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AZIRIDINE-2-CARBOXYLATES: PREPARATION, NUCLEOPHILIC RING OPENING, AND RING EXPANSION

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Abstract – Preparation methods of aziridine-2-carboxylates are discussed. The chemical reactivities, focusing on ring opening by various nucleophiles and ring expansion to larger heterocycles, are also surveyed.

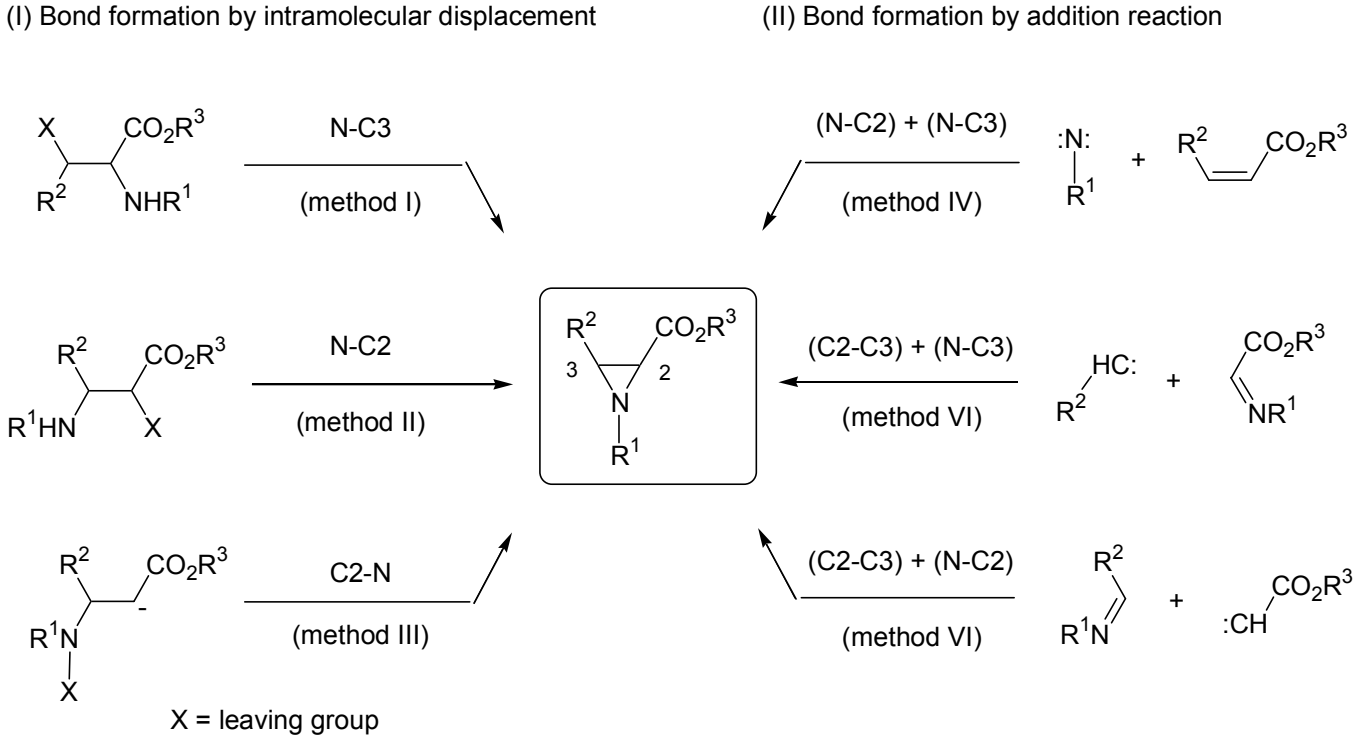
INTRODUCTION

Aziridines are the smallest nitrogen-containing heterocycles and are susceptible to ring-opening reactions by the inherent strain (26-27 kcal/mol) due to three-membered ring system. Thus, aziridines play an important role as versatile synthetic intermediates in the synthesis of biologically active nitrogen-containing compounds. In particular, nucleophilic ring opening of aziridine-2-carboxylates (aziridinecarboxylates) has been a common strategy used for the synthesis of α- and β-amino acids. Aziridines, the ring nitrogen of which is activated by an electron-withdrawing group (EWG) such as benzyloxycarbonyl (Cbz) and *p*-toluenesulfonyl (Ts), react more rapidly than non-activated, *N*-alkylated or *N*–unsubstituted aziridines.[1] It is well known that heteroatom nucleophiles attack the β-carbon (C3) giving rise to α-amino acids.[2] With the exception of nucleophilic Wittig reagents[3] and indoles,[4] which attack regioselectively at the β-carbon, carbon nucleophiles generally attack in a non-regioselective manner.[5] An additional problem with carbon nucleophiles is that the ester functionality is also subject to nucleophilic attack, thereby limiting this method further. Hydrolysis of the ester to the corresponding acid has been shown to correct this problem, and gives rise to regioselective attack at the β-carbon of the aziridine.[6] When enantiopure aziridines are required as synthetic intermediates, asymmetric synthesis could, as expected, be applied for the preparation of aziridines. They are also prepared from chiral pool available materials (amino acids,[5b,7] sugars[8]) or from other readily available enantiopure starting materials, especially epoxides.[9] Furthermore, lipase-mediated stereoselective transesterification[10] of aziridinecarboxylates has been developed. Excellent and exhaustive reviews[2,11] have discussed on the

syntheses and ring opening reactions of aziridine derivatives. Here, we will survey the reports for the preparation of aziridinecarboxylates and their ring manipulation such as nucleophilic ring opening and ring expansion to 5-membered heterocycles, including literatures appeared after 2004. However, the syntheses by the use of natural source-derived materials, enzymatic transformations, and the hydrogenation of azirine, in addition to chemical modification of the ester function[12] and *cis-trans* ring isomerization,[13] are excluded because of limited pages. Reaction examples with asymmetric version are basically cited in schemes of this review, and in non-asymmetric cases the scheme caption is marked with asterisk.

I. PREPARATION

Synthetic approaches to aziridinecarboxylates based on bond connection for the construction of aziridine ring system are schematically illustrated in Scheme 1, in which each three types of intramolecular nucleophilic displacement reactions and addition reactions could be nominated.



Scheme 1. Schematic bond formations for the construction of aziridine ring system

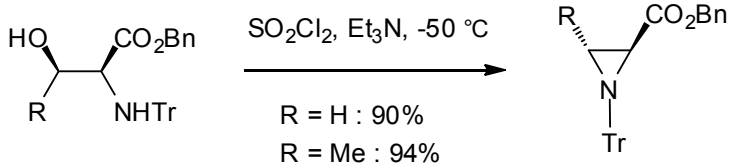
The former displacement reaction involves an attack of a nucleophilic nitrogen atom on an adjacent carbon atom bearing a leaving group (X) to afford the aziridine ring system. The cyclization of hydroxyamino acids (method I or II) and the well-known Gabriel-Cromwell method (method II)[14] are examples of this approach. In the asymmetric version, it is modified with the use of chiral auxiliaries such as

camphorsultam[14c] or imidazolidin-2-one.[14d] The aza-Darzens reaction (method II) of *N*-bromoacetylcamphorsultam has also been used and gives high stereoselectivities.[15] The steps of the formation of a stabilized carbanion and of ring closure on an electrophilic nitrogen carrying a good leaving group (X) are involved as an alternative intramolecular nucleophilic displacement *via* C2-N bond connection, known as aza-Michael reaction (method III). Insertion of an electron-deficient sextet atom (nitrene or carbene) to a double bond is nominated as the latter addition reaction (methods IV - VI) and, in the asymmetric version, nitrene addition to α,β-unsaturated acid derivatives (method IV) bearing a chiral auxiliary[16] has been explored.

I-1. By Intramolecular Nucleophilic Displacement Reaction

I-1-1. From Amino Alcohols (Method I or II): A conceptually obvious synthesis of aziridines utilizes 1,2-amino alcohol precursors: the reaction can be readily achieved when the hydroxyl functional group is converted to a good leaving group. Intramolecular nucleophilic displacement reaction by either the amide anion or the amine lone pair provides the aziridine ring. The reaction is generally stereospecific and relies upon the ability of the amine and leaving group to adopt a *trans* coplanar relationship. Treatment of an amino alcohol with triphenylphosphine (Ph_3P) and either bromine (Br_2), carbon tetrachloride (CCl_4), or diethyl diazocarboxylate (DEAD) has widely been employed to effect aziridine ring closure.[2]

Optically active, non-activated, benzyl (Bn) aziridinecarboxylates with *N*-trityl (Tr) group was prepared by treatment of the Bn-esters of *N*-Tr-(*S*)-serine or *N*-Tr-(*S*)-threonine with sulfuryl chloride and triethylamine (Et_3N) at -50 °C.[17] It has been concluded that a bulky substituent on nitrogen and a non-sterically hindered carboxylate protecting group are essential for favorable cyclization to occur, affording the required aziridines in good yield (Scheme 2).

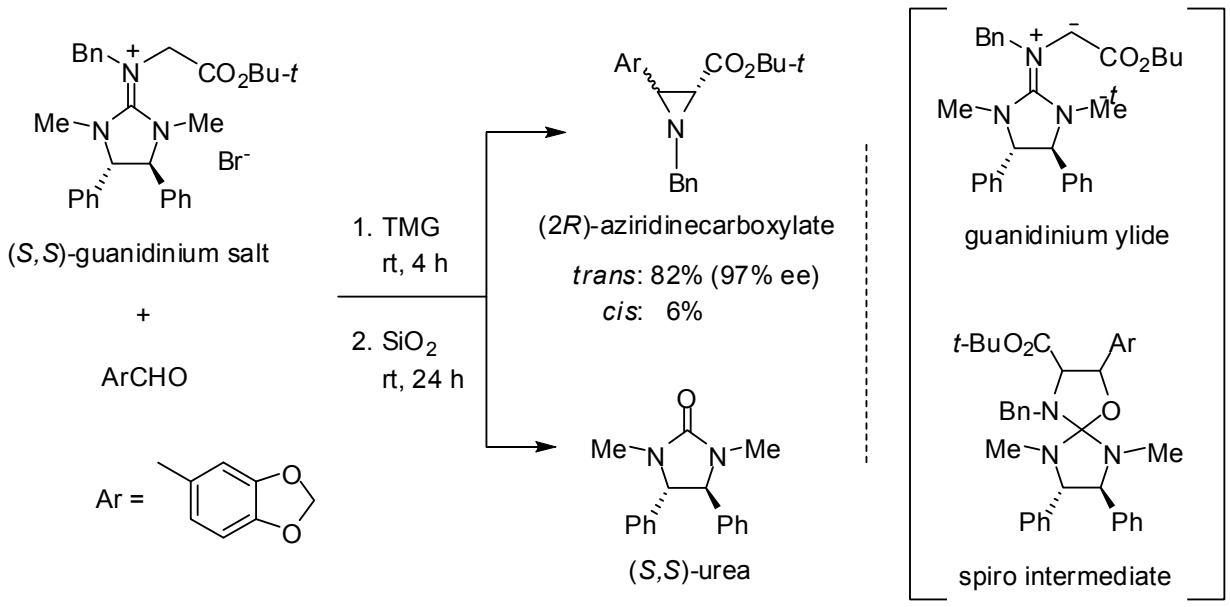


Scheme 2. Preparation of *N*-Tr-aziridinecarboxylates from amino alcohols

Activated *N*-Ts-aziridinecarboxylates were also prepared from *N*-Ts-(*S*)-serinate or *N*-Ts-(*S*)-threoninate, *p*-toluenesulfonyl chloride (TsCl), and potassium carbonate (K_2CO_3), under phase-transfer catalyst conditions. The same methodology, when applied to the *N*-Ts-(*S*)-serine amide, afforded the corresponding newly prepared aziridinecarboxamide, as an enantiopure compound.[18]

Unique non-activated 3-arylaziridinecarboxylate formation from guanidinium salts involving an ester

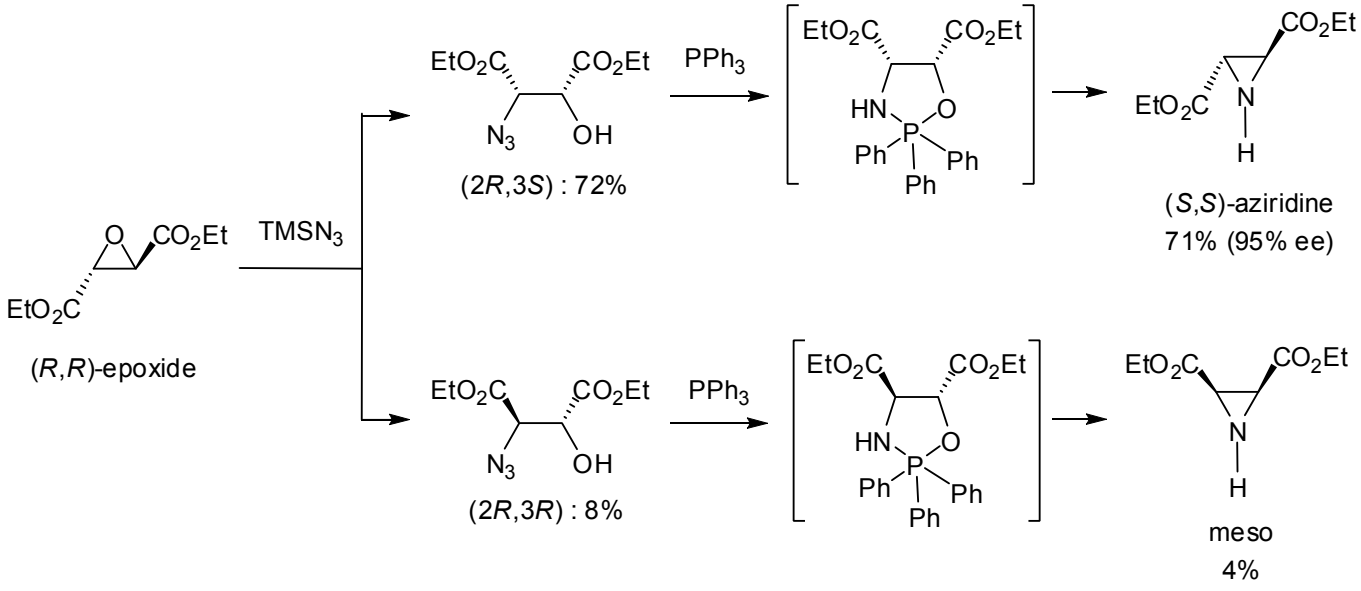
function and aromatic aldehydes under basic conditions has been discovered by our group, in which tetramethylguanidine (TMG) or sodium hydride (NaH) serve effectively as a base.[19] In the reaction urea derivatives are recovered as re-usable precursors for the starting guanidinium salts. This aziridination reaction is applicable to asymmetric synthesis when chiral guanidinium salt derived from 1,2-diphenylethylenediamine is used and, generally, high diastereo- and enantioselectivity are allowed in the products derived from electron-rich aromatic aldehydes. (2*R*)-Excess aziridinecarboxylate is formed from the (*S,S*)-guanidinium salt. For example, *trans*-*N*-Bn-3-(3,4-methylenedioxyphenyl)-aziridinecarboxylate was afforded in 82% yield with 97% ee when piperonal was used as an electrophile (Scheme 3). α,β-Unsaturated aldehydes can also be used as electrophiles.[20] This aziridination may be composed of three steps: (i) nucleophilic addition of guanidinium ylides, derivable from guanidinium salts by treatment with base, to aldehydes, (ii) formation of an imidazolidine-oxazolidine spiro intermediate by attack of the alkoxide ion formed to the guanidinium carbon, and (iii) fragmentation of the spiro intermediate to aziridine and urea components. Plausible mechanisms, dependent upon the electronic character of aldehyde electrophiles, have been proposed based on systematic reactions using a series of *p*-substituted benzaldehydes.[21] This aziridination can be classified to method I because the spiro intermediate is equivalent to an activated form of amino alcohol.



Scheme 3. Example of asymmetric aziridination from guanidinium salts and aromatic aldehydes

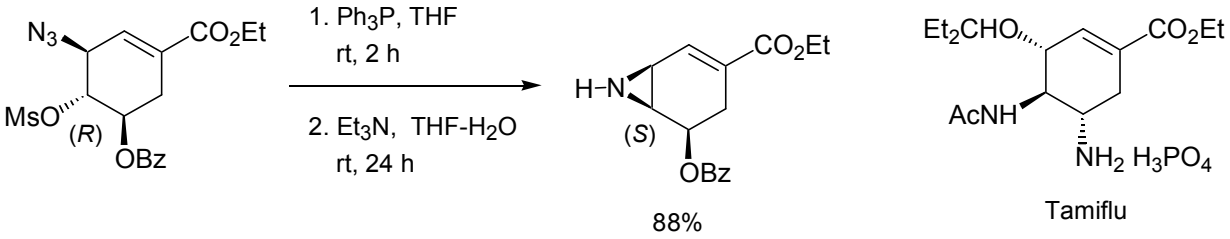
I-1-2. From Epoxides (Azido Alcohol) (Method I or II): The regiospecific ring opening of epoxides by azide ion could lead to the synthesis of aziridines.[22] Reduction of the azide moiety in azido alcohol formed, for example with Ph_3P in the Staudinger reaction,[1c,8b,23] yields first an imino phosphorane and then an

oxazaphosphorine intermediate which are normally not isolated prior to thermally induced cyclization to yield an aziridine. The method was applied to the synthesis of possible isomers of aziridine-2,3-dicarboxylate as a chiral version[24] (Scheme 4).



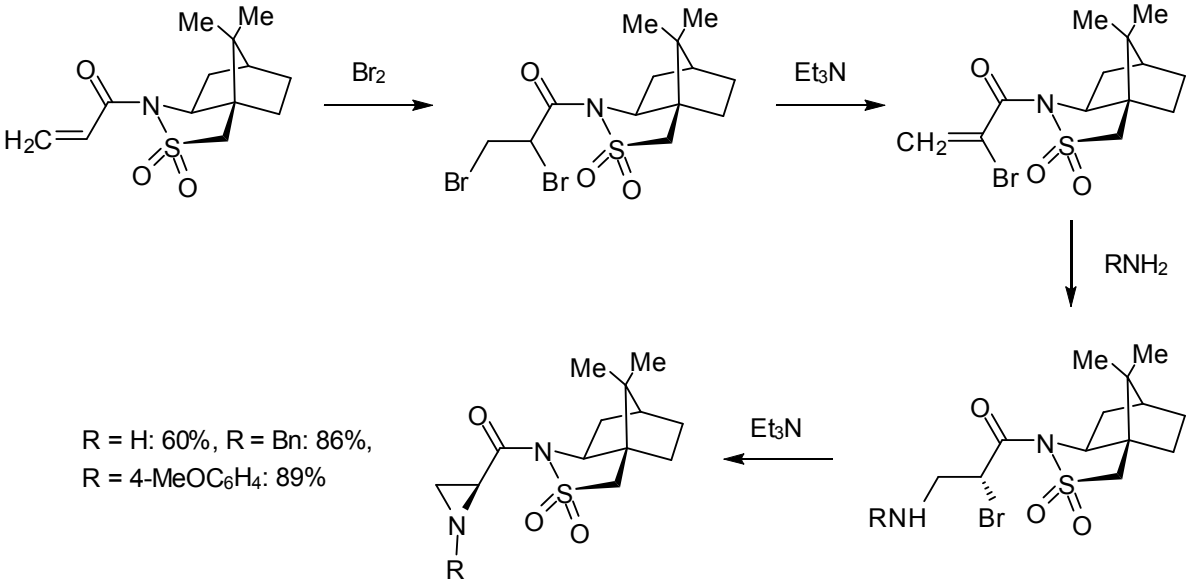
Scheme 4. Synthesis of aziridine-2,3-dicarboxylates *via* Staudinger reaction

In the asymmetric synthesis of oseltamivir phosphate (Tamiflu) from (-)-shikimic acid, aziridination by intramolecular nucleophilic displacement of azido alcohol derivative was applied[25] (Scheme 5). Aziridine was prepared in 88% yield by successive treatment of 2-azidocyclohexenyl methanesulfonate with Ph_3P, Et_3N, and some water in tetrahydrofuran (THF). In this transformation, reduction of the diazo group and formation of the aziridine *via* an intramolecular nucleophilic substitution of the neighboring methanesulfonyloxy (MsO) group took place simultaneously, and meanwhile the (*R*)-configuration is inverted to the (*S*)-one.



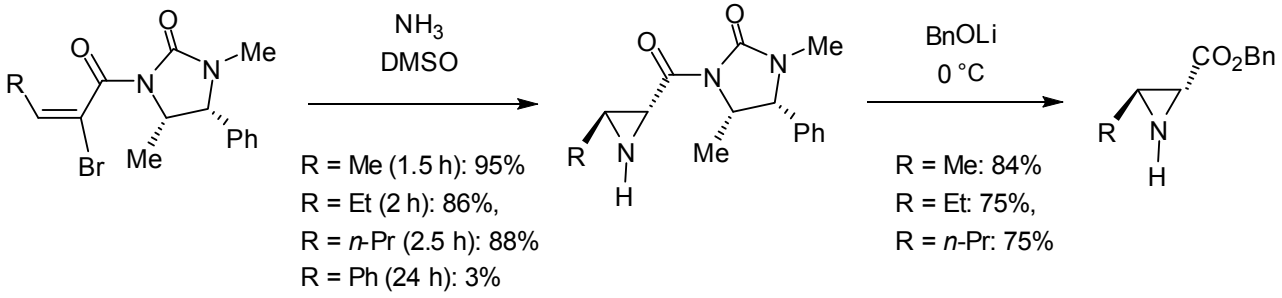
Scheme 5. Aziridination toward Tamiflu synthesis *via* Staudinger reaction

I-1-3. From Haloamines (Gabriel-Cromwell Reaction: Method II): Gabriel[26] demonstrated the utility of haloamines for aziridine synthesis. 1,2-Dibromoalkanes, prepared *via* addition of bromine to alkenes, can be elaborated to yield racemic aziridines on treatment with amines.[27] *trans*-Methyl *N*-Ts-3-arylaziridinecarboxylates and its nosyl (Ns) derivatives were easily synthesized by mixing alkyl cinnamate-derived haloamines with K_2CO_3 in acetonitrile (MeCN) at room temperature. Good to excellent yields have been achieved (83-97% for the *N*-Ts- and 75-94% for the *N*-Ns-derivatives).[28] An asymmetric Gabriel-Cromwell reaction of primary amine with enantiopure 2-bromocarboxamides, leading to non-activated aziridines, has been described; best results were obtained utilizing camphorsultam as a stoichiometric chiral controller[14c,29] (Scheme 6).



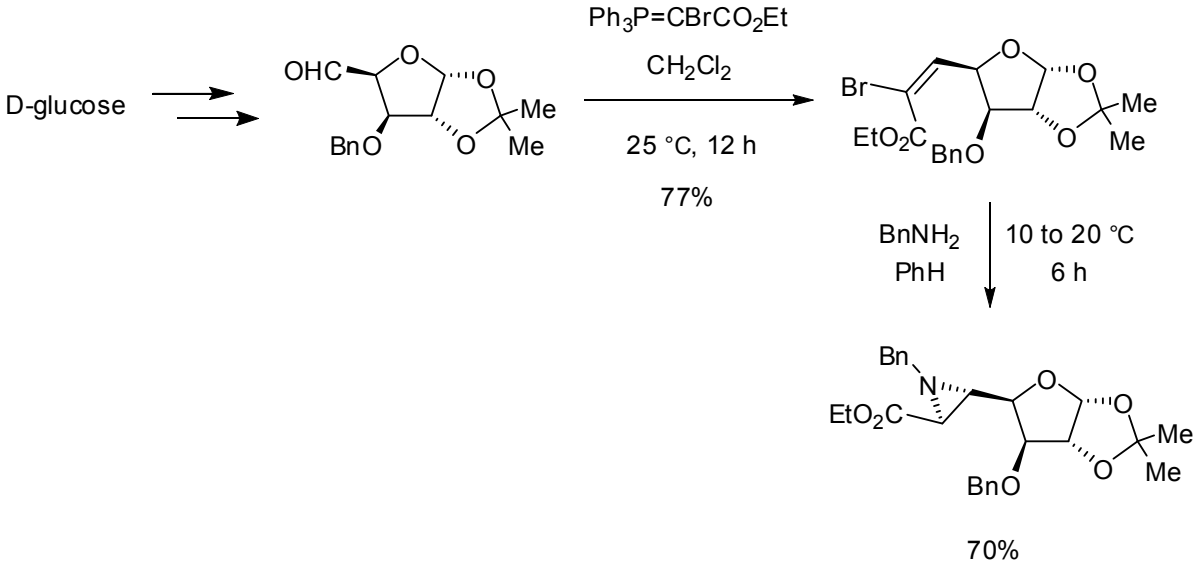
Scheme 6. Asymmetric Gabriel-Cromwell reaction of bromoacryl camphorsultam

A similar stoichiometric reagent-controlled strategy utilizes a chiral imidazolidin-2-one auxiliary in place of camphorsultam to prepare 1*H*-aziridinecarboxylates[14d,30] (Scheme 7).



Scheme 7. Aziridination *via* asymmetric Gabriel-Cromwell reaction of bromoacryl imidazolidinones

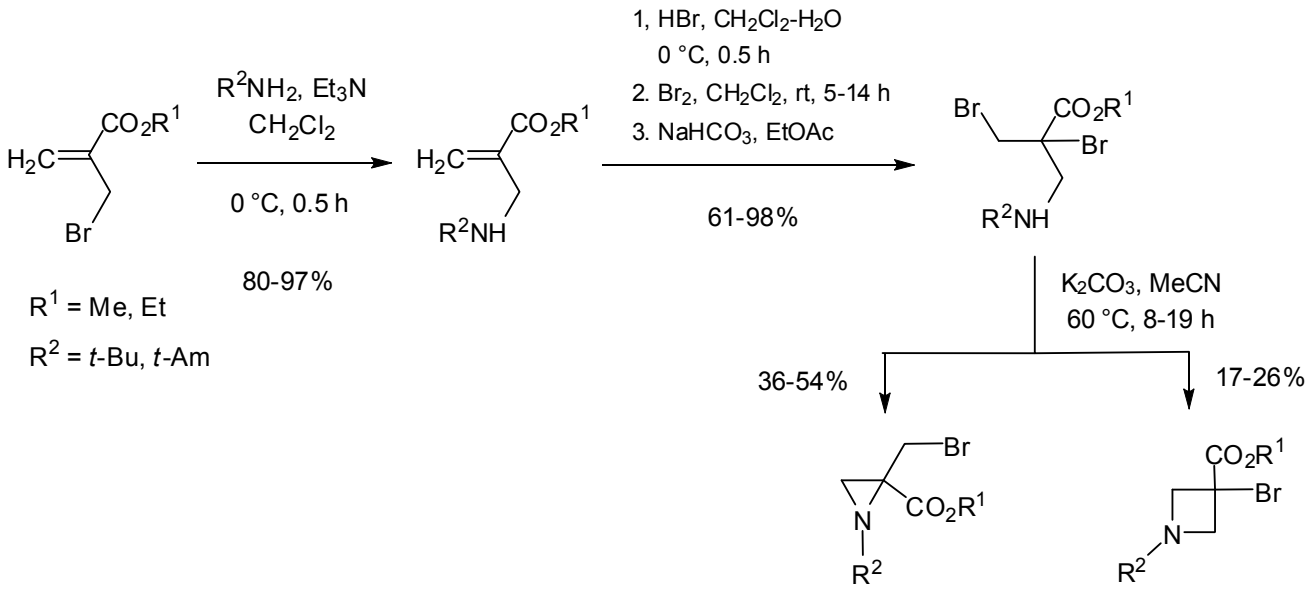
The Wittig olefination of α-D-xylo-pentodialdose, derived from D-glucose, using ethyl bromo(triphenylphosphino)acetate in dichloromethane (CH_2Cl_2) afforded the required bromocarboxylate in 77% yield. The exclusive formation of the *E*-isomer was confirmed by ^{1}H NMR spectra. Treatment with benzylamine provided aziridinecarboxylate in 70% yield[31] (Scheme 8). The *trans*-geometry of aziridine product was also established by ^{1}H NMR analysis which showed a small vicinal coupling constant between C2-H and C3-H ($J_{5,6}$ = 2.9 Hz) against the large J_{vic} (ca 7.0 Hz) known for the *cis*-aziridine derivative.[32] The *trans*-(2*S*,3*S*)-configuration was completely established by the single crystal X-ray analysis and reasonably deduced by the *Re*-face attack of benzylamine at the prochiral β-carbon of the ester function.



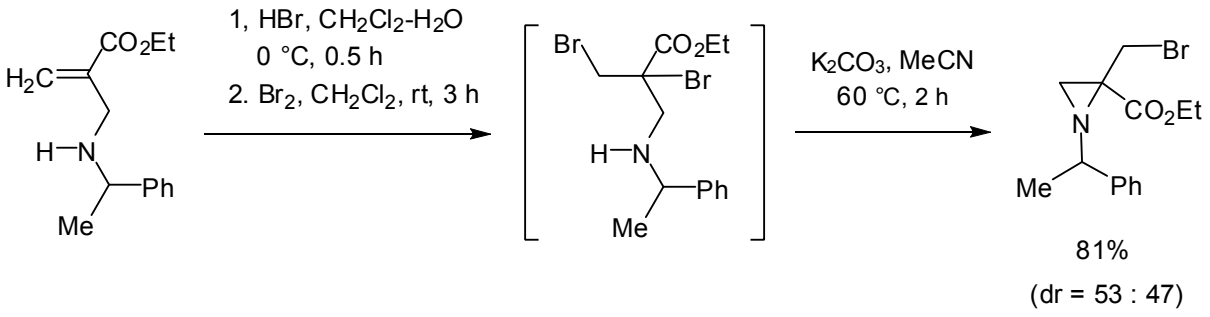
Scheme 8. Gabriel-Cromwell reaction of glucose-derived bromoacrylate

The amino group of alkyl aminoacrylate, derived from the corresponding bromoacrylates by aminolysis, was protected by treatment with aqueous hydrobromic acid in CH_2Cl_2 to the corresponding hydrobromide salts which were subsequently treated with bromine. After bromination, neutralization of the reaction mixture with sodium hydrogen carbonate ($NaHCO_3$) afforded dibromoaminopropanoates as precursors for Gabriel-Cromwell reaction. Conversion of the dibromo-amines to the aziridines as major products in moderate yields, together with the azetidines as minor compounds, was achieved under conditions with K_2CO_3 in MeCN at 60 °C[33] (Scheme 9). Interestingly, bromination of the tosylaminoacrylate (R^2 = Ts in Scheme 9) proceeded uneventfully without pre-treatment with hydrobromic acid and post-treatment with $NaHCO_3$. The dibromopropanoate was efficiently and selectively cyclized to *N*-Ts-aziridine (95% yield). An attempt was also made to perform the bromination and cyclization in a one-pot reaction.[33] Bromination of 2-[(1-phenylethylamino)methyl]acrylate was subjected to the conditions in Scheme 9, after which CH_2Cl_2 was replaced by MeCN. Upon adding K_2CO_3, a selective cyclization of the intermediate

hydrobromide salt occurred to yield aziridine in an excellent overall yield (81%) (Scheme 10).

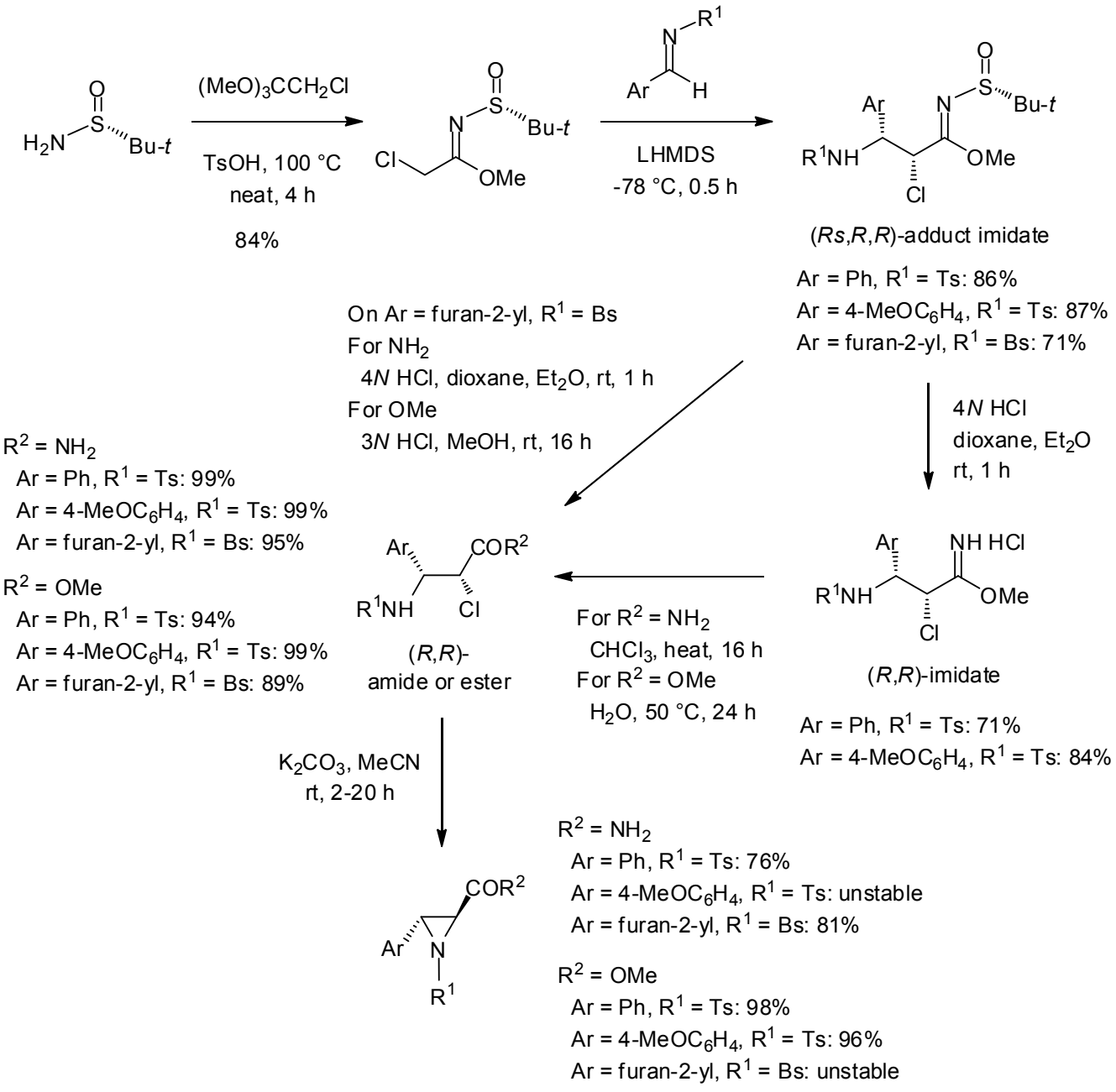


Scheme 9. Ring closure reactions of 2-aminomethyl-2,3-dibromopropanoates*



Scheme 10. On-pot reaction under the conditions in Scheme 9*

(2*S*,3*R*)-3-Arylaziridinecarboxamides and (2*S*,3*R*)-3-arylaziridinecarboxylates have asymmetrically prepared from (*Rs*)-*t*-butanesulfinamide as a chiral source by the application of Gabriel-Cromwell reaction[34] (Scheme 11). Condensation of (*Rs*)-*t*-butanesulfinamide and excess of 2-chloro-1,1,1-trimethoxyethane in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH) without solvent at 100 °C for 4 h afforded (*Rs*)-α-chloro-*N*-(*t*-butanesulfinyl) imidate in 84% yield. The addition reaction of the imidate to aldimine was optimized by systematically changing the reaction

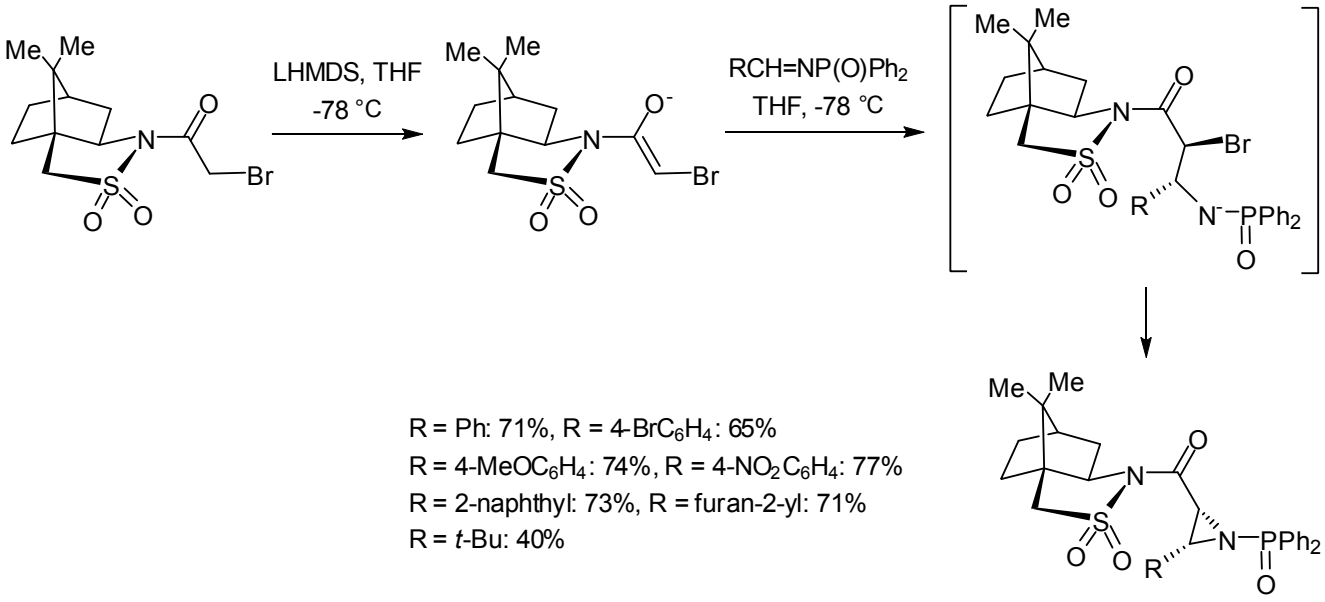


Scheme 11. Asymmetric synthesis of (2*S*,3*R*)-3-arylazirdinecarboxylic amides and esters from (*R*s)-*t*-butanesulfinamide through Gabriel-Cromwell reaction

conditions in the synthesis of adducts, α-chloro-β-(sulfonylamino)sulfinyl imidates, and finally the use of lithium hexamethyldisilazide (LHMDS) as a base led to the isolation of the optically pure (*Rs,R,R*)-adduct imidate (Ar = Ph, R^1 = Ts) in 86% yield. Analogously (hetero)aromatic chiral imidates (Ar = 4-$MeOC_6H_4$, R^1 = Ts and Ar = furan-2-yl, R^1 = Bs) were prepared with excellent diastereoselectivity. *N*-Deprotection of *t*-butanesulfinyl group on the imidate function in the (*Rs,R,R*)-adduct imidates was simply achieved by treatment with a 4*N* solution of anhydrous hydrogen chloride (HCl) in dioxane to yield the corresponding

(*R,R*)-imidate hydrochlorides (Ar = Ph or 4-$MeOC_6H_4$, R^1 = Ts), which were easily transformed to new chiral (*R,R*)-α-chloro-β-sulfonylamino amides and esters in excellent yields (94-99%), upon simple heating in chloroform ($CHCl_3$) and hydrolysis, respectively. The HCl-promoted *N*-deprotection of the adduct imidate (Ar = furan-2-yl, R^1 = Bs) in dioxane led directly to the corresponding (*R,R*)-amide in 95% yield, whereas (*R,R*)-ester was formed in 89% yield by treatment with 3*N* HCl in methanol (MeOH). (*R,R*)-Amides and esters could be easily cyclized to the corresponding (2S,3*R*)-3-arylaziridinecarboxylic amides and esters *via* addition of K_2CO_3 in MeCN.

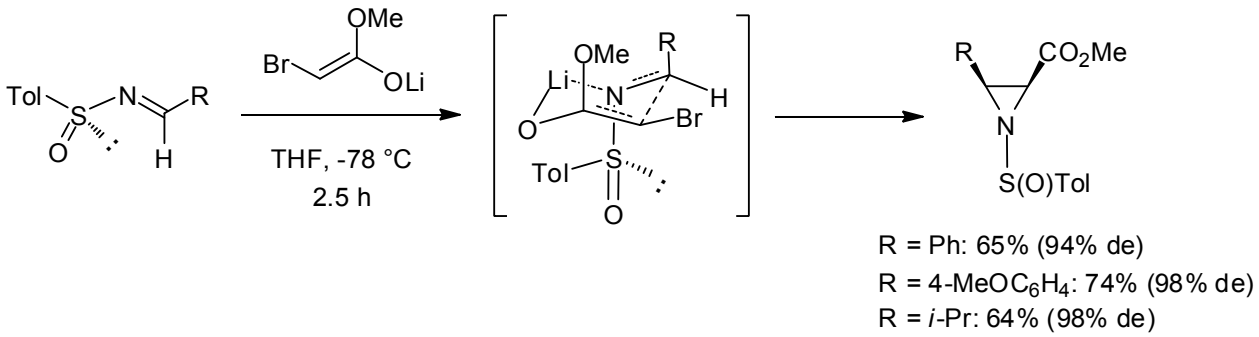
I-1-4. From Imines (Aza-Darzens Reaction: Method II): Aza-Darzens reactions of the chiral enolate derived from bromoacylcamphorsultam with *N*-(diphenylphosphinyl) imines (R = Ar or *t*-Bu) were reported as means of asymmetric access to aziridinecarboxylic acid derivatives[35] (Scheme 12). Enantiopure *cis*-aziridinecarboxylates may then be obtained after alcoholysis of these sultams.



Scheme 12. Asymmetric aziridine synthesis *via* aza-Darzens reaction of bromoacyl camphorsultam

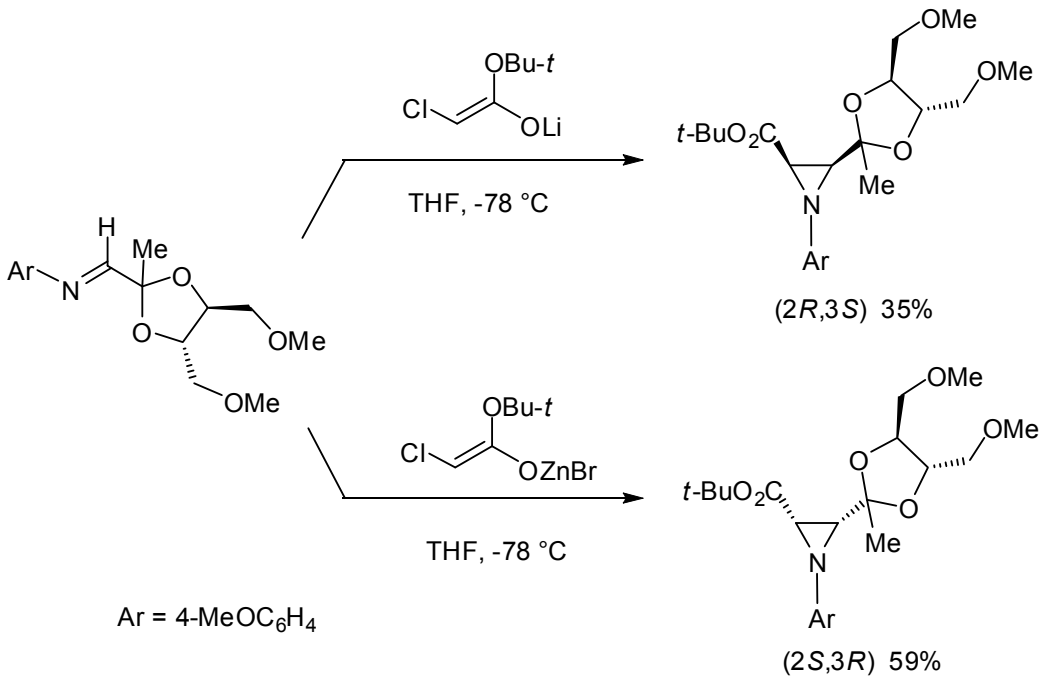
Condensation of enantiopure sulfinimines with the lithium enolate of methyl bromoacetate[36] or of methyl α-bromopropanoate[37] allows entry to *cis*-*N*-(*p*-toluenesulfinyl)aziridinecarboxylates in moderate yields (Scheme 13). Diastereoselectivities of up to 98% in favor of the *cis*-diastereoisomer are achieved. A chair-like transition state is proposed in which the sulfinyl nitrogen is also coordinated to the lithium cation. Both the enolate and the *N*-sulfinimine are required to have the *E*-configuration in the transition state. However, sulfinimines are known to possess relatively low barriers to inversion,[38] and it has, therefore, been argued that the lithium cation may coordinate to both the nitrogen and oxygen of the transition state to

lock the imine in the necessary *E*-geometry. Oxidation of the *N*-sulfinylaziridines with *m*-chloroperbenzoic acid (mCPBA) readily afforded the *N*-Ts analogues and, alternatively, the sulfinyl group could be removed under acidic or basic conditions, yielding 1*H*-aziridines.[32c]



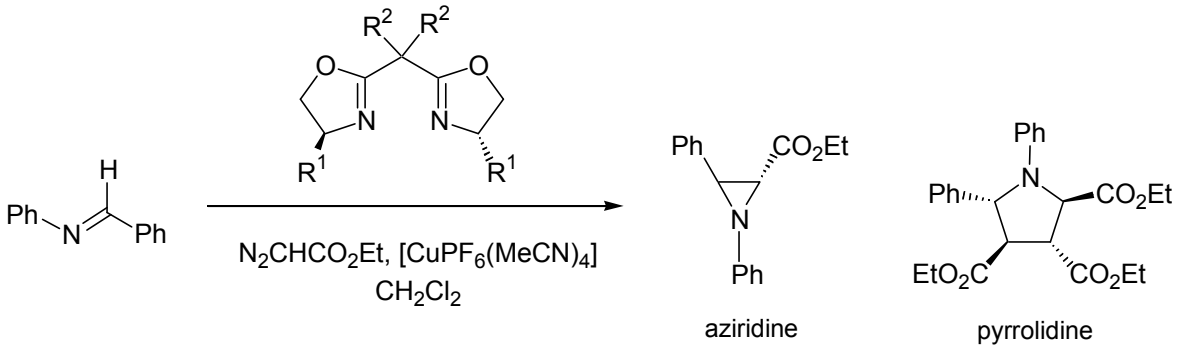
Scheme 13. Aza-Darzens reaction between bromoacetate and enantiopure sulfinimines

A chiral auxiliary based approach using tartrate-derived auxiliaries attached to imines has also been reported and a range of *cis*-aziridines was allowed to prepare on consideration with lithium or zinc enolates.[39] It was observed that lithium enolates afford the (2*R*,3S)-aziridine whereas zinc enolates afford the (2*S*,3*R*)-diastereoisomer, presumably as a consequence of the different coordinating abilities of these metals[39b] (Scheme 14).



Scheme 14. Enolate-controlled aza-Darzens reactions using tartrate-derived imines

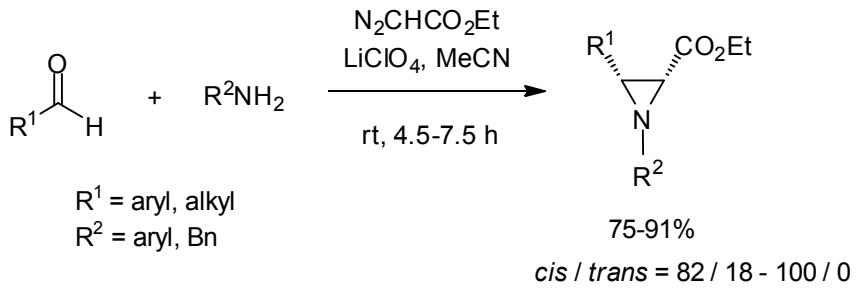
The nucleophilic addition of ethyl diazoacetate to imines is one of the most versatile methods for the synthesis of aziridinecarboxylates[40] and represents a complementary alternative to nitrene addition to alkenes (method IV) for the synthesis of aziridines. Copper (Cu) salts[41] and transition metal salts[42] are typically employed to promote the reactions of ethyl diazoacetate and imines. Lewis acids such as methylruthenium trioxide, boron trifluoride etherate ($BF_3 \cdot Et_2O$), indium chloride ($InCl_3$), and metal triflates, including zinc triflate [$Zn(OTf)_2$] and yttribium triflate [$Y(OTf)_3$], can also be used for the addition ractions.[43] In most cases, the products are obtained as a mixture of *cis*- and *trans*-aziridines and also the yields and selectivities reported are far from satisfactory. For example, Cu-catalyzed diazoacetate decomposition in the presence of an imine has indicated that the efficiency of the reaction is strongly dependent upon the nature of the imine nitrogen substituent and favor *N*-aryl substituents.[41a] A bisoxazoline Cu(I) complex has been known to act as a useful catalyst for the control of stereochemistry in this process;[41b] however, effectiveness in the aziridine formation was lower than for the racemic process (Scheme 15).



bisoxazoline	aziridine (*cis* / *trans*)	ee (*cis* / *trans*)	pyrrolidine
R^1 = Ph, R^2 = Me	37% (4)	44 / 35	10%
R^1 = Ph, R^2 = H, CN	19% (3)	15 / 7	11%
R^1 = *t*-Bu, R^2 = H	10% (2)	11 / 2	5%
R^1 = H, R^2 = Me	65% (>10)	-	<5%

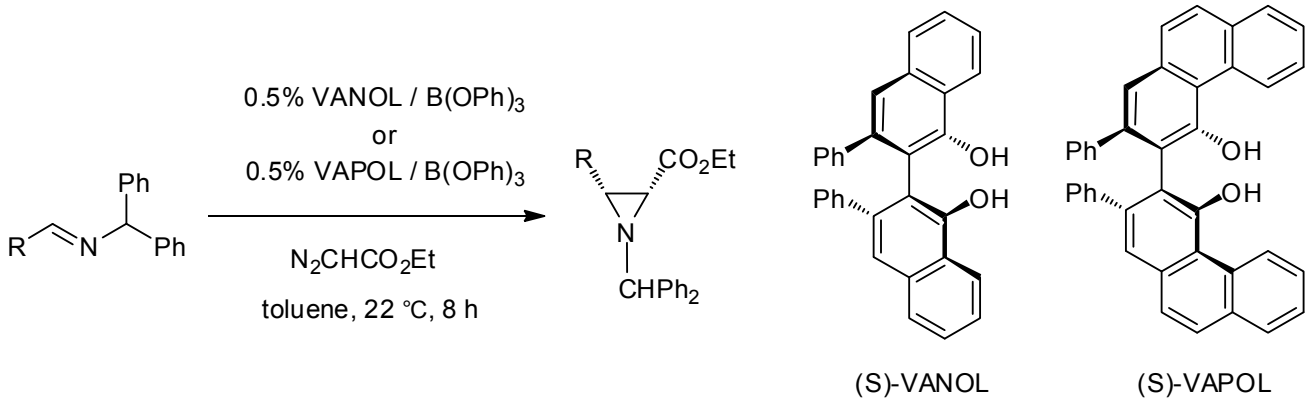
Scheme 15. Cu-catalyzed asymmetric aza-Darzens reactions

Furthermore, many of these reactions cannot be carried out in a one-pot operation with an aldehyde, amine, and ethyl diazoacetate, because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids. A one-pot procedure was developed for this conversion using lanthanide triflate as a novel catalyst.[44] Aldimine (generated *in situ* from aldehydes and amines) undergo ready addition with ethyl diazoacetate in the presence of a catalytic amount of lithium perchlorate ($LiClO_4$) in MeCN to afford the corresponding *cis*-aziridinecarboxylates in high yields with high diastereoselectivity[45] (Scheme 16).



Scheme 16. $LiClO_4$-catalyzed one-pot aziridination*

Wulff's group has developed a protocol for the 3,3'-diphenyl-2,2'-bi(naphthol) (VANOL)-triphenoxyborane [$B(OPh)_3$]-catalyzed asymmetric aziridination between benzhydryl imines, prepared from aminodiphenylmethane and an aldehyde, and ethyl diazoacetate.[46] Scheme 17 illustrates the generality of this protocol over a broad spectrum of benzhydryl imines derived from not only aromatic but also aliphatic aldehydes. The 2,2'-biphenyl-3,3'-(4-biphenanthrol) (VAPOL) catalyst gives essentially the same asymmetric induction. The exemplified benzhydryl aziridines can be readily crystallized up to almost optical purity by single crystallization with good to excellent recovery. Reduction of the amount of catalyst did not result on less than complete conversion for the VANOL catalyst until the loading was reduced to 0.25 mol% and raising the concentration of imine to 1.0 M increased the conversion to 95%.



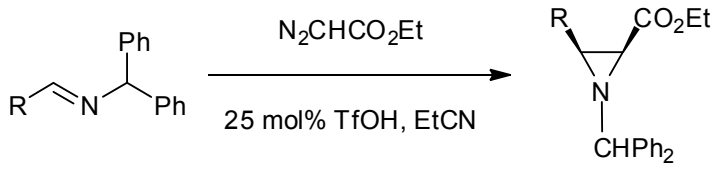
catalyst	Ph	2-MeC_6H_4	4-$NO_2C_6H_4$	4-BrC_6H_4	4-$MeOC_6H_4$
(*S*)-VANOL	87% (93% ee)	67% (90% ee)	86% (89% ee)	86% (94% ee)	61% (87% ee)
(*S*)-VAPOL	82% (94% ee)	63% (91% ee)	79% (79% ee)	78% (90% ee)	51% (86% ee)

catalyst	3,4-$(AcO)_2C_6H_3$	*n*-Pr	*c*-C_6H_{11}	*t*-Bu
(*S*)-VANOL	84% (93% ee)	54% (77% ee)	79% (82% ee)	89% (85% ee)
(*S*)-VAPOL	87% (89% ee)	40% (81% ee)	73% (81% ee)	72% (87% ee)

Scheme 17. VANOL (or VAPOL)-catalyzed asymmetric aziridination of imines and diazoacetate

N-Ts-Imino ester was reacted with (trimethylsilyl)diazomethane ($TMSCHN_2$) in the presence of catalytic 2,2-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) and bisoxazoline-Cu salts to give *cis*- and *trans*-aziridines with moderate enantiomeric excess.[47]

The proton is arguably the most abundant and least expensive of the Lewis acids. Brønstead acids are also readily removed from an organic reaction-an attractive feature with substantial strategic and practical implications. Brønsted acid catalysis was turned to extend the scope of Lewis acid-catalyzed aza-Darzens reactions[48] and to facilitate construction of the more Lewis basic and functionally diverse *N*-alkylaziridines.[49] Screening of various Brønsted acids revealed to be triflic acid (TfOH) as the most effective catalyst for the aza-Darzene reaction: in the addition of diazoacetate to α-imino glyoxalates in the presence of 25 mol% TfOH, *cis*-aziridinecarboxylates were provided in good yield with excellent selectivity. Aldimines derived from simple aliphatic aldehydes afforded low isolated yields (41-45%) of the *cis*-aziridine. A dramatic improvement came by employing pyridine-2-carbaldehyde imine, which provided the desired *cis*-aziridine (R = 2-Py) (90 : 10 ds) in 73% isolated yield[49] (Scheme 18).



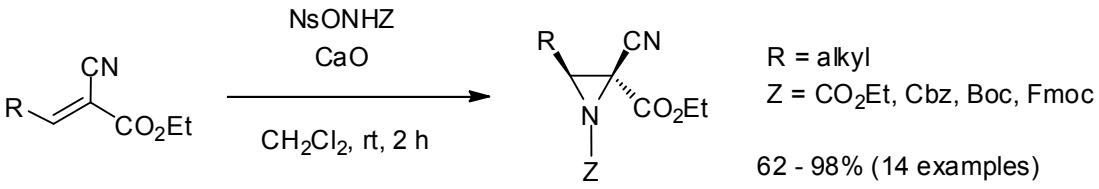
R = CO_2Me	86% (>90% de) at -78 °C
R = CO_2Bu-*t*	89% (>90% de) at -78 °C
R = *c*-C_6H_{11}	42% (60% de) at 42 °C
R = Ph	42% (64% de) at 0 °C
R = 2-Py	73% (80% de) at -78 °C

Scheme 18. TfOH-catalyzed aziridination of imines and diazoacetate*

Aza-Darzens reaction of ethyl diazoacetate with aldimines, derived from phenyl glyoxal, has furnished *cis*-aziridinecarboxylates with excellent enantioselectivities by means of a chiral phosphoric acid.[50]

I-1-5. From α,β-Unsaturated Esters (Aza-Michael reaction: Method III): Direct conversion of (*E*)-2-cyanoacrylates into the aziridine products was achieved by aza-Michael addition of *N*-protected *O*-sulfonylhydroxylamine derivatives[51] (Scheme 19). 2-Cyanoaziridinecarboxylates were prepared in good yields and with high purity by reaction of the easily obtainable corresponding cyanoacrylates with sulfonyloxycarbamates in the presence of calcium oxide, after only a fast filtration of crude mixtures through plugs of silica gel. The reactivity was found to be influenced by steric hindrance of the R

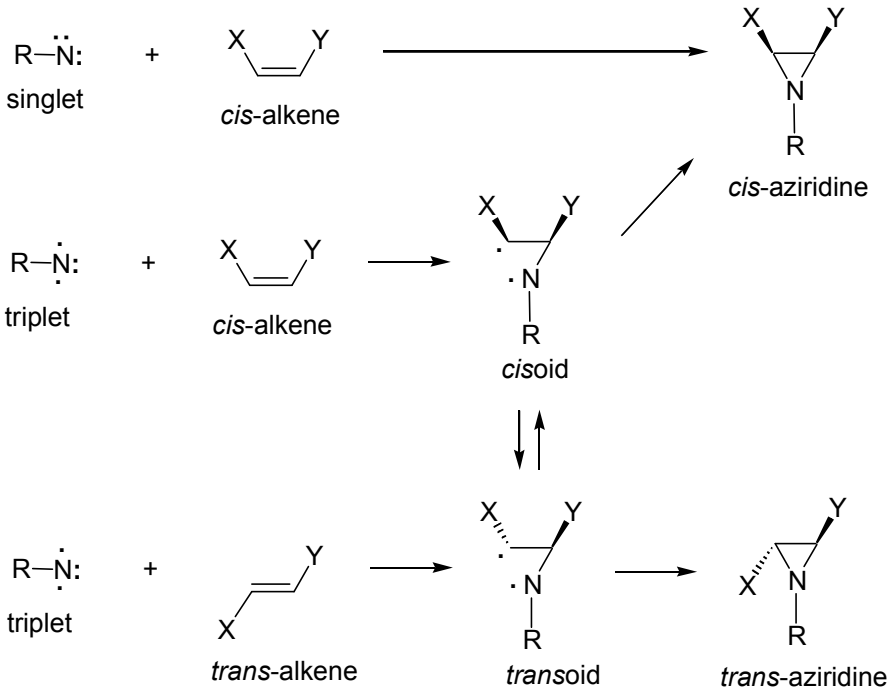
substituents on acrylates.



Scheme 19. Aza-Michael addition of *N*-protected *O*-Ns-hydroxylamines to 2-cyanoacrylate*

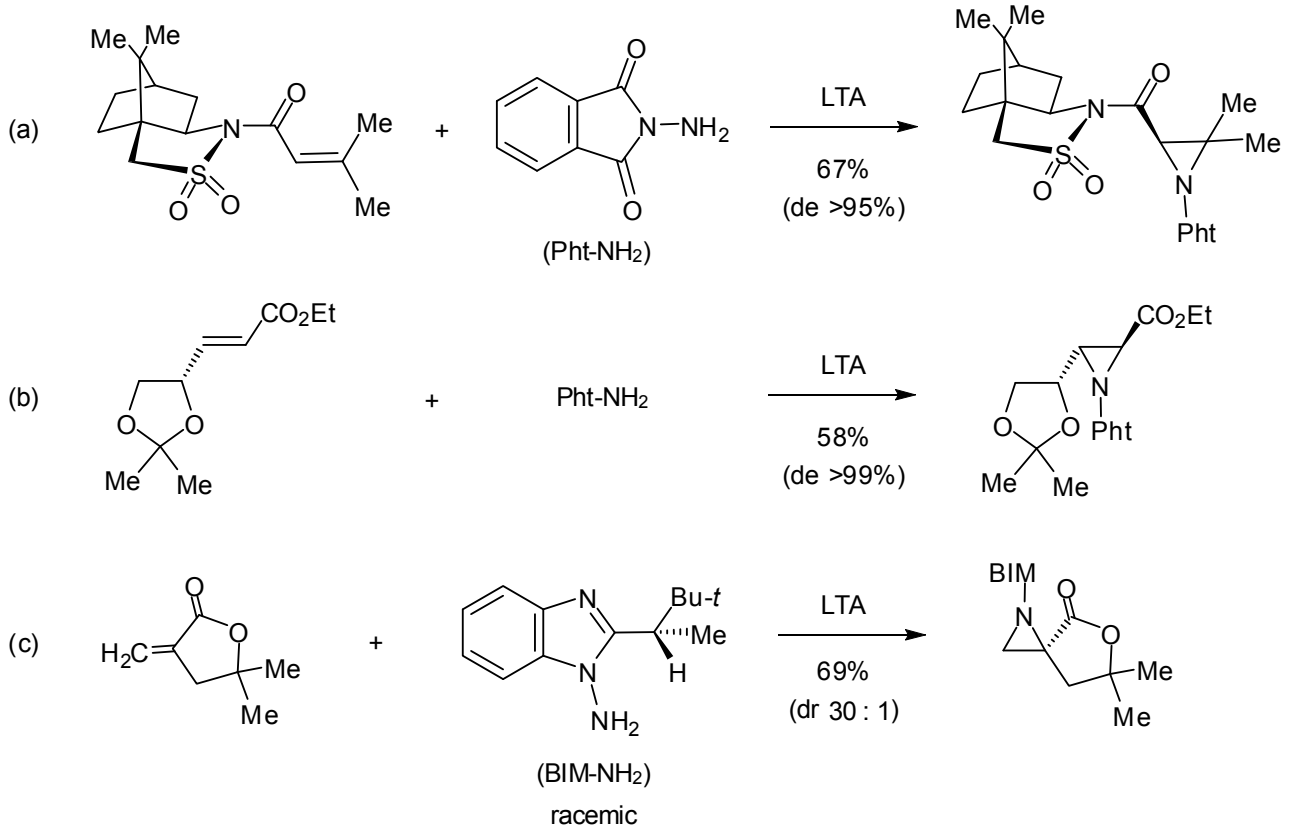
I-2. By Addition Reaction

I-2-1. From Alkenes (Nitrene Addition: Method IV): Direct aziridination of alkenes by nitrenes is a well-studied reaction particularly using alkoxycarbonylnitrenes. However, there are severe limitations to this method in synthesis arising from competitive insertion into C-H bonds and from conversion of the initially formed singlet state of the nitrene into the triplet state which reacts non-stereospecifically with alkenes. Thus, the addition of free nitrenes to an alkene is generally not well stereochemically-controlled to provide a mixtures of *cis*- and *trans*-aziridines[52] (Scheme 20).



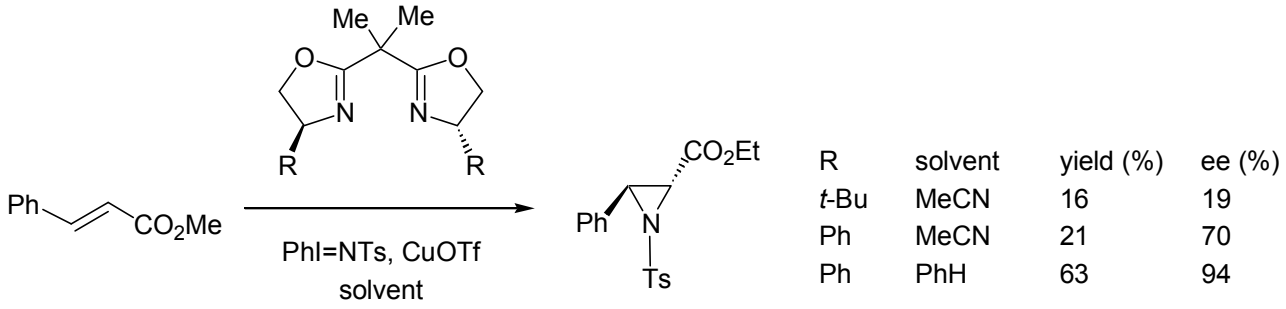
Scheme 20. Schematic synthesis of aziridines by nitrene addition to alkenes

There are few general methods for highly diastereoselective aziridination of alkenes with the chiral element (chiral center) present in the alkene (substrate-controlled diastereoselectivity)[2] and even fewer with the chiral center contained in the reagent (reagent-controlled diastereoselectivity). However, both the α,β-unsaturated ketone bearing Oppolzer's chiral auxiliary[53] and sugar-derived α,β-unsaturated ester[54] are aziridinated by oxidative addition of *N*-aminophthalimide (Pht-NH_2) mediated by lead tetraacetate (LTA) with excellent diastereoselectivity (Scheme 21a, b). A similar oxidative addition of the *N*-aminobenzimidazole (BIM-NH_2) to an α-methylene-γ-butyrolactone gave only the aziridine diastereoisomer (reagent-controlled diastereoselectivity) (Scheme 21c). Atkinson and co-workers have explored 3-acetoxyaminoquinazolinone and its analogs as a nitrogen source in asymmetric aziridination through these nitrene additions.[11b]



Scheme 21. Asymmetric aziridine synthesis *via* nitrenes

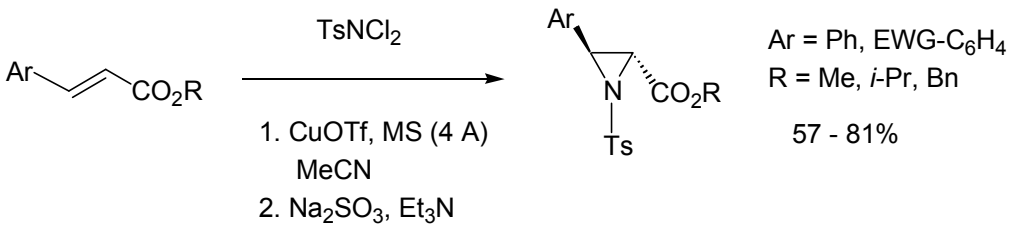
It was reported that (*N*-Ts-imino)phenyliodinane (PhI=NTs) could aziridinate alkenes in the presence of catalytic quantity of low-valent metal complexes.[55] A variety of catalysts capable of effecting asymmetric aziridination was also reported.[56] These include benzylidne derivative of 1,2-diaminocyclohexane,[56a] chiral 4,4'-disubstituted bisoxazolines,[56b,c] and binaphthyl salen-manganese (III) complexes.[57] Examples using methyl cinnamate are shown in Scheme 22.



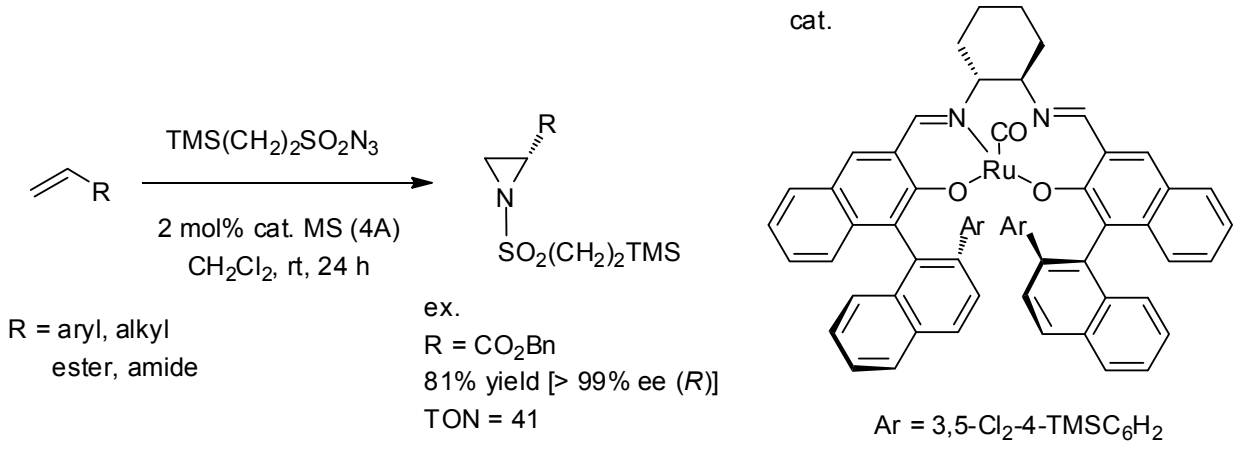
R	solvent	yield (%)	ee (%)
t-Bu	MeCN	16	19
Ph	MeCN	21	70
Ph	PhH	63	94

Scheme 22. Cu-catalyzed asymmetric aziridination of nitrene addition to methyl cinnamate

The synthesis of *trans*-*N*-Ts-3-arylaziridinecarboxylates from cinnamate was conducted *via* a one-pot procedure consisting of aminohalogenation and *in situ* intramolecular S_N2 substitution[58] (Scheme 23). Et_3N was found to be an effective base for the *in situ* cyclization for most substrates. Moderate to good yields of products and excellent *anti*-stereoselectivity for *trans*-aziridine formation were achieved. This method is applicable to only phenyl and EWG-substituted cinnamates, but α,β-unsaturated ketones worked.



Scheme 23. One-pot synthesis of *trans*-*N*-Ts-aziridinecarboxylates from cinnamates*



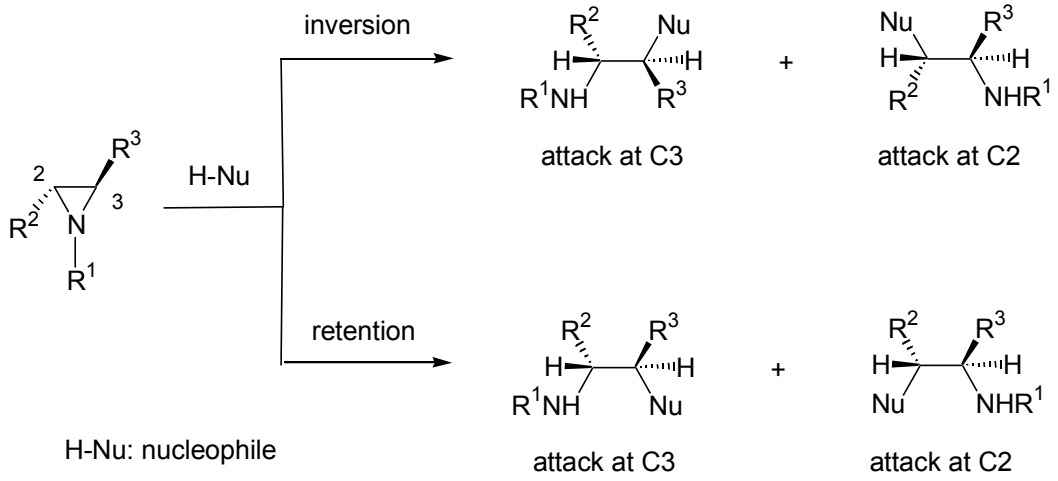
Scheme 24. Ru(salen)CO complex-catalyzed asymmetric aziridination of nitrene addition to alkenes

Aziridination with good to excellent enantioselectivity was achieved by using 2-(trimethylsilyl)ethanesulfonyl azide as a nitrene precursor in the presence of newly prepared ruthenium salen complex [Ru(salen)(CO)] of high durability[59] (Scheme 24). Aziridiantion of less reactive α,β-unsaturated esters (and amides) proceeded with excellent enantioselectivities.

I-2-2. From Imines (Carbenoid Addition: Method V or VI): The alternative [2+1] cycloaddition route to aziridines involves carbenoid addition to imine double bond. Aza-Darzens reaction of imines with diazoesters discussed in I-1-4 section may be categorized to method VI; however, to the best of our knowledge, no reports by methods V and VI are basically available.

II. NUCLEOPHILIC RING OPENING

The nucleophilic ring opening of a 2,3-disubstitued aziridine can deliver two regioisomers, from which, in principle, four products are possible with inversion or retention of configuration[2,11] (Scheme 25). In particular, completely stereoselective ring opening almost always arises from inversion of configuration.

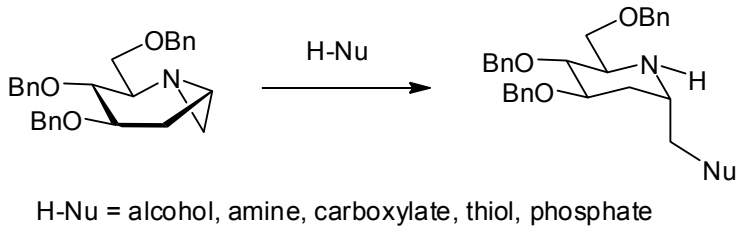


Scheme 25. Possible modes of nucleophilic ring opening of *trans*-2,3-disubstituted aziridine

The conformational stability and reactivity of the aziridine ring toward nucleophiles are dependent on the nature of the substituent on nitrogen, according to which aziridines can be classified to two groups. The first "non-activated" aziridines contain a basic nitrogen atom and their aziridine ring conformation is more stable and less reactive toward nucleophiles. Thus, ring opening reactions usually occur after protonation, quaternization, or formation of a Lewis acid adduct. The second "activated" aziridines contain a substituent which can conjugatively stabilize the negative charge that develops on the nitrogen atom in the transition

state for ring opening by a nucleophile, which is consistent with conformational destabilization of the aziridine ring. Most of ring opening reactions have focused on *N*-activated aziridines, whereas there have been few reports on the ring opening reactions of *N*-alkylaziridines.[2,11]

A general synthesis of α-1-*C*-substituted derivatives of fagomine (2-deoxynojirimycin-α-*C*-glycoside) by ring opening reactions of an iminosugar-derived non-activated aziridine with various heteroatom nucleophiles, including alcohol, amine, carboxylate, thiol, and phosphate, has been achieved [60] (Scheme 26).

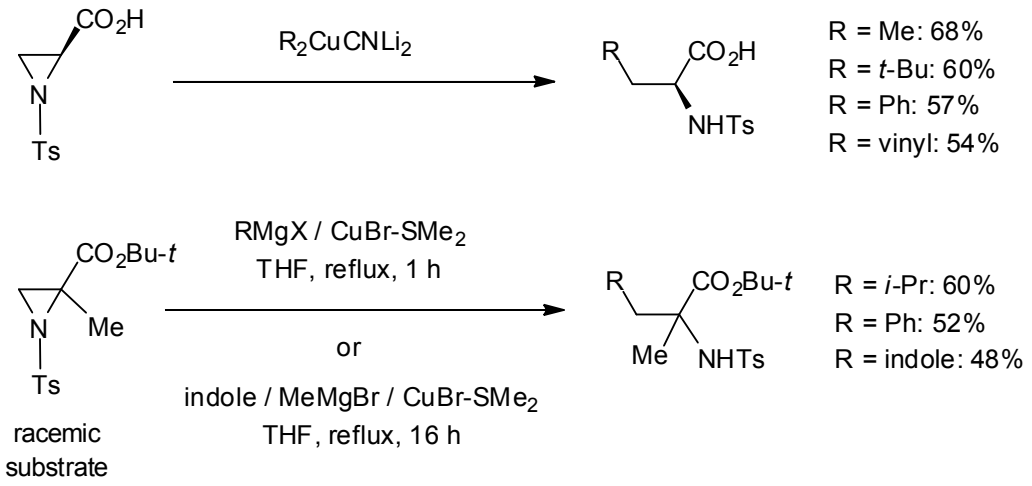


Scheme 26. Ring openings of an iminosugar-derived aziridine with heteroatom nucleophiles

In this chapter, nucleophilic ring openings by various nucleophiles will be discussed in the order of carbon, hydrogen, and heteroatom nucleophiles.

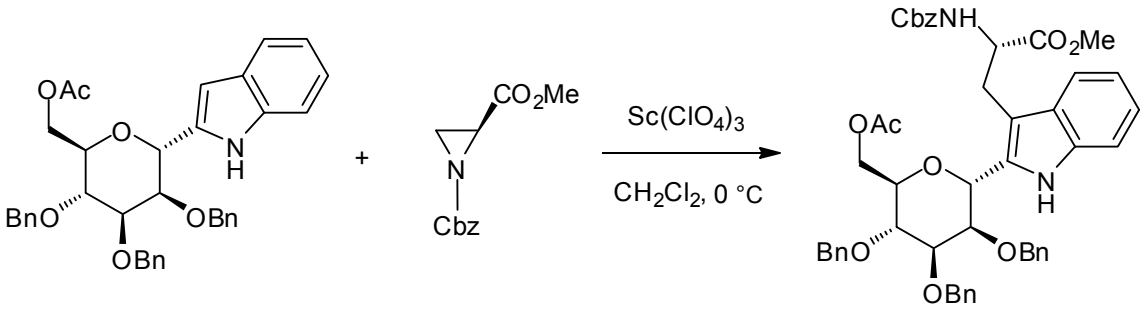
II-1. With Carbon Nucleophiles

Nucleophilic ring opening of aziridines by organometallic reagents has been known for over four decades.[61] However, the application of the carbanion addition was not significantly accelerated until a more efficient method developed in the $BF_3 \cdot Et_2O$-catalyzed opening of non-activated aziridines by organocuprates was reported.[62] A subsequent report for the ring opening of *N*-sulfonated aziridines with requirement of no catalysis further enhanced its broad use.[5a] The use of organometallics to open aziridinecarboxylates appears an excellent route for the synthesis of α-amino acids,[3] but the competing reaction at the ester functionality is problematic. While organocuprate reagents have obviated this problem, regioselectivity in ring opening was poor.[63] Hydrolysis of the ester to an acid, then treatment with higher order cuprates overcome this regioselectivity problem for 3-unsubstituted aziridinecarboxylic acid[64] (Scheme 27). In accordance with the expected steric effect of methyl substitution at C2 in aziridine, *in situ*-prepared cuprates attack the C3 of the *t*-butyl aziridinecarboxylate with complete control of regioselectivity.



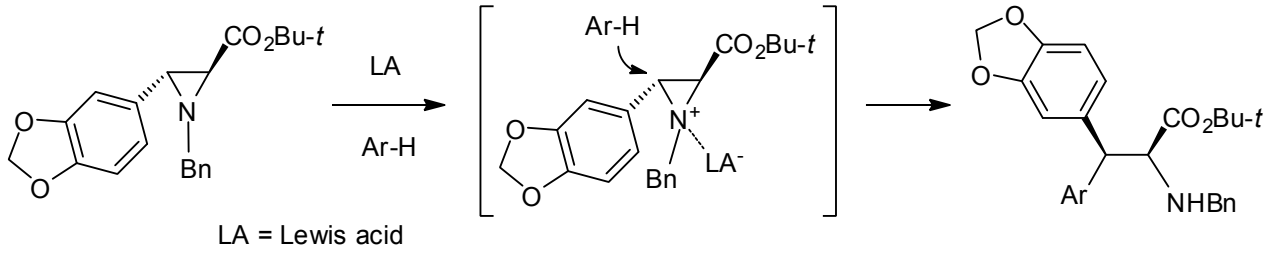
Scheme 27. Ring openings of 3-unsubstituted aziridinecarboxylic acid derivatives with carbon nucleophiles

Indoles, containing enamine functionality embedded in the heteroaryl ring, have been found to be good substrates for the Lewis acid-catalyzed ring opening of aziridines.[4] 2-Substituted indole readily underwent nucleophilic addition to activated aziridinecarboxylate, when facilitated by scandium perchlorate [$Sc(ClO_4)_3$], to give 2-substituted tryptophan in good yield[65] (Scheme 28), whereas a mixture of regioisomers were obtained when catalyzed by tin triflate [$Sn(OTf)_3$]. Other Lewis acids such as $BF_3 \cdot Et_2O$, metal triflates [$Zn(OTf)_2$, $Yb(OTf)_3$, and $In(OTf)_3$] and $InCl_3$ were less effective catalysts than $Sc(ClO_4)_3$ in the ring opening of the aziridine with respect to regioselectivity and reproducibility.[66]



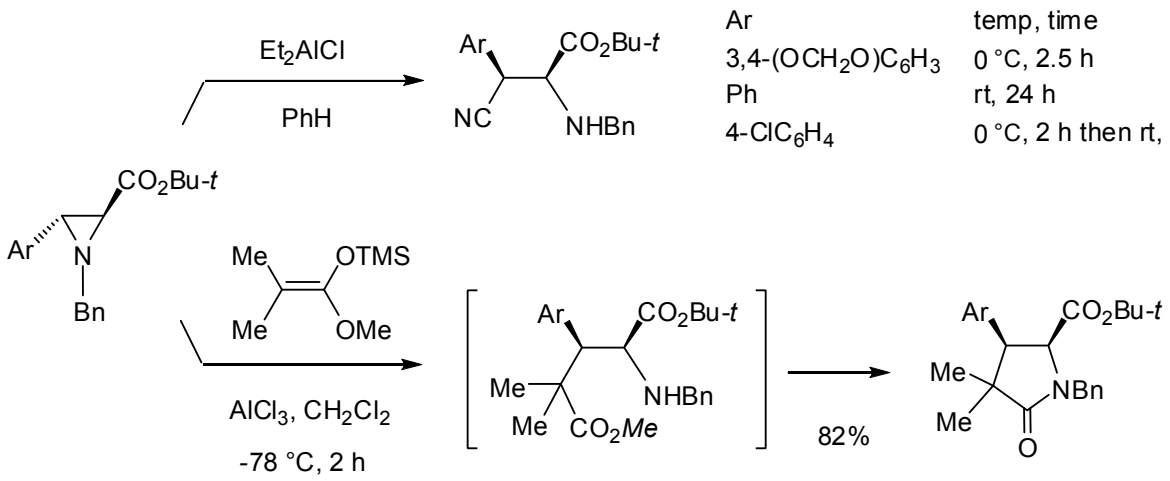
Scheme 28. Ring opening of an activated aziridinecarboxylate with an indole derivative

We have reported Lewis acid-catalyzed ring opening of non-activated *trans*-*N*-Bn-3-arylaziridinecarboxylate using electron-rich aromatic nucleophiles, including indole, which preferentially attack at the benzylic C3 of the starting aziridine with inversion to give 2-amino-3,3-diarylpropanoates[13] (Scheme 29).



Scheme 29. Lewis acid-catalyzed ring opening of *N*-Bn-3-arylaziridinecarboxylate with aromatics*

We also examined ring opening of non-activated 3-arylaziridinecarboxylates using non-aromatic carbon nucleophiles[67] (Scheme 30). Effective cyanation (92% yield) with high regio- and stereoselectivity was observed when *trans*-3-arylaziridinecarboxylate carrying an electron-rich aryl substituent was treated with a freshly prepared diethylaluminum cyanide [Nagata reagent: Et_2AlCN] as a cyanide source. Treatment with ketene silyl acetal as an alternative carbon nucleophile in the presence of aluminum chloride ($AlCl_3$) successfully provided the corresponding ring cleaved product, even a pyrrolidone derivative was formed after cyclization. It was found that aluminum-containing Lewis acid catalysts were effective in these ring opening reactions; however, less effective ring opening and no reaction were observed when used the electron-deficient aryl-substituted *trans*-derivatives and the *cis*-aziridines, respectively.



Ar	temp, time	yield (%)
3,4-$(OCH_2O)C_6H_3$	0 °C, 2.5 h	92
Ph	rt, 24 h	40
4-ClC_6H_4	0 °C, 2 h then rt, 13 h	27

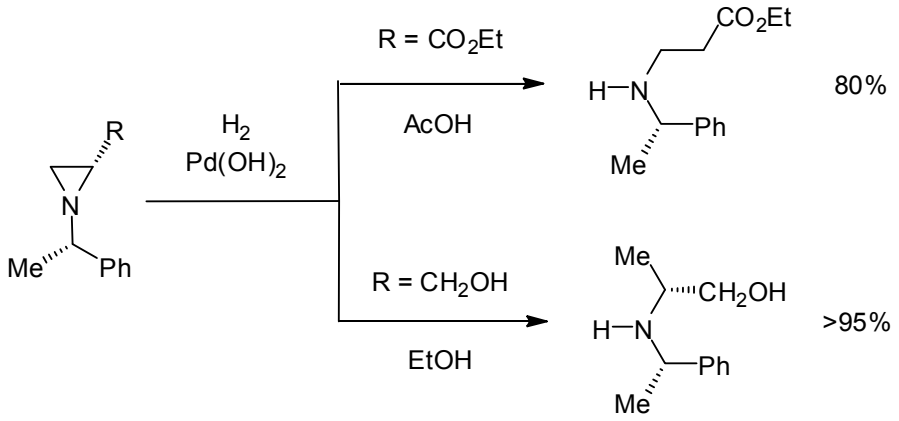
Scheme 30. Aluminum-catalyzed ring opening of *trans-N*-Bn-3-arylaziridinecarboxylate with carbon nucleophiles*

II-2. With Hydrogen Nucleophiles

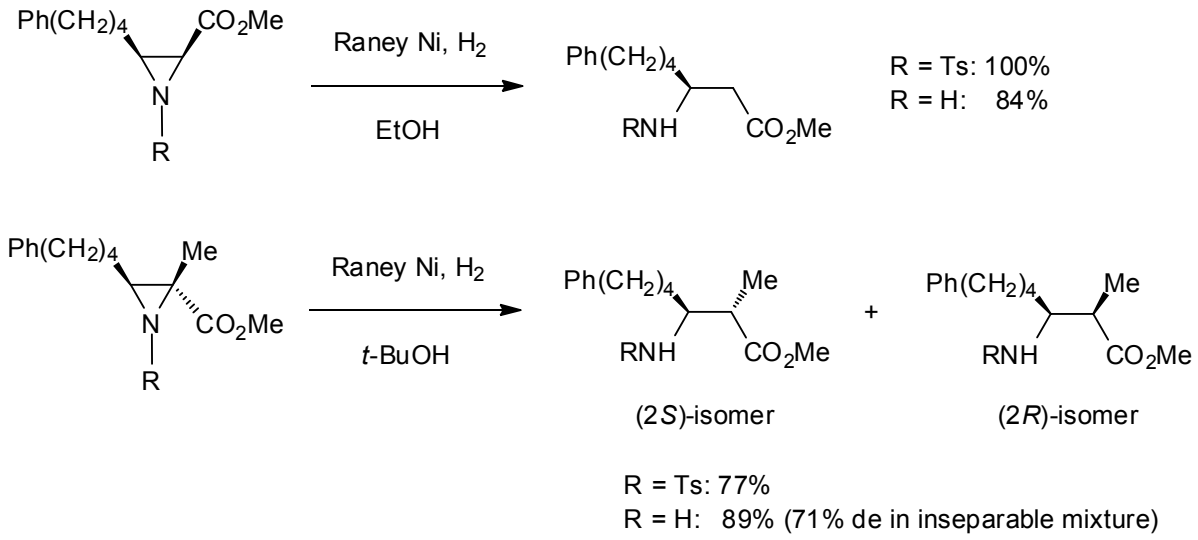
Although hydrogen is not characterized as a nucleophile, it serves the purpose of aziridine ring cleaving.[11] Catalytic hydrogenolysis of both activated and non-activated aziridines produces amines as useful building

blocks for other synthesis and synthon for the synthesis of biologically active products.[36,37,56b,68] Hydrides could undergo ring opening of aziridines; however, hydride reduction requires activation of aziridines for the completion. In addition, hydrogenolysis of aziridines provides the corresponding amines with high regiocontrol, whereas hydride reduction is less appreciable in terms of site of the ring cleavage.

II-2-1. Hydrogenolysis: With 3-arylaziridinecarboxylates, regiospecific hydrogenolysis at the benzylic carbon was observed to give α-amino acid products and such ring opening does not affect the C2 stereochemistry.[13,19,69] In the case of (*R*)-*N*-[(*S*)-1-phenylethyl]aziridinecarboxylate, lacking benzylic



Scheme 31. Hydrogenolysis of enantiopure 3-unsubstituted aziridines

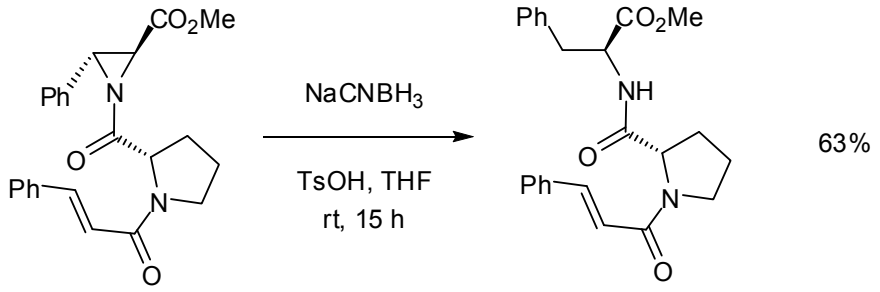


Scheme 32. Hydrogenolysis of 3-alkylaziridinecarboxylates with Raney Ni in alcohol solvents

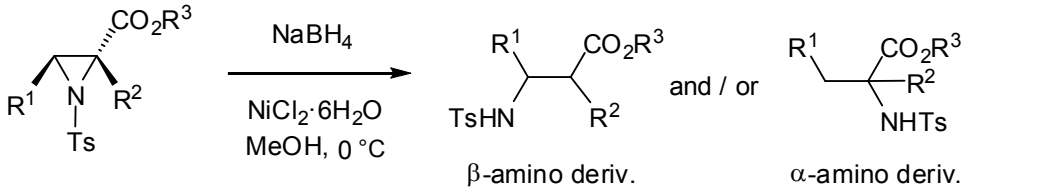
aziridine carbon center, hydrogenolysis occurred at C2 to give β-amino ester.[70] However, the corresponding (2*R*,1*S'*)-aziridine alcohol gave a chiral (2*R*,1*S'*)-amino alcohol with C3 opening[70,71] (Scheme 31). No reaction occurred with the sterically crowded trityl group on nitrogen.

The catalyst and solvent effects on hydrogenolysis of 3-alkylaziridinecarboxylates have been examined[72] (Scheme 32). The optimum results with nearly quantitative yield was obtained by the use of Raney nickel (Ni) in ethanol (EtOH). On the other hand, the 2-methyl derivative yielded two diastereoisomers and the diastereoselectivity was dependent upon the alcohol solvent used. The (2*S*)-isomer was yielded as a major isomer with retention of configuration in the ring opening reaction of the (2*R*)-methylaziridine when the more hindered *t*-butanol (*t*-BuOH) was used as solvent.

II-2-2. Hydride: The reductive cleavage of 3-phenylaziridinecarboxylate containing peptidemimics using sodium cyanoborohydride ($NaCNBH_3$) under acidic conditions was reported[73] (Scheme 33). Ring opened product was regioselectively derived by hydride attack at the benzylic carbon.



Scheme 33. Ring opening of 3-phenylaziridinecarboxylate with $NaCNBH_3$

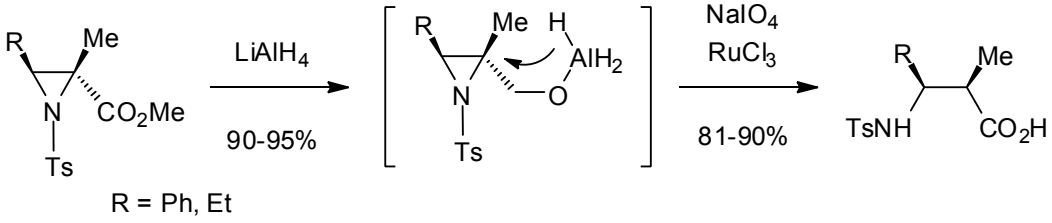


R^1 = H, R^2 = Ph, R^3 = *t*-Bu: β-amino deriv. (90%)
R^1 = Ph, R^2 = H, R^3 = Et: α-amino deriv. (95%)
R^1 = Ph, R^2 = Me, R^3 = Et: 90% (1 : 1 of β- and α-amino derivs.)

Scheme 34. Ring opening of *N*-Ts-aziridinecarboxylate with $NaBH_4$*

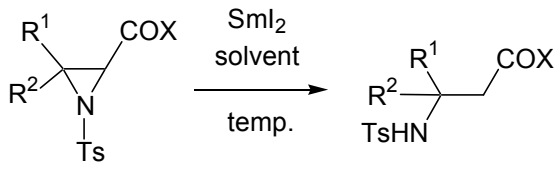
Sodium borohydride ($NaBH_4$) was also used for regioselective ring cleavage of *N*-Ts-aziridinecarboxylates; however, no selectivity was observed in the presence of additional substituent at the C2, resulting in ca 1 : 1 mixture of α- and β-aminopropanoates[74] (Scheme 34).

The regiochemistry of ring opening can also be directed towards C2 through chelation of the nucleophile.[75] Treatment of (2*R*,3*S*)-2-methylaziridinecarboxylate with lithium aluminum hydride ($LiAlH_4$) afforded alkoxide by reduction of the ester function, which directed the delivery of hydride to open the aziridine at C2. (2*R*,3*S*)-β-Amino acids were obtained by re-oxidation of the alcoholic group[75b] (Scheme 35).



Scheme 35. C2-Directed ring opening of 2-methylaziridinecarboxylates

II-2-3. Reductive Ring Opening through Electron Transfer: Samarium (II) iodide (SmI_2) is subjected to reduction of a number of functional groups due to its single-electron transfer capability. Application to ring opening of carbonyl functionalized aziridine derivatives provides β-amino carbonyl derivatives not only in high yields, but in excellent regioselectivity.[76] Use of *N,N*-dimethylethanolamine (DMEA) as the proton source was recommended for effective ring opening reactions. Reduction of the 2-ketoaziridine required no DMEA as a proton source, whereas reduction of the aziridinecarboxylic esters and amides involved the DMEA additive, a possible ligand to the Sm(II) reductant for the reactivity and rectifier for regioselectivity (Scheme 36). A mechanism, in which a ketyl or a radical species is initially formed and the adjacent C-N bond is cleaved, has been proposed. Although stereochemistry was preserved β to the carbonyl, the stereochemistry at the α position cannot be controlled in this process.



R^1 = H, R^2 = Ph, X = Me, in MeOH, 0 °C: 82%
R^1 = R^2 = X = Me, in MeOH, 0 °C: 88%
R^1 = H, R^2 = Ph, X = OEt, in THF-DMEA, 0 °C: 87%
R^1 = R^2 = Me, X = OMe, in THF-DMEA, 0 °C: 87%
R^1 = R^2 = H, X = NMe_2, in THF-DMEA, -25 °C: 86%
R^1 = Me, R^2 = H, X = NEt_2, in THF-DMEA, -25 °C: 70%

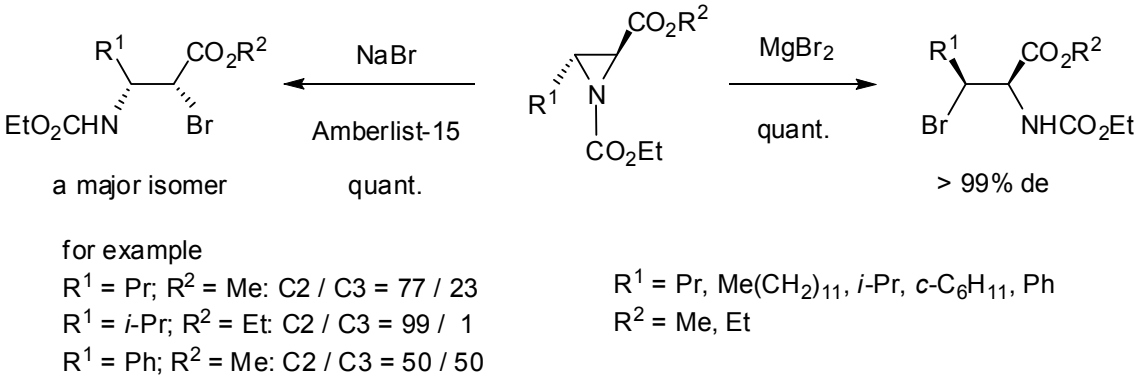
Scheme 36. Reduction of carbonyl functionalized *N*-Ts-aziridines with SmI_2*

Magnesium in MeOH was employed as the electron transfer reagent in the reduction of 2-cyano-, 2-halomethyl-, and 2-(phenylsulfonylmethyl)aziridines; however, elimination, not ring opening, products were given on the latter two aziridines.[77]

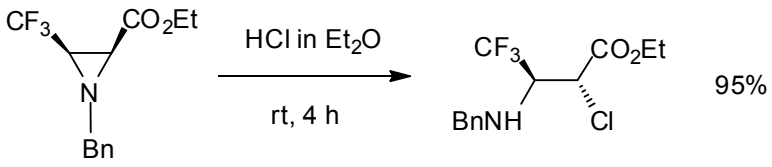
II-3. With Heteroatom Nucleophiles

The regioselective introduction of a heteroatom nucleophile into enantiopure 2-substituted aziridines makes it possible to synthesize polyfunctional chiral compounds. The reaction of heteroatom nucleophiles with aziridinecarboxylates generally proceeded at C3.

II-3-1. Halogen: Regioselectivity in the ring opening of aziridines by halogen nucleophiles is dependent on the nucleophilic reagent rather than aziridine substrate. Regioselective ring opening at C3 was proceeded for a variety of activated (2*S*,3*R*)-3-alkylaziridinecarboxylates by treatment with magnesium bromide ($MgBr_2$), but C2 opening generally predominated when used sodium bromide (NaBr) [or sodium iodide (NaI)] as a halogen source[78] (Scheme 37). However, reaction of phenylaziridines under the latter conditions gave a 1 : 1 regiochemical mixture. Removal of the halogen using radical reduction allowed the preparation of either α- or β-amino acid derivatives.



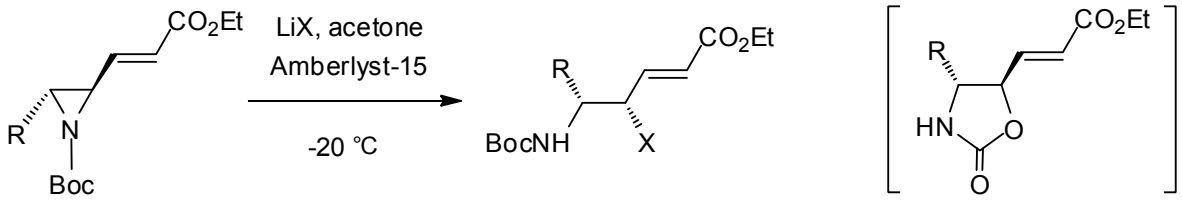
Scheme 37. Halogenolysis of activated aziridinecarboxylates with bromide nucleophiles



Scheme 38. Halogenolysis of non-activated aziridinecarboxylate with HCl in Et_2O*

HCl [or hydrogen bromide (HBr)] itself is a source of a proton for activation and of a chloride anion for the ring opening of aziridines. Ring cleavage of a non-activated aziridinecarboxylate smoothly proceed with dry HCl in diethyl ether (Et_2O) to give a β-amino ester in excellent yield with exclusive regioselectivity[79] (Scheme 38). The use of an aqueous HCl solution in the ring opening of non-activated aziridines was also reported.[80]

Reaction of *N*-Boc-2-[(2-ethoxycarbonyl)vinyl]aziridines with lithium chloride (LiCl) or lithium bromide (LiBr) in the presence of Amberlyst-15 led to the effective production of ring cleaved products with high regio- and stereoselectivity.[81] Amberlyst-15 can also catalyze the same reaction with lithium iodide (LiI). The reaction proceeded at very mild conditions, but somehow reduced chemical yields of iodo adduct and the formation of oxazolidinone**,** due to the activity of the iodide anion as a leaving group, were observed (Scheme 39).



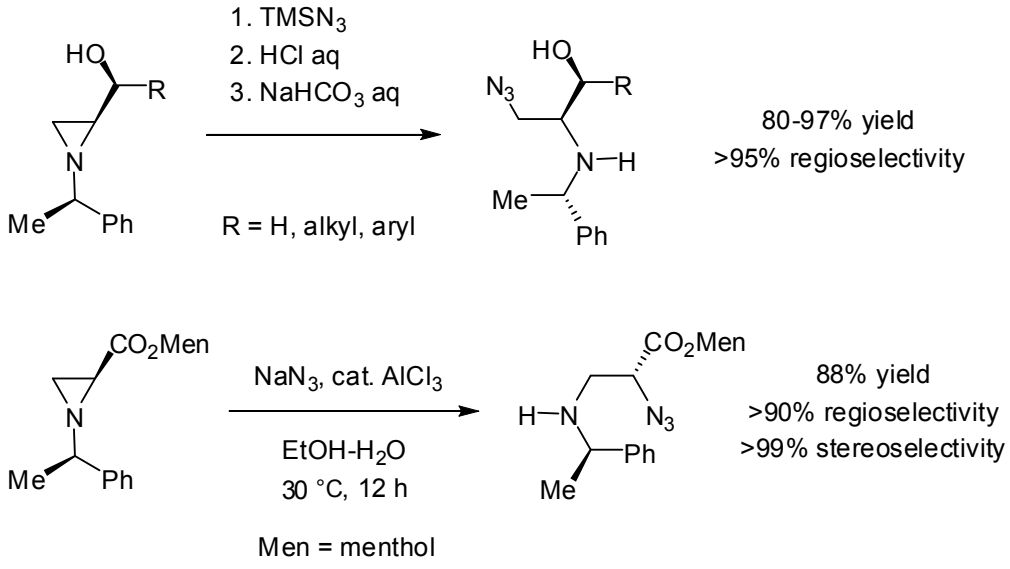
R	X = Cl	X = Br	X = I
Pr	84%	94%	70%
c-C_6H_{11}	86%	94%	72%
t-Bu	82%	87%	67%

Scheme 39. Halogenolysis of 2-[(2-ethoxycarbonyl)vinyl]aziridines with lithium halide*

Iodo-amines could be produced as ring opened products when non-activated aziridines were treated with trimethylsilyl iodide (TMSI), in which the ring nitrogen was initially activated with the silyl reagent. In contrast to other halide nucleophiles, fewer reports for the ring opening of aziridine with a fluoride anion have been documented.

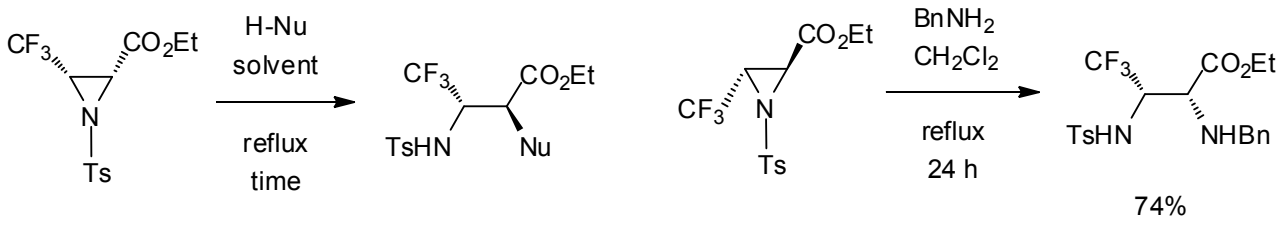
II-3-2. Nitrogen: Increased activities in methods for ring opening of aziridines with azides have been developed. Most of the reported methodologies are practically useful, and all these provide multiple options with consideration of substrate and product criteria. Sodium azide (NaN_3) has traditionally been used as a nitrogen nucleophile in the ring opening of activated aziridines. Trimethylsilyl azide ($TMSN_3$) serves a dual function like TMSI: it activates the basic ring nitrogen and provides a nitrogen source (N_3^-), which attacks the less substituted C3 of 3-unsubstituted aziridines to give a ring opened product.[82] In contrast, a different

regioselectivity is observed in the $AlCl_3$-catalyzed reaction of enantiopure aziridinecarboxylate with NaN_3 in aqueous EtOH (pH 4), in which N_3^- selectively attacks the more electron-deficient C2 to regioselectively yield 3-amino-2-azidopropanoate in high yield[83] (Scheme 40).



Scheme 40. Ring opening of non-activated 3-unsubstituted aziridines with azide nucleophiles

The stereospecific preparation of α,β-diamino-β-(trifluoromethyl)propanoates could be achieved from the *N*-Ts- and *N*-Ns-3-(trifluoromethyl)aziridinecarboxylates using amines or NaN_3 as nucleophiles without a Lewis acid catalyst.[84] Examples of *N*-Ts-aziridines with amines are shown in Scheme 41.

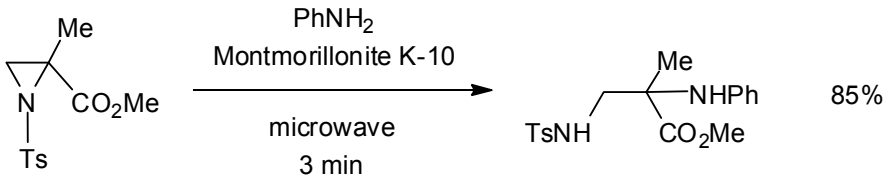


H-Nu	solvent	time (h).	yield (%).
$BnNH_2$	CH_2Cl_2	24	78
morpholine	$ClCH_2CH_2Cl$	22	90

Scheme 41. Ring opening of activated 3-(trifluoromethyl)aziridinecarboxylate with amines*

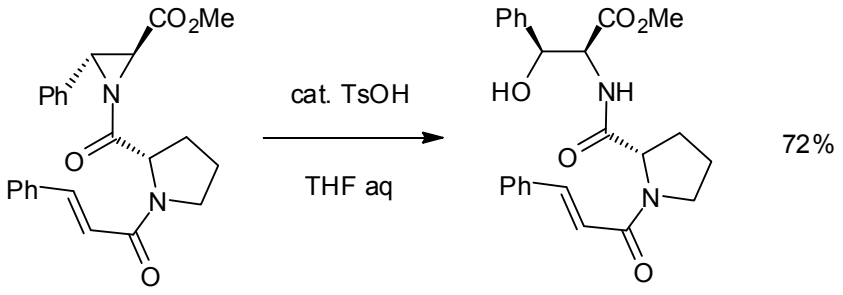
N-Ts-Aziridines react efficiently with amines in the presence of Montmorillonite K-10 as catalyst under microwave irradiation in solvent-free conditions to yield the corresponding achiral and chiral diamines in a few minutes and in high yields with regio- and stereoselectivity.[85] In the case of the

2-methylaziridinecarboxylate, 3-(*N*-Ts-amino)-2-methyl-2-(phenylamino)propanoate was afforded in 85% yield when treated with aniline for 3 min (Scheme 42).



Scheme 42. Microwave-assisted ring opening of *N*-Ts-2-methylaziridinecarboxylate with amine*

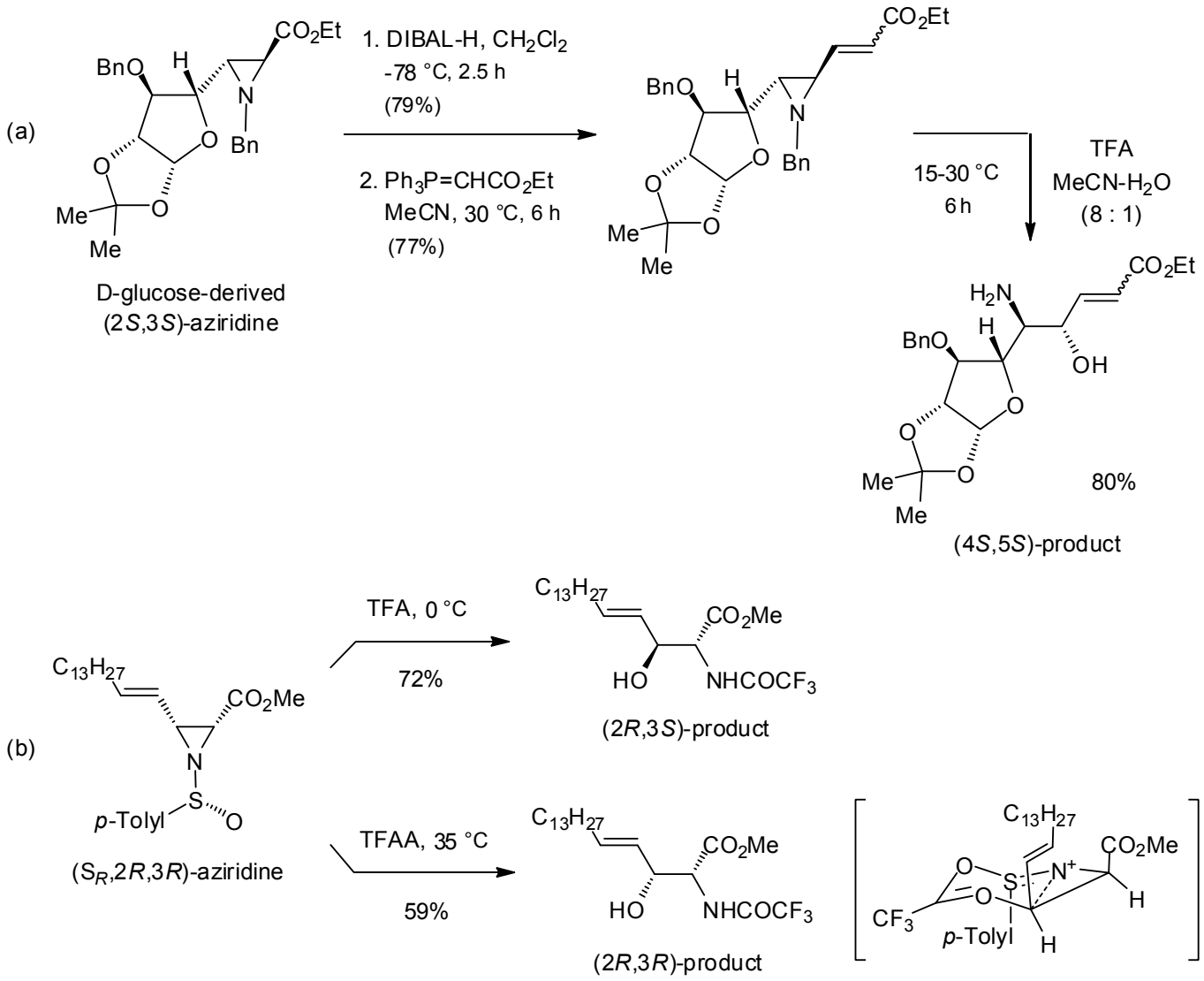
II-3-3. Oxygen: Aziridines show lower reactivity toward oxygen nucleophiles compared to epoxides. The activation at the ring nitrogen either by attaching EWG and / or on the use of appropriate Lewis acids in oxygen nucleophilic addition is normally needed for the ring opening of aziridines. The ring opening of both activated and non-activated aziridines with a water molecule can be achieved similarly to that with alcohols. The stereochemistry of the addition is generally controlled by *anti*-attack and the regiochemistry is largely dependent on the reaction conditions used. Steric effects and effects from the functional group in substrates also govern the site of the addition. Proton-promoting ring opening of 3-phenylaziridinecarboxylates preferentially proceeded at the C3 to give β-hydroxyamino acid derivatives. Thus, β-hydroxyphenylalanine was provided in 72% yield as a single stereoisomer by addition of water to the aziridine in the presence of TsOH[86] (Scheme 43).



Scheme 43. Ring opening of 3-phenylaziridinecarboxylate with a water molecule

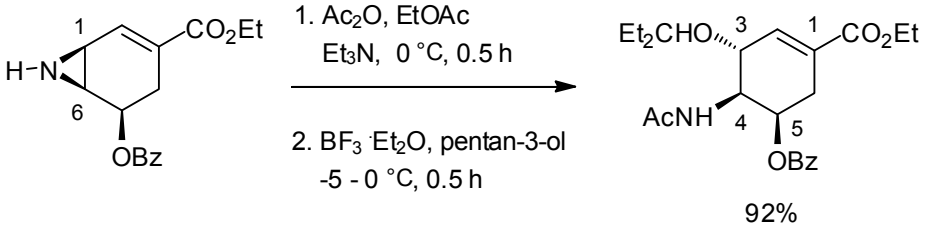
Aziridine ring openings virtually proceed *via* S_N2 mechanism. Treatment of *N*-Bn-3-(1-pentadecenyl)aziridinecarboxylate with oxygen nucleophiles under conventional conditions, as expected, afforded the ring opened α-amino-β-hydroxy esters with regio- and stereoselectivity.[20a] Reduction of (2*S*,3*S*)-aziridinecarboxylate derived from D-glucose with diisobutylaluminum hydride (DIBAL-H) resulted in the chemoselective formation of aziridine aldehyde. Its two-carbon homologation

using a Wittig reagent afforded an inseparable *E* / *Z* mixture of (4*R*,5*S*)-γ,δ-aziridino-α,β-unsaturated ester in a ratio of 8.5 : 1.5, which was treated with trifluoroacetic acid (TFA) in aqueous MeCN to, as expected, afford a ring opened product, (4*S*,5*S*)-δ-amino-γ-hydroxy-α,β-conjugated ester, with regio- and stereoselectivity[31b] (Scheme 44a). One notable exception was the trifluoroacetic anhydride (TFAA)-induced ring opening of an enantiopure (S_R,2*R*,3*R*)-*N*-toluenesulfinyl-3-(1-pentadecenyl)-aziridinecarboxylate.[87] Treatment with aqueous TFA gave the expected C3-ring opening product, L-*threo*-(2*R*,3*S*)-sphingosine precursor, but TFAA predominantly affords (2*R*,3*R*)-isomer, in the formation of which a [3,3]-stereospecific rearrangement of the activated sulfoxide complex was proposed (Scheme 44b).



Scheme 44. Ring opening of aziridinecarboxylates with TFA or TFAA

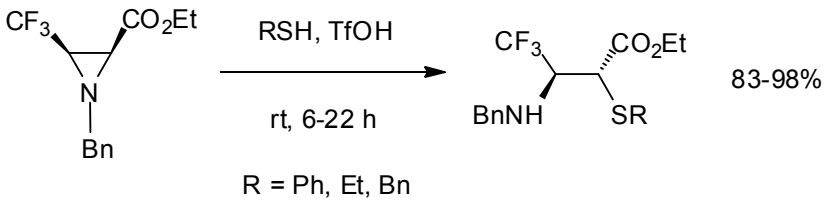
In the asymmetric synthesis of oseltamivir phosphate (Tamiflu) from (-)-shikimic acid, aziridination by intramolecular nucleophilic displacement and ring opening reaction of the formed aziridine system with an oxygen nucleophile were applied.[25] The aziridine prepared in Scheme 5 was exposed to acetic anhydride and Et_3N in ethyl acetate (EtOAc) to form *N*-acetylaziridine almost quantitatively, which was regio- and stereoselectively ring opened by treatment with $BF_3 \cdot Et_2O$ using pentan-3-ol as solvent to give (3*R*,4*S*)-3-(1-ethylpropoxy)-4-acetamidocyclohexene-1-carboxylate in 92% yield (Scheme 45). The reaction temperature is crucial here, it should be kept in the range of -5 °C to 0 °C, and the slow addition of $BF_3 \cdot Et_2O$ was necessary because the reaction is exothermic. In this aziridine ring opening reaction, the nucleophile (pentan-3-ol) approaches the face of the cyclohexene ring opposite to the benzoyloxy (BzO) group at the C5 position. The allylic position (C1) of the aziridine is much more reactive than the non-allylic position (C6), so the Lewis acid-catalyzed nucleophilic attack of pentan-3-ol at allylic position was completely regiospecific.



Scheme 45. Ring opening of aziridine toward Tamiflu synthesis

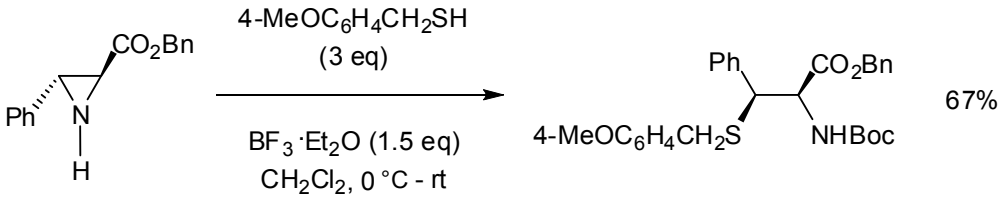
Other oxygen containing acids such as TsOH[88] and phosphoric acid[9b] themselves were also reported as effective nucleophiles to undergo ring opening of aziridines.

II-3-4. Sulfur: The ring opening reaction of aziridines by thiols can readily proceed in either an activated or a non-activated form and, in general, not only high chemical yields but also high regioselectivity have been observed.[89] The ring nitrogen in the non-activated aziridine can serve as a base to abstract a proton from the thiols to form a reactive aziridinium intermediate. The aziridine ring carbon at a less hindered site is then attacked by the deprotonated thiol anion to provide 2-amino sulfide products. On the other hand, activated aziridines, lacking basic nitrogen, often require a Lewis acid for further activation. The highly regioselective ring opening of non-activated 3-(trifluoromethyl)aziridinecarboxylate at the α-carbon of the carboxylate was observed in the thiol addition and the stereoselective *anti*-attack to the ring yielded the corresponding adducts in high chemical yields[79] (Scheme 46).



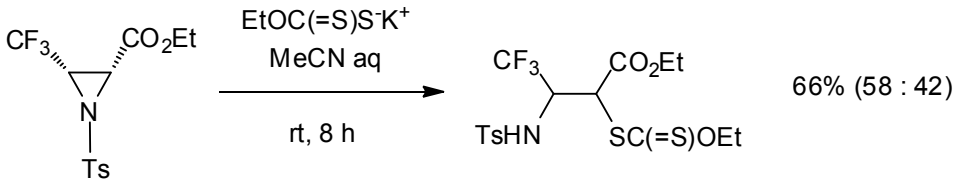
Scheme 46. Ring opening of 3-(trifluoromethyl)aziridinecarboxylate with thiols*

$BF_3 \cdot Et_2O$ has been widely used as a catalyst in the ring opening of aziridines with thiol nucleophiles; however, at least a stoichiometric amount of $BF_3 \cdot Et_2O$ and excess thiol were requested for practical achievements. Thus, (2*S*,3*S*)-β-phenylcysteine derivative was obtained from (2*S*,3*R*)-phenylaziridinecarboxylate in 67% yield by treatment with *p*-methoxybenzyl thiol (3 eq) in the presence of $BF_3 \cdot Et_2O$ (1.5 eq) [90] (Scheme 47).



Scheme 47. $BF_3 \cdot Et_2O$-catalyzed ring opening of 3-phenylaziridinecarboxylate with thiol

Although stereoselectivity on the ring opening of activated 3-(trifluoromethyl)aziridinecarboxylate with nitrogen nucleophiles was observed (see, Scheme 41), a 58 : 42 mixture of both diastereoisomers was obtained in 66% yield in the reaction with potassium ethyl xanthate[84] (Scheme 48). Lack of diastereoselectivity is probably the result of an isomerization due to the higher acidity of proton, vicinal to the carboxylate and xanthate functions.



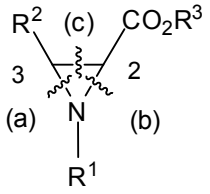
Scheme 48. Ring opening of 3-(trifluoromethyl)aziridinecarboxylate with xanthate*

II-3-5. Miscellaneous: Phosphites, organosilane anions, and selenols could serve as heteroatom nucleophiles in ring opening of aziridines; however, only limited reports were found in the literature. Direct

conversion of aziridines to β-lactams has been realized by carbonylations catalyzed with transition metal cobalt.[11f]

III. Ring Expansion

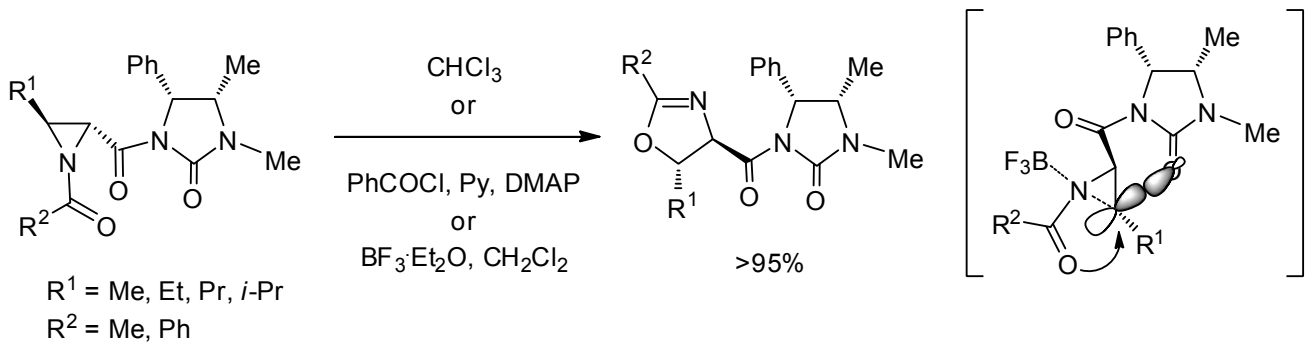
The aziridine ring is a valuable synthon for the preparation of larger heterocycles *via* ring expansion. For aziridinecarboxylates, ring enlargement *via* the scission of either of the C-N bonds [paths (a) and (b)] or the C-C bond [path (c)] can be programmed (Scheme 49). Examples, including our case,[67] of intermolecular [3+2] cycloaddition of azomethine ylide, derived from the path (c) bond scission, with electron-deficient olefins yielding pyrrolidine derivatives have been studied; however, no reports on ring expansions through path (c) have appeared to the best of our knowledge.



Scheme 49. Schematic bond scissions for ring expansion

III-1. Through Path (a)

Lewis acids promote the rearrangement of acylaziridines into oxazolines and $BF_3 \cdot Et_2O$ is the most widely used Lewis acid catalyst. Both chemical evidence and *ab initio* calculations have shown that this reaction occurs with retention of configuration at the stereogenic centers.[91] *N*-Acylaziridine-2-carboximides undergo completely regioselective ring expansion to afford oxazolines as the only products[92] (Scheme 50).

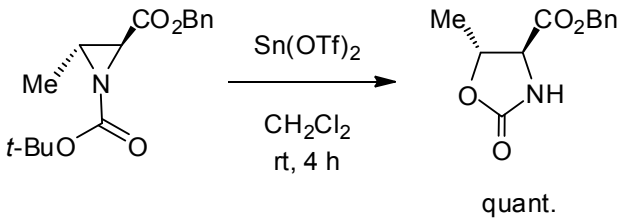


R1 = Me, Et, Pr, *i*-Pr
R2 = Me, Ph

Scheme 50. Effect of the imide auxiliary for ring expansion of aziridinecarboximides

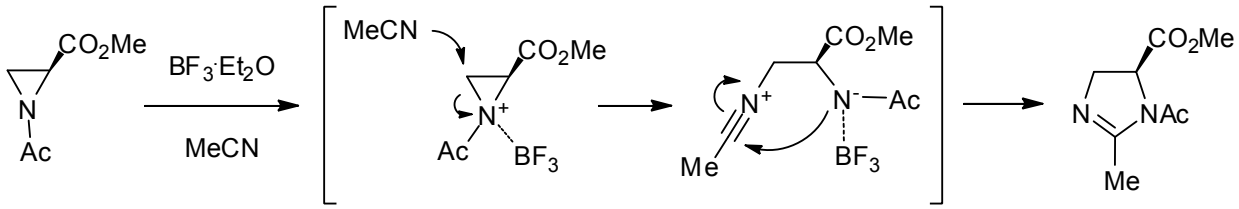
Semi-empirical calculations suggest that the imidazolidin-2-one chiral auxiliary could be responsible for the completion of reaction and for the regiochemistry.[93] The incipient positive charge would presumably be stabilized by a preferred conformation, in which the endocyclic carbonyl oxygen is in proximity of the aziridine C3. Ring expansion and ring opening of aziridine derivatives are complementary. Ring opening of *trans*-acylaziridines by an oxygen nucleophile affords the *anti*-amino acids, whereas ring expansion followed by hydrolysis leads to the *syn*-isomers. Furthermore, (*R*)- or (*S*)-amino acids may be isolated dependent on the chiral imidazolidin-2-one auxiliary used.

Optically active *N*-Boc-aziridinecarboxylate was converted to the corresponding oxazolidin-2-one in quantitative yield with complete regio- and stereoselectivity[94] (Scheme 51). Both of the bond breaking and forming processes proceed with the retention of the C3 configuration.



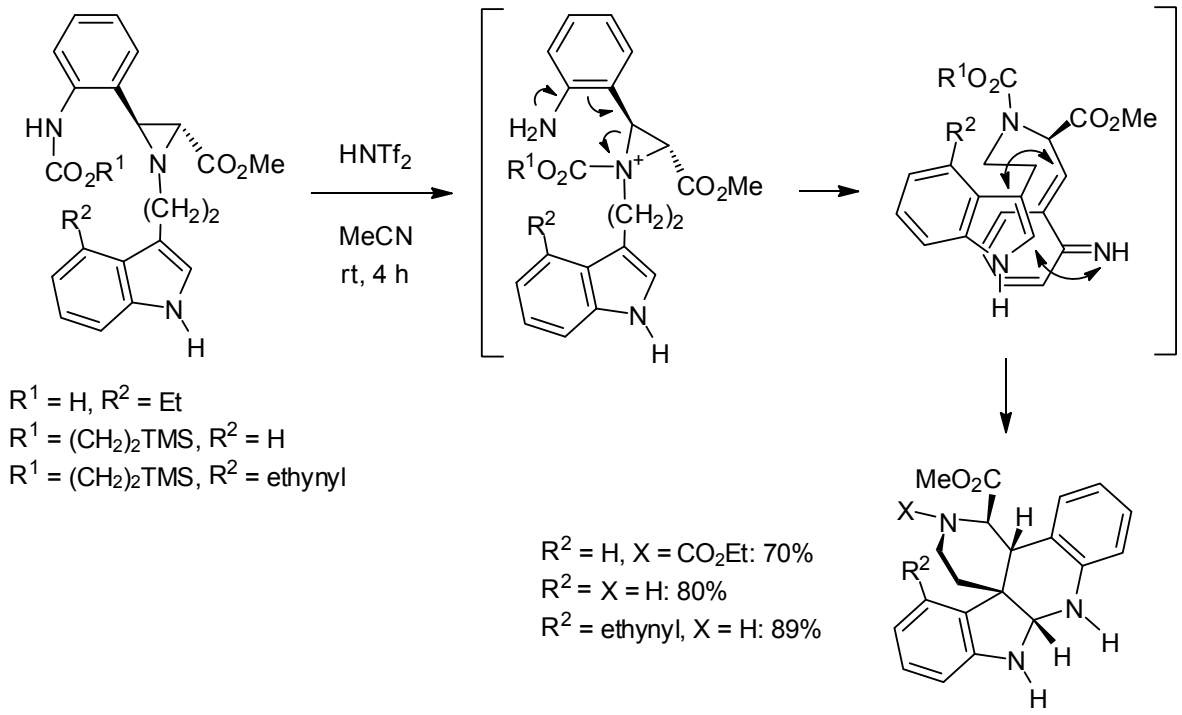
Scheme 51. Ring expansion of *N*-Boc-aziridinecarboxylate to oxazolidinone

Incorporation of MeCN into an imidazoline skeleton was observed when a solution of *N*-acetyl (Ac)-aziridinecarboxylate in MeCN was treated with $BF_3 \cdot Et_2O$[88] (Scheme 52).



Scheme 52. Ring expansion of *N*-Ac-aziridinecarboxylate to imidazoline skeleton

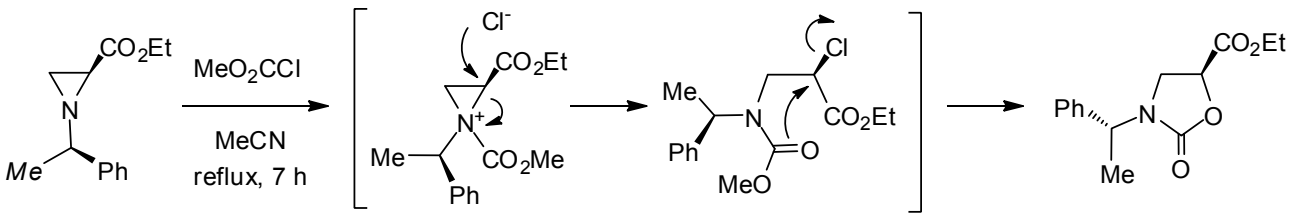
A new protocol for generating aza-*ortho*-xylylenes *via* acid-catalyzed (or fluoride-promoted) ring opening of 3-(2-acylaminophenyl)aziridinecarboxylates, which were prepared by Gabriel-Cromwell method, is explored[95] (Scheme 53). The aza-*ortho*-xylylenes then intercepted with indoles in intramolecular hetero Diels-Alder reactions to give pentacyclic ring systems.



Scheme 53. Aza-*ortho*-xylylenes *via* ring opening of 3-(2-acylaminophenyl)aziridinecarboxylates*

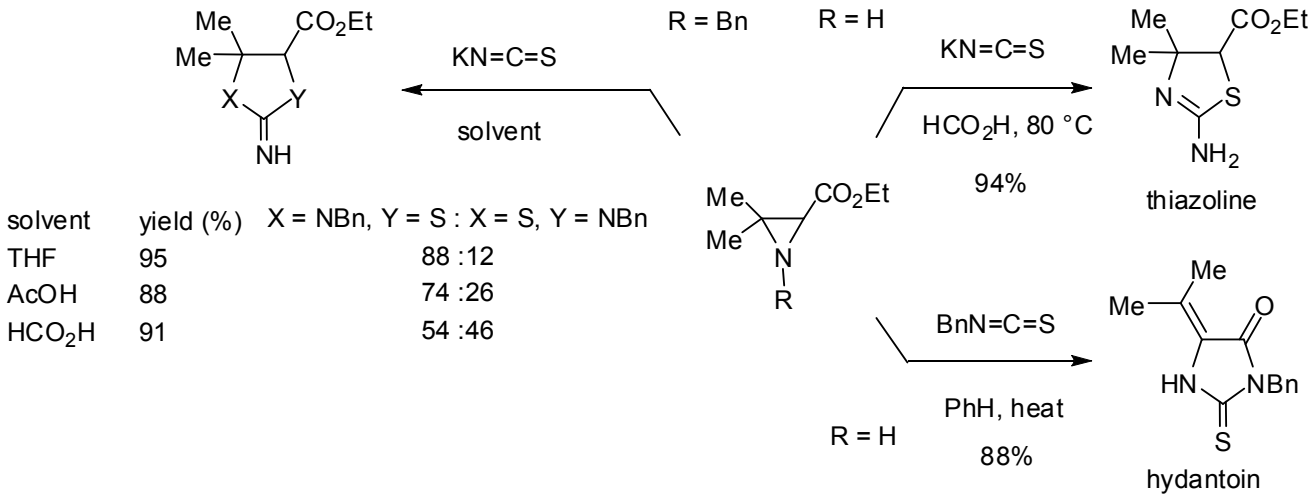
III-2. Through Path (b)

When non-activated aziridinecarboxylate was treated with chloroformates, the ring opening could be initiated by the formation of the aziridinium ion intermediates, which then underwent double nucleophilic addition to form oxazolidinones with high chemical yields[96] (Scheme 54). Retention of the configuration was observed because double nucleophilic additions occur at the C2 chiral center of the starting aziridine. Isocyanates can also serve ring expansion of non-activated aziridinecarboxylates to form imidazolidin-2-ones.[97] The treatment of *N*-[(*R*)-1-phenylethyl]aziridinecarboxylate with isocyanates afforded 4-functionalized imidazolidin-2-ones in high yields. A plausible mechanism with retention of the configuration at C2 of the aziridine *via* a double inversion process at the C2 position of the chiral aziridine was proposed[97] (see, Scheme 54).



Scheme 54. Chloroformate-triggered ring expansion of non-activated aziridinecarboxylate to oxazolidinone

Exposure of *N*-unsubstituted 3,3-dimethylaziridinecarboxylate to potassium thiocyanate in hot formic acid led to cleanly crystalline thiazoline (94%), indicating that aziridine cleavage in this case followed path (b).[98] On the other hand, treatment with benzyl isothiocyanate in benzene at reflux gave the hydantoin derivative in 88% yield. The latter is believed to be formed *via* transient *N*-substituted aziridine which undergoes initial acylation by the carboxylate. Aziridine fragmentation through path (a) then generates the isopropylidene substituent (Scheme 55). The analogous reaction of *N*-benzylaziridinecarboxylate with potassium thiocyanate produced a mixture of regioisomeric thiazolidines, the ratio of which depended upon polarity of the solvent. In a neutral solvent such as THF, the major was a product through path (b), but as the acidity of the reaction medium was increased the proportion of path (a) product also increased. This suggests that opening of the protonated aziridine increasingly favors path (a), as would be expected on the basis of relative carbocation stabilization at C2 *vs* C3.



Scheme 55. Ring expansion of 3,3-dimethylaziridinecarboxylates with thiocyanate or isothiocyanate*

CONCLUDING REMARKS

Aziridines have proven to be versatile building blocks for the synthesis of bioactive compounds and the increasing interests in amine-containing molecules and their broad utility in organic and medicinal chemistry have made aziridines, in particular aziridinecarboxylates, more important and attractive substrates in contemporary synthetic chemistry. Therefore, the development of new methodologies for the construction and ring manipulation of aziridine skeleton, focusing on issues of cost efficiency and environment friendliness for potential manufacture, will be further requested in the future.

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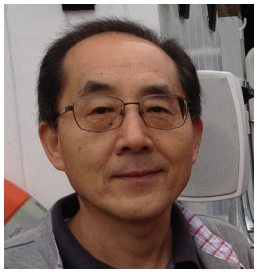

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