziridines to lead to ring opening products. In addition, hydrogenation of aziridines provides the corresponding amine products with highly controlled regio-selectivity, whereas hydride reduction is less appreciable in terms of site of the ring cleavage.



Scheme 97.



Scheme 98.

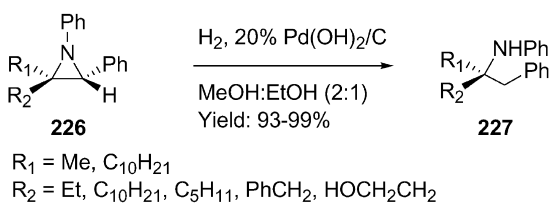


Scheme 99.

7.1. Hydrogen from hydrogenation

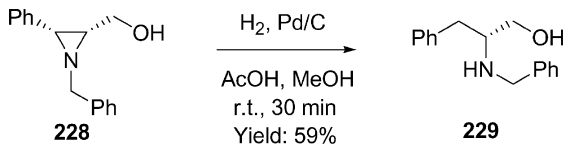
Davis et al. examined the catalyst and solvent effects on hydrogenation ring opening of aziridine-2-carboxylates.[138,139] It was found that Raney-Ni/EtOH conditions provided the optimum results (**222**) with nearly quantitative yield in the case of **221**, whereas two diastereomers **224** and **225** were obtained in the case of 2-methylaziridine **223**, and the major isomer was derived from the ring opening with retention of configuration (Scheme 99).

Hydrogenation ring opening of aziridines catalyzed by Pearson's palladium reagent appears to be a widely used method to cleave the C–N bond. A recent study by Satoh and co-workers described an effective method to convert aziridines **226** to amines **227** bearing a quaternary chiral center.[140] The reaction was catalyzed by 20% $Pd(OH)_2/C$ in 100–300 wt% in excellent chemical yields and low catalyst loading resulting in incomplete ring opening (Scheme 100). It should be noticed that all aziridines reported in the study involved benzylic type amine functionality, which was the site of the cleavage. Optically active quaternary amines can also be synthesized from this method.



Scheme 100.

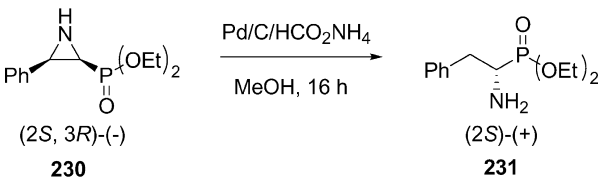
Less frequent reports were also found in the literature in hydrogenation ring opening of aziridines with palladium on carbon. One recent example is shown below in Scheme 101, in which a non-activated (2*S*,3*R*)-(−)-*cis*-aziridine derivative **228** underwent ring opening under hydrogenation conditions in the presence of acetic acid for protonation.[141] The reaction proceeded with selective ring opening at the benzylic carbon, whereas the benzyl group was not cleaved.



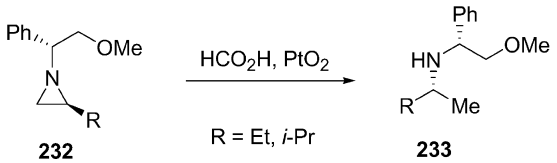
Scheme 101.

This result may be related to the release of the aziridine ring strain in the cleavage. However, the chiral amine product **229** was obtained in only moderate chemical yield (59%).

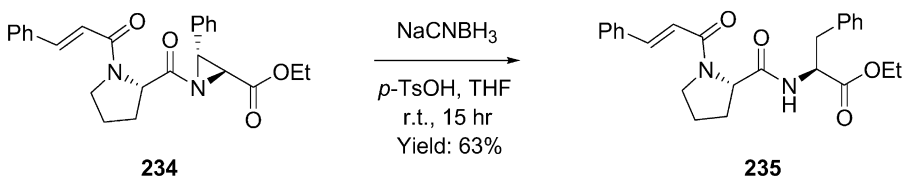
In general, N-activation of the aziridine ring was required to facilitate ring opening by hydrogenation. However, cases without activation were also found in the literature, in which the ring opening occurred at the benzylic position as an exceptional example of benzylamine type reduction.[142] As shown in Scheme 102, hydrogenation was carried out by the hydrogen transfer agent ammonium formate. Because of the benzylic amine type reduction of **230**, the ring opening proceeded specifically at the benzyl carbon to give the corresponding amino acid mimic **231** with good to excellent yields (67–98%). On the other hand, aziridines **232** could also be cleaved with Adam's catalyst[143] as presented in



Scheme 102.



Scheme 103.



Scheme 104.

Scheme 103, in which cleavage occurred at the sterically preferred carbon to give amines **233**.

7.2. Hydride

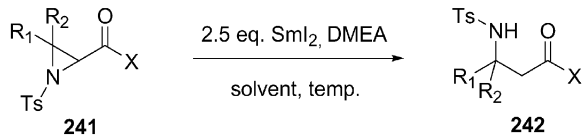
In comparison to the reports of the ring opening of aziridines by reductive hydrogenation, much less occurrence of ring opening methods of aziridines by hydride reduction has appeared in recent years. One application involved the reductive cleavage of aziridine containing peptidomimetics using $NaCNBH_3$ under acidic conditions.[144] As shown in Scheme 104, a dipeptide analog **234** underwent hydride nucleophilic ring opening regio-selectively at the benzylic ring carbon to give a corresponding L-Pro-L-PheOEt derivative **235** in 63% yield.

A second method was recently described in the literature using $NaBH_4$ to cleave aziridine rings.[145] The researchers intended to demonstrate methods of asymmetric synthesis of α or β-aminophosphonates from enantiomerically enriched aziridines. However, the $NaBH_4$ reductive ring opening of aziridine **236** resulted in only a nearly 1:1 ratio mixture of α or β-aminophosphonates (**237** and **238**) (Scheme 105), which proved the method was much less attractive for preparative synthesis. Identical lack of regio-selectivity results were also seen in other reports in the ring opening of aziridines with $NaBH_4$.[146]

Regio-selectivity of reductive ring opening of aziridines with hydrides has posed a considerable challenge. In order to improve the regio-selectivity, Davis and co-workers[147] found a hydroxyl group directing effect of the hydride addition by taking advantage of those studying the ring opening of aziridines with other nucleophiles in the presence of neighboring group effect. When 2,3-disubstituted aziridine-2-carboxylate **239** was treated with LAH, the initial intermediate alcohol from carboxylate reduction chelated the reducing agent. Then, the hydride was delivered via a five membered-ring transition state to give the exclusive C2 addition products **240** in very high yields (Scheme 106). The hydroxyl group was then oxidized to the corresponding carboxylic acids, which led to the synthesis of α-alkyl-β-amino acids, compounds relatively hard to synthesize via reductive ring opening of aziridines.

7.3. Miscellaneous

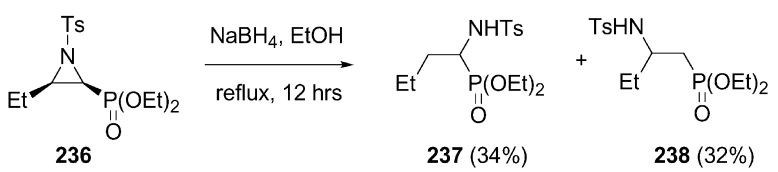
Samarium(II) iodide (SmI_2) has a wide range of application in reducing a number of functional groups due to its single-electron transfer capability. Similar to a process of SmI_2 cleavage of α-heterosubstituted carbonyl substrates, ring opening of aziridines can also be achieved by SmI_2 reductive method developed by Molander and co-workers.[148] A number of aziridine carbonyl functional groups (**241**) were examined for the ring opening including ketones, esters and amides. The reaction provided β-amino carbonyl derivatives **242** not only in high yields, but also in



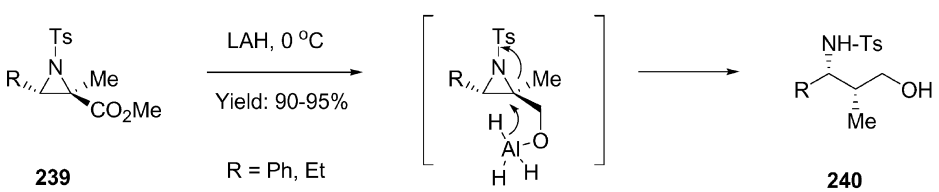
Scheme 107.

Table 55. Reduction of *N*-Ts aziridine-2-carboxamides with SmI_2

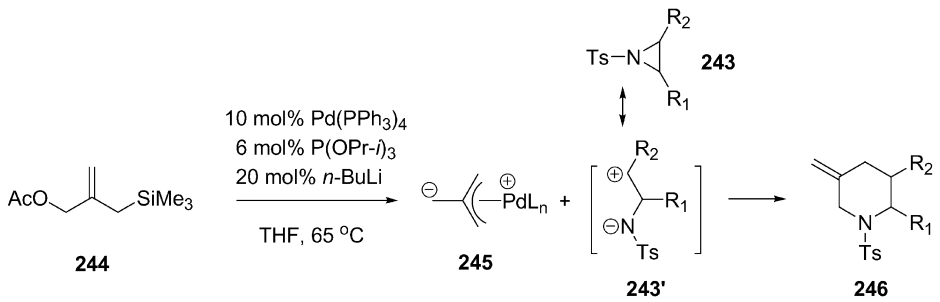
R_1	R_2	X	DMEA	Solvent	Temperature (°C)	Yield (%)
H	Ph	Me	0	MeOH	0	82
H	H	Me	0	MeOH	0	79
Me	Me	Me	0	MeOH	0	88
H	Ph	OEt	5.0	THF	0	87
H	H	OEt	5.0	THF	0	98
Me	Me	OMe	5.0	THF	0	87
H	H	NMe_2	5.0	THF	−25	86
Me	H	NEt_2	5.0	THF	−25	70



Scheme 105.



Scheme 106.



Scheme 108.

excellent regio-selectivity, due to initial formation of a ketyl or a radical species, which cleaved the adjacent N-C bond (Scheme 107 and Table 55). Reduction of the 2-keto-aziridine required no additive *N*,*N*-dimethylethanolamine (DMEA), whereas reduction of the 2-ester-aziridines and 2-amide-aziridines involved the DMEA additive serving as an effective proton source, a possible chelator to the Sm(II) reductant for the reactivity and rectifier for regio-selectivity. This method was also useful in the presence of other *N*-activating groups, such as Ac, Boc, Fmoc, CO_2Et, trityl and phenyl, thereby demonstrating generality of the procedure.

8. Cycloaddition

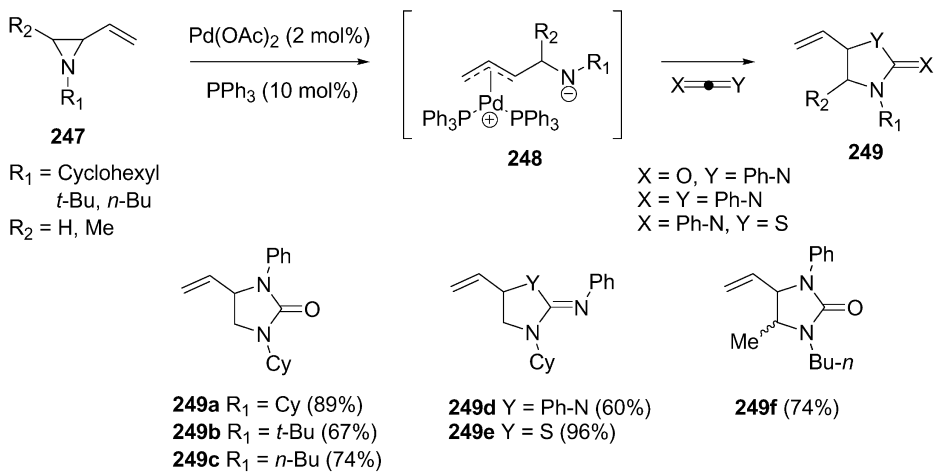
Aziridines are also known to undergo cycloaddition reaction, although their addition by various nucleophiles has been well established as summarized in this review above. The cycloaddition reaction of aziridines involves either the formation of double charged 1,3-dipole species or azahomoallyl radical species as reacting intermediates to react with a double bond and then generate a five- or six-membered ring skeleton from simple substrates. From this single step transformation, the cycloaddition can provide some complex heterocyclic scaffolds to demonstrate a powerful tool in organic synthesis.

Table 56. [3+3] Cycloadditon of aziridines with Pd-TMM complex

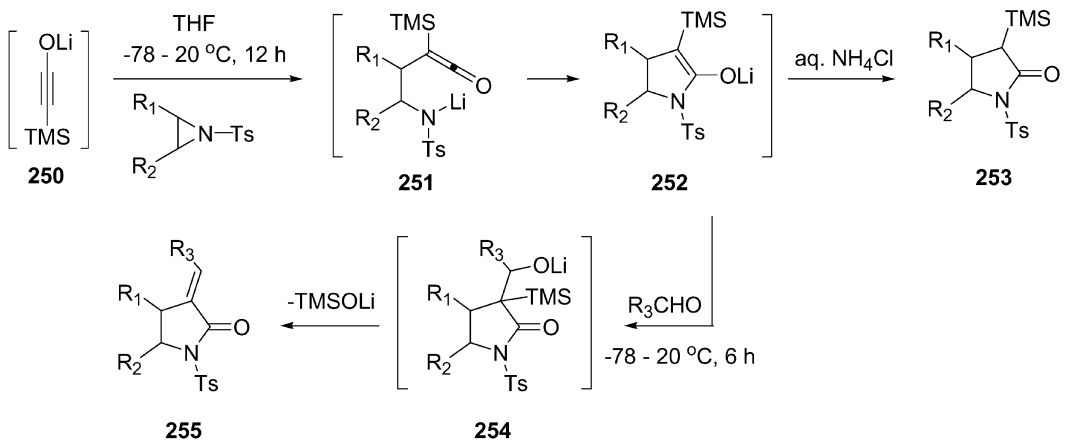
R_1	R_2	Yield (%)	Configuration
(*S*)-Me	H	82	(*S*)-
(*S*)-*i*-Pr	H	72	(*S*)-
(*R*)-*n*-Pr	H	44	(*R*)-
Ph	H	68 (1:1.6)	—
(*S*)-Bn	H	79	(*S*)-
$-(CH_2)_4-$		31	—

Recent work presented by Harrity et al.[149] illustrated the method via a [3+3] cycloaddition of aziridines with a complex of Pd-trimethylenemethane (Pd-TMM) **245** to build functionalized piperidines. Pd-TMM was generated by mixing commercially available 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **244** with $Pd(PPh_3)_4$ in the presence of $P(OPr\text{-}i)_3$ and reductant *n*-BuLi in THF. This complex was in turn treated with the requisite aziridine substrates **243** in situ as shown in Scheme 108. The reactive species, a known double charged 1,3-dipole **243′**, can be proposed,[35] which readily formed the ring with the Pd-TMM complex to afford piperidine product **246**. Notably, the aziridines underwent regio-selective addition with the Pd-TMM complex at the less hindered site and furnished the products in enantiomerically pure form. In contrast, 2-phenyl aziridine resulted in almost non-regio-selective cycloaddition with a nearly equal mixture of regio-isomers (Table 56). In addition, the cycloaddition required activation by an aryl sulfonyl group at the aziridine nitrogen, whereas carbamate (Boc or Cbz) and diphenyl phosphinoyl moieties failed to provide the corresponding piperidines.

2-Vinyl aziridines **247** could be catalyzed by Pd(0) to undergo [3+2] cycloaddition with a number of hetero-cumulenes in a regio-selective manner to afford five-membered heterocyclic products.[150] This reaction required



Scheme 109.



Scheme 110.

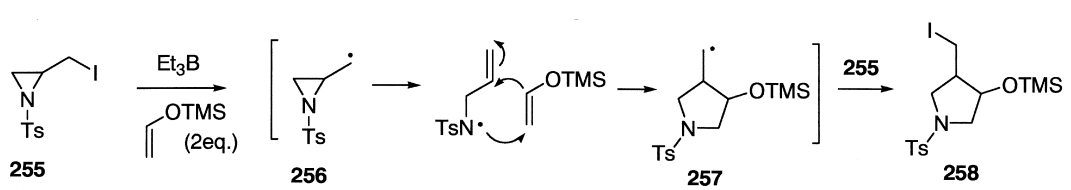
Table 57. Reaction of silylynolate with aziridines and olefination with aldehydes

Cyclization of ynolate with aziridines				Cyclization and olefination				
R_1	R_2	Yield (%)	Diast. ratio	R_1	R_2	R_3	Yield (%)	*E*/*Z*
H	H	61	—	H	H	*t*-Bu	71	100:0
H	Me	65	68:32	H	H	Pr	49	96:4
H	*i*-Pr	72	60:40	H	H	2-furan	64	96:4
$-(CH_2)_4-$		77	77:23	H	Me	*t*-Bu	80	100:0
Et	Et (*cis*)	39	52:48	$-(CH_2)_4-$		*t*-Bu	70	60:40
Et	Et (*trans*)	36	100:0					

only 2 mol% of $Pd(OAc)_2$ with 10 mol% of PPh_3 to complete the conversion of the aziridines to cycloaddition products. The heterocumulenes used in this study include isocyanates, carbodiimides and isothiocyanates. The cycloaddition, in general, provided imidazolidin-2-ones **249a**, imidazolidin-2-ylideneamine **249b** and thiazolidin-2-ylideneamine **249c** in high yield and high regio-selectivity (Scheme 109). A plausible mechanism was proposed for this transformation via an intermediate **248** by forming a (π-allyl)palladium complex. However, the process was less stereo-selective in the case of *cis*-aziridine to give a mixture of *cis* and *trans* product **249f** in 2:1 ratio, when R_2=Me. Trost et al. took the advantage of cycloaddition of vinyl aziridines with heterocumulenes and performed dynamic kinetic asymmetric cycloaddition with isocyanates using chiral ligands.[151] High yields and enantio-selectivity were obtained. The cyclized imidazolidinones were precursors to chiral diamines useful for the synthesis of SALEN ligands.

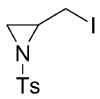
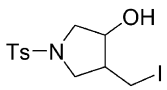
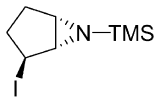
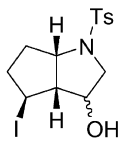
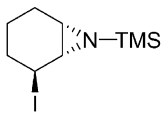
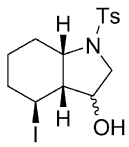
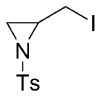
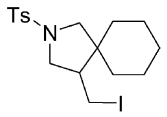
A silylynolate, generated from the carbonylation of lithium silyldiazomethane, was reacted with *N*-tosyl aziridines to produce various γ-lactams in respectable yields.[152] As outlined in Scheme 110, the ynolate **250** initially added to the aziridine to produce ring opening ketenylation of **251**. This intermediate readily underwent lactam ring formation leading to the lithium enolate **252**. Upon hydrolysis, five-membered lactam **253** was obtained. The ketenylation took place at the less hindered carbon of the aziridine (R_2=Me and *i*-Pr) to give highly regio-selective products. However, the stereo-selectivity was rather disappointing with only limited selectivity of unidentified preference as shown in Table 57. A *trans*-bicyclic γ-lactam of high ring constraint was synthesized from a cyclohexane aziridine precursor through this ketenylation-cyclization process. The lactam enolate could also be trapped by aldehydes to give Peterson olefination product **255** after elimination of siloxy anion from primary adduct **254**. Thermodynamically stable *E*-olefins were obtained as major products from less hindered aziridines, whereas poor selectivity was seen from the hindered cyclohexane aziridine.

Taguchi and co-workers recently disclosed their results of [3+2] cycloaddition reaction via azahomoallyl radical precursors.[153] The azahomoally radical precursors, reactive radical species, were derived from *N*-tosyl aziridines, and then underwent ring formation with electro-rich alkenes such as enol ethers and ketene acetals. As illustrated in Scheme 111, radical species **256** originated from iodomethyl aziridine **255** by radical initiator Et_3B in CH_2Cl_2 at room temperature. Isomerization of **256** led to the azahomoallyl radical intermediate, which readily cyclized with alkene to form pyrrolidinyl methyl radical **257**. The iodo-transformation completed the radical reaction cycle to give the corresponding iodomethylated pyrrolidine **258**. Representative examples are shown in Table 58 with monocyclic, bicyclic- and spiro-pyrrolidine products in respective yields. The stereo-selectivity, however, was less impressive with only marginal bias in favor of *cis*



Scheme 111.

Table 58. Radial [3+2] cycloaddition of various iodoaziridines with vinyloxytrimethylsilane

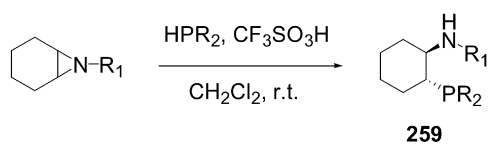
Aziridine	Olefin	Product	Yield (%)	*cis/trans*
			66	1.3/1
			60	1.5/1
			62	1/1.4
			56	—

isomers. Enantio-selectivity was also demonstrated by the researchers, when an optically active aziridine was used to carry out the cycloaddition with essentially complete reservation of the chirality as introduced.

9. Miscellaneous: other heteroatom nucleophilic addition

9.1. Phosphorus nucleophilic addition

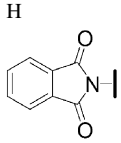
Only limited reports were found in the literature using phosphines as nucleophiles in ring opening of aziridines. The most practical preparative method was developed by Yudin's group in the synthesis of cyclohexane-based P,N-ligands in recent years, which were used as effective ligands for transition metal catalysis.[154] Acid catalyzed ring opening of 7-azabicyclo[4.1.0]heptane with diphenylphsphine resulted in a moderate yield of *trans*-1-amino-2-diphenylphosphino cyclohexane **259**. Dicyclohexylphosphine led to the formation of *trans*-1-amino-2-dihexylphosphino cyclohexane in only 30% yield. However, the aziridine activated by a phthalimide group under the same reaction conditions gave the ring opening product in 65% yield (Scheme 112 and Table 59). The new P,N-ligand was used to successfully catalyze the Suzuki coupling between sterically hindered substrates.



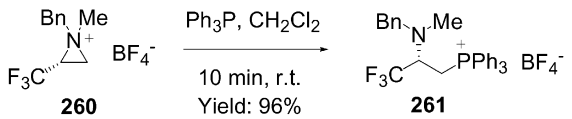
259

Scheme 112.

Table 59. Ring opening with diphenyl- and dicyclohexylphospines

R_1	R_2	Yield (%)
H	Ph	50
H	Cyclohexyl	30
	Ph	65

A highly activated aziridinium salt could undergo nucleophilic ring opening with triphenylphosphine to give an α-amino phosphonium salt adduct in 96% yield. Phosphine and other nucleophiles attacked exclusively at the unsubstituted ring carbon.[155] Although organophosphines are sufficiently nucleophilic to open the aziridinium ring of **260**, the formed phosphonium salt product **261** has not been shown to be useful in organic chemistry and other fields. Such phosphonium salts were only used as catalytic bases in nucleophilic addition to catalyze ring opening of aziridines (see Section 3.1, 3.3, 4.1 and 5.1) (Scheme 113).



260 **261**

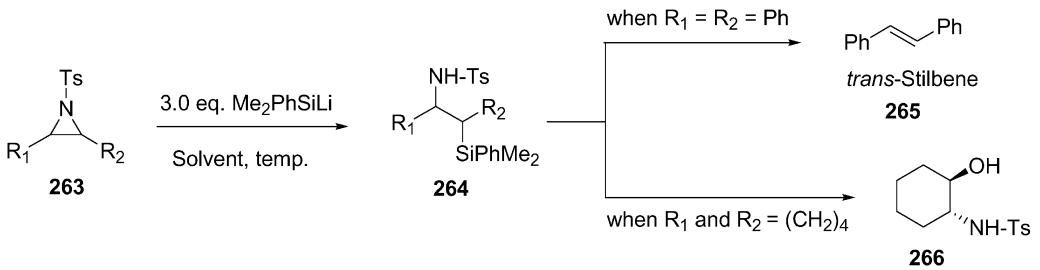
Scheme 113.

9.2. Silanes

Organosilane anions are well known to have wide application as organosilane bases for deprotonation of carbonyls and esters to form enolates, and also as nucleophiles to undergo additions to a number of electrophiles, including esters, carbonyls, imines and α,β-unsaturated carbonyls. However, rare reports were seen in the literature regarding organosilane anion addition to aziridines, and the latest ring opening of aziridines was published by Fleming and co-workers[156] describing nucleophilic attack of dimethylphenylsilyllithium to aziridines **262**. The ring opening reaction proceeded with 3.0 equiv. of the organosilyllithium reagent to give regio- and stereoselective β-silylethyl sulfonamides **263** as shown in Scheme 114. The *trans*- and *cis*-2,3-diphenyl aziridines gave *anti* addition products as diastereomers. The optimal solvent was found to be toluene, as presented in Table 60. The applications outlined in their publication include β-elimination of either threo- or erythro-β-silylethyl sulfonamides to give *trans*-stilbene **264** in good yields and oxidation with peroxide to afford β-hydroxyl sulfonamides **265**.

9.3. Selenols

Similar to alcohols and thiols, selenols are also nucleophiles attacking aziridines to give corresponding ring opening products. Non-activated aziridines **267** reacted with phenylselenol to give ring opening products **268** in high yields and regio-selectivity[157] as shown in Scheme 115. Presumably, the organoselenol was sufficiently acidic to protonate the non-activated aziridines so as to catalyze the ring opening process. The organoselenides are precursors for radical ring closure under tributyltinhydride/AIBN conditions to form pyrrolidines **269** in high stereoselectivity. Further extension of this methodology was reported recently for the formation of pyrrolidin-3-ones.[158]



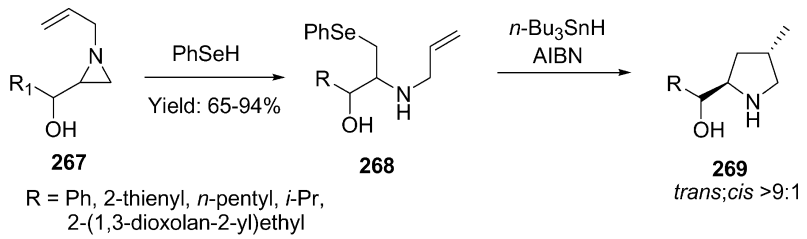
Scheme 114.

Table 60. Ring opening of aziridines with dimethylphenylsilyllithium

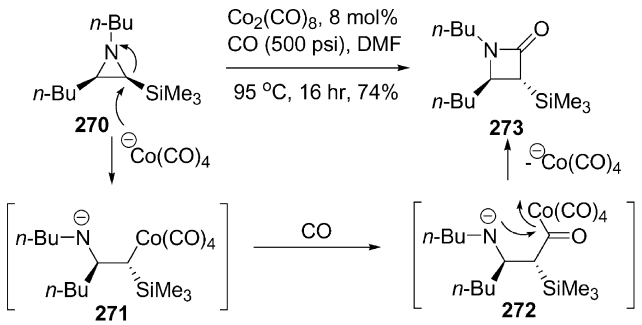
R_1	R_2	Solvent	Temperature (°C)	Yield (%)
trans-Ph	Ph	THF	0	56 (*erythro*)
cis-Ph	Ph	THF	−78	43 (*threo*)
Ph	H	Toluene	0	73
n-C_6H_{13}	H	THF	0	44
$-(CH_2)_4-$		THF	0	48 (*trans*)

9.4. Cobalt

Single step conversion of aziridines to β-lactams, or so called carbonylation of aziridines, was realized under transition metal cobalt catalyzed carbonylation conditions. Aggarwal and et al. found that the ring expansion took place with non-activated aziridines **270** catalyzed by $Co(CO)_8$, whereas activated aziridines gave only recovered starting material.[159] As shown in Scheme 116, the cobalt attacked

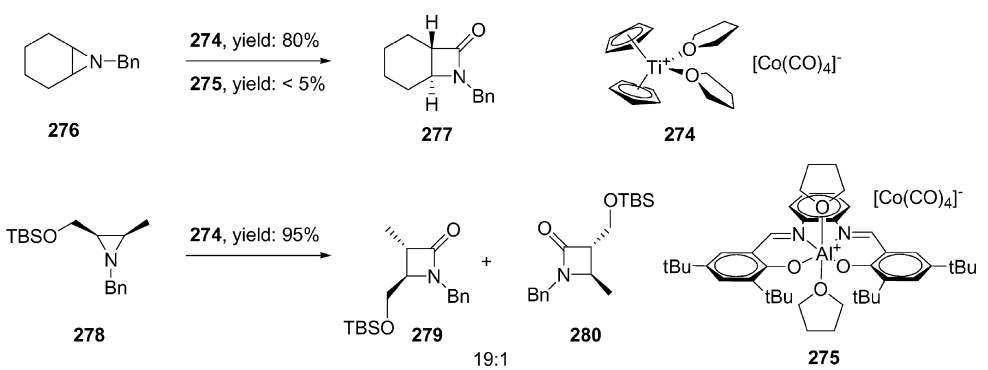


Scheme 115.



Scheme 116.

the aziridine from the backside at the $SiMe_3$ attached carbon to give intermediate **271** with inversion of the stereochemistry. The carbonyl insertion took place with retention of the chiral center in **272**. Then, the ring closure provided the β-lactam ring formation (**273**) in 74% yield. Although a single electron transfer mechanism was proposed for the ring opening reaction by others,[160] the nucleophilic addition approach seems to provide a more convincing way to rationalize the stereochemical outcome.[161,162] The ring expansion of aziridines to β-lactams provides a versatile tool for stereo-selective construction of diverse β-lactams, which was further exemplified by Coates et al. using new catalysts $[Cp_2Ti(THF)_2][Co(CO)_2]$ (**274**) and

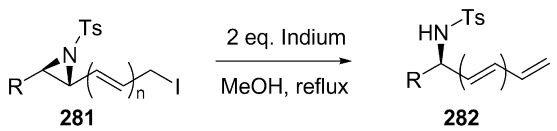


Scheme 117.

[(salph)Al(THF)$_2$][Co(CO)$_2$] (**275**)[163] and generating more complex β-lactam systems (**277** and **279**) with improved chemical yields and regio-selectivity as shown in Scheme 117.

9.5. Conversion of 2-iodomethyl aziridines to allylic amines

Indium mediated transformation of functional groups has recently attracted much interest of organic chemistry due largely to its water and air stability, and readily reacting with electrophiles. Indium initiated efficient conversion of 2-iodomethyl aziridines to ring opening products of allylic amines is an example of recent advances in indium chemistry.[164] When 2-iodomethyl aziridines **281** or conjugated iodomethy aziridines containing a vinyl group were treated with indium in refluxing methanol, the conversion proceeded smoothly to give allylic amines in excellent yields (90–96%). The ring opening products **282** were the result of the double bond migration (Scheme 118). This useful method provides potential for the synthesis of chiral allylic amines (Table 61).



281 **282**

Scheme 118.

Table 61. Indium mediated conversion of 2-iodomethyl *N*-Ts aziridines to chiral allylic amines

R	*n*	Time (h)	Yield (%)
n-C_5H_{11}	0	4	96
n-C_8H_{17}	0	4	96
BnO$(CH_2)_2$	0	4.5	92
PMBO$(CH_2)_4$	0	5	90
n-C_5H_{11}	1	4.5	91
BnO$(CH_2)_2$	1	5	93

A much less known tellurium agent in organic chemistry found application in ring opening of aziridines as reported by Dittmer et al.[165] Te^{2-}, generated from reduction of Te(0) by $NaBH_4$ in water, initially displaced tosylate of **283** under phase transfer conditions (Adogen-464), which then underwent aziridine ring opening with concurrent tellurium containing ring formation (Scheme 119). Subsequent reductive elimination led to allylic amines **284** along with a black powder precipitate of Tellurium metal. However, a phenyl aziridine did not react under the conditions, probably due to attack of telluride ion at the benzylic carbon favored by benzyl stabilization (Table 62). This procedure was applied to asymmetric synthesis of amines, when optically active aziridinemethanol tosylates were used.

Table 62. *N*-Tosylallylic amines from *N*-tosylaziridinemethyanol tosylates

R_1	R_2	R_3	Yield (%)
n-Pr	H	H	74[a]
H	Me	H	81[a]
Me	Me	H	85
$BnOCH_2$	H	H	88
H	$-(CH_2)_3-$		95
Ph	H	H	0

[a] Optically active amines.

10. Concluding remarks

Aziridines have proven to be versatile building blocks toward a number of nucleophiles for ring opening reactions. The development of new methodologies has provided choices for improvement of reaction conditions, chemical yields, regio-selectivity and ease of operation. Some of the procedures have been intended to address issues of cost efficiency and environment friendliness for potential manufacture needs. Moreover, [3+2] cycloadditon of aziridines has expanded its application to the construction of sophisticated cyclic and bicyclic scaffolds in a simple operation. The increasing interests in amine containing molecules both by organic and in pharmaceutical researches have further strengthened the important position of nucleophilic ring opening of aziridines in contemporary synthetic chemistry. Furthermore, aziridine chemistry has found its broad utility in organic and medicinal chemistry in particular, which is anticipated to increase in the future.

Acknowledgements

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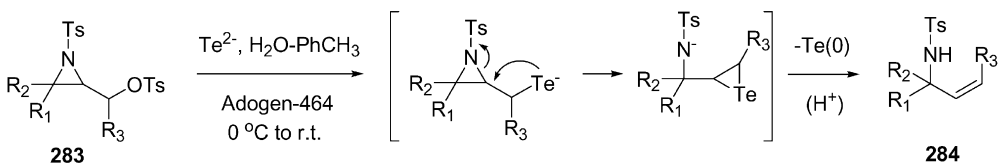

283 **284**

Scheme 119.

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