Part One
Asymmetric Synthesis of Nitrogen Heterocycles Containing Only One Heteroatom

Asymmetric Synthesis of Nitrogen Heterocycles. Edited by Jacques Royer

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1
Asymmetric Synthesis of Three- and Four-Membered Ring Heterocycles

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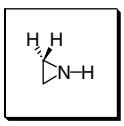
1.1
Substituted Aziridines

1.1.1
Generalities

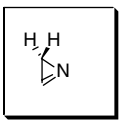
Small heterocyclic rings constitute systems of central importance in theoretical, synthetic organic, bioorganic, and medicinal chemistry, and in particular aziridines and azirines are very useful and interesting systems as they occur in a number of natural and biologically active substances and as they are useful building blocks and versatile synthetic intermediates. Therefore, the development of efficient and stereoselective methods for synthesis and elaboration of aziridines is an inviting ongoing challenge [1]. Very often, stereogenic centers within such strained heterocycles can be used to direct the stereochemical outcome of subsequent transformations.

Aziridines and their dehydro derivatives, 2H-azirines, can be regarded as representatives of the first and most simple heterocyclic systems [2].



Aziridine

C–C 1.48 Å
C–N 1.49 Å
Endocyclic angle 60°
Exocyclic angle 153–160°
Nitrogen inversion barrier 64.8 kJ mol^{-1}
Nitrogen deviation from planarity 69.7°



Azirine

C–C 1.46 Å
C=N 1.23–1.28 Å
C–N 1.59 Å
Endocyclic angle 48–60°
Exocyclic angle 142–160°

While numerous members of the aziridine ring systems are known and have been fully characterized, derivatives of the azirine ring system are mainly known as useful intermediates and only few examples of naturally occurring azirine derivatives have been reported.

Aziridines are present as structural motifs in a variety of strongly biologically active compounds such as azinomycins A and B [3]. which are potent antitumors as well as antibiotic agents against both Gram-positive and Gram-negative bacteria

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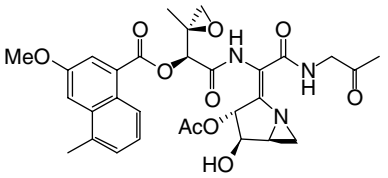
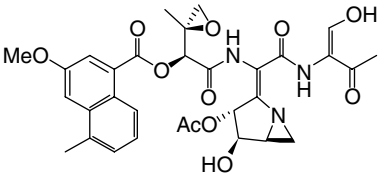
and have been isolated from the fermentation broth of *Streptomyces griseofuscus* S42227.

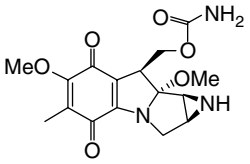


Azinomycin A

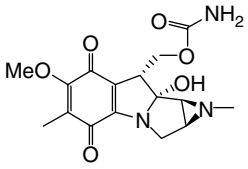


Azinomycin B

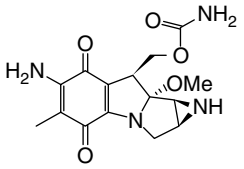
The antineoplastic activity of mitomycins A, B, and C [4], produced by *Streptomyces caespitosus*, is associated with the high reactivity of the strained heterocycle. Furthermore, some synthetic aziridines show strong activity as enzyme inhibitors [5], or are versatile intermediates for bioactive compounds.



Mitomycin A



Mitomycin B



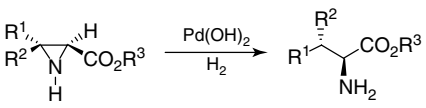
Mitomycin C

The first example of azirine-ring-containing natural compound was azirinomycin [6], an unstable antibacterial agent isolated from *Streptomyces aureus* fermentation broth in 1971. Only several years later, the cytotoxic compound dysidazine [7], the second structure showing the azirine motif, was extracted from *Dysidea fragilis*, a sponge collected in Fiji islands.

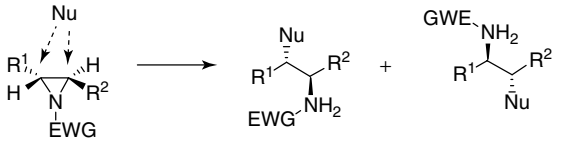
Since their discovery by Gabriel [8], aziridines have attracted attention as starting materials for further transformations in organic synthesis. The ring strain of aziridines, which amounts to 26–27 kcal mol^{-1}, renders these compounds susceptible to ring opening with excellent stereo- and regiocontrol and allows their use as precursors of a variety of nitrogen-containing compounds such as amino acids, aminoalcohols, and β-lactams.

The main transformations of three-membered ring [9] are reported below:

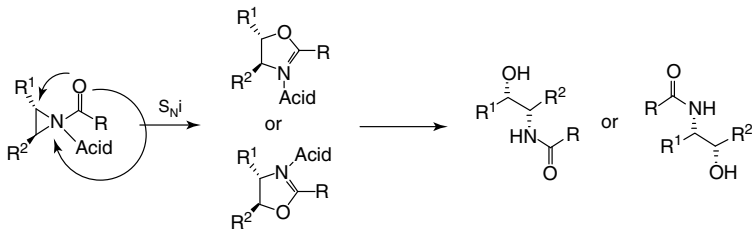
1. Hydrogenolysis: this allows chiral amine derivatives to be obtained via the regiospecific cleavage of a C–N bond. The process induces ring opening usually with inversion of the reacting stereocenter and without any modification of the stereochemistry at the unaffected carbon.



2. Hetero- and carbon nucleophile ring opening: this gives access to a variety of optically active ramified amines or amino alcohols, amino thiols, diamines, etc. While the reactivity of N-unsubstituted aziridines is relatively low, high reactivity is associated with aziridines incorporating an electron-withdrawing group on the nitrogen atom. For instance, the presence of an acyl group strongly activates the ring toward opening by a nucleophile. This reaction is generally favored by the presence of Lewis acids and proceeds with inversion of configuration at the stereogenic center of the aziridine. Unlike their acyclic amide counterparts, acylaziridines are highly pyramidalized at nitrogen, which makes the acyl-aziridine nitrogen more basic. The stereoselectivity is usually high and the regioselectivity depends upon the ring substituents and the nature of the nucleophile.

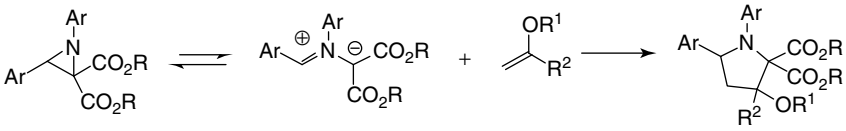


3. Ring expansion: this is another important reaction characteristic of *N*-acylaziridines, which represents the isomerization to the corresponding oxazolines, protected form of chiral amino alcohols. This reaction generally occurs in the presence of a Lewis acid and leads to the five-membered ring with retention of configuration.

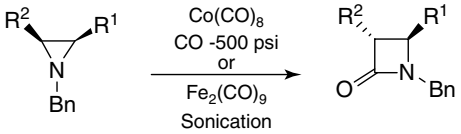


4. aza-Payne reaction: this is the rearrangement of aziridine-2-methanols under basic conditions to the corresponding epoxide-2-amines. These last compounds can be further transformed by reaction with nucleophiles.

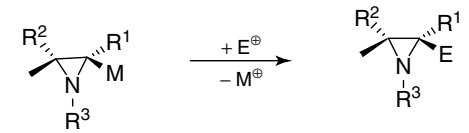
5. 1,3-dipolar cycloaddition of aziridine-2,2-dicarboxylates: this is an interesting reaction that involves generation of 1,3-dipoles from three-membered rings and π systems, giving access to larger size heterocycles.



6. Carbonylation: this allows the formation of β-lactams via insertion of the carbonyl group and inversion of configuration at the reacting carbon terminal.



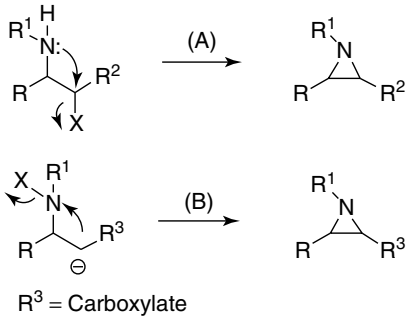
7. Formation and reactivity of aziridinyl anions: these are stable species at low temperature, which may react with a variety of electrophiles allowing introduction of functionalized chains on the heterocycle.



M = Li, Mg, Zn, Zr

1.1.2
Asymmetric Aziridination via Cyclization Methods

General approaches to the asymmetric synthesis of aziridines through cyclization methods can be divided into two main categories: (A) nitrogen nucleophilic cyclization on the adjacent position bearing a leaving group and (B) ring closure to three-membered ring via attack of a stabilized carbanion on the electrophilic nitrogen bearing a leaving group. The last approach is particularly suitable for the preparation of aziridine-2-carboxylates.



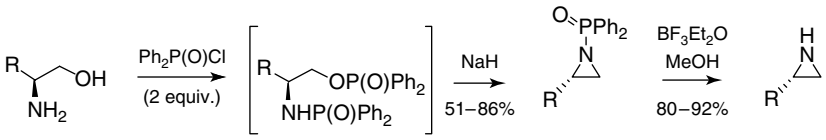
R^3 = Carboxylate

In both cases, the asymmetric induction may be exerted by the chirality of the substrate, by the introduction of a chiral auxiliary, by the presence of a chiral metal catalyst, or by the application of organocatalytic processes.

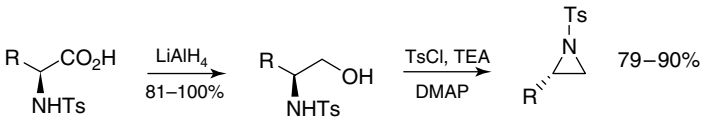
1.1.2.1 Cyclization of a Nucleophilic N on an Electrophilic C (Pathway A)

Cyclization of Amino Alcohols The most general and conceptually simple method for the synthesis of optically active aziridines is the cyclization of amino alcohols and amino halides. The availability of enantiopure amino alcohols directly from the chiral pool or by simple reduction of amino acids makes this approach extensively exploited. Protection of the amino function is sometimes required, and in these cases sulfonyl or phosphinyl groups are usually preferred to carbamates or acyl groups, to avoid competitive formation of larger heterocycles such as oxazolines or oxazolidinones.

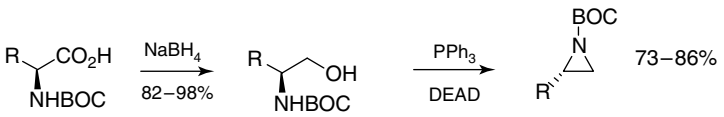
Thus, conversion of the hydroxyl moiety into a good leaving group such as tosyl [10], mesyl, nosyl, tetrahydropyranyl (THP) [11], diphenylphosphinyl (Dpp) [12], ^{t}butyldimethylsilyloxy (TBS) [2] allowed the preparation of an activated intermediate to be easily converted to aziridine under basic conditions through an intramolecular S_N2 reaction.



When reduction of the carboxylic function is needed to produce the proper aminoalcohol, *N*-tosyl amino acids have been used as reagents of choice to avoid difficulties in the isolation of water-soluble amino alcohols [10].

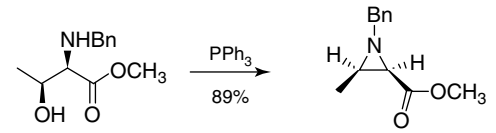


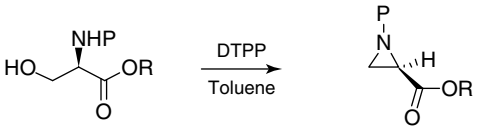
Activation of the hydroxyl function may be preformed also under Mitsunobu conditions. Treatment of *N*-Boc-amino alcohols, easily obtained by reduction of the corresponding amino acids, with triphenylphosphine and Diethyl azodicarboxylate (DEAD) afforded optically active *N*-Boc-aziridines in good yields [13].



Aziridine-2-carboxylates have been successfully obtained starting from serine or threonine. Starting from D-threonine, Rapoport and coworkers [14] synthesized enantiopure *N*-benzyl-aziridine-2-esters by treatment with triphenylphosphine. On

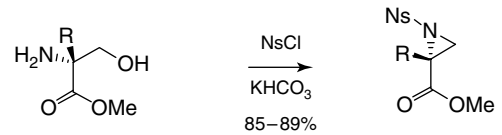
the other hand, ring closure of *N*-protected-serine esters with diethoxyphenylphosphorane (DTPP) gave aziridines-2-tert-butylate in satisfactory yield [15].



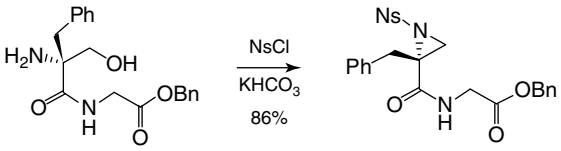


P = Boc, Trt
R = ^{t}Bu, Bn

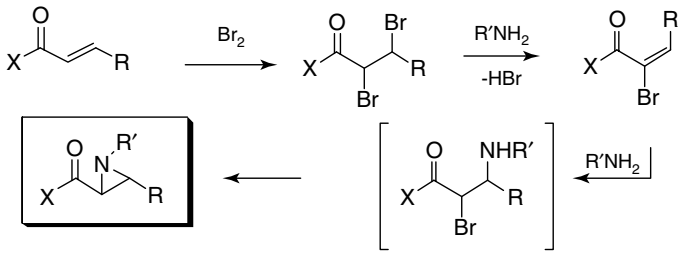
Generally, enantiopure aziridine-2-carboxylates are synthesized as precursors of α- or β-amino acids in a multistep sequence directed to the preparation of bioactive peptides and peptidomimetics. To this purpose, Palomo and coworkers reported the easy formation of the aziridine ring by treatment of the dipeptide serine–glycine benzyl ester via nosylation of the oxygen atom under basic conditions. This procedure allowed the authors to reduce protection/deprotection steps, directly performing the reaction on glycine benzylester derivative [16].



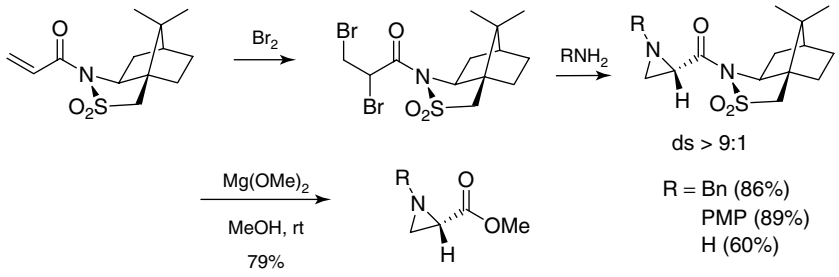
R = Me, Bn



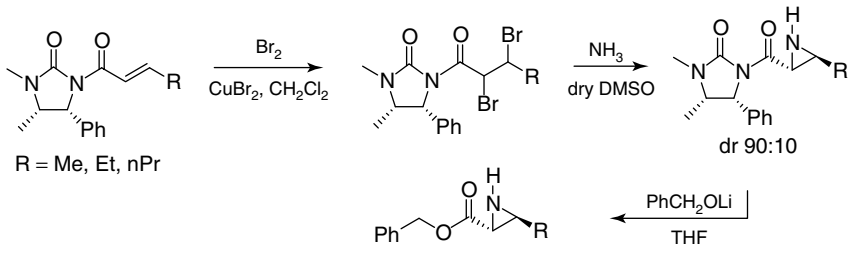
Asymmetric Synthesis of Aziridines via Gabriel-Cromwell Reaction The Gabriel-Cromwell reaction is a general and convenient method for aziridination of α, β-unsaturated compounds. Since its introduction in 1952 [17]. many variations on the standard procedure have been explored to broaden the field of application. The reaction occurs via addition of bromine to the double bond followed by treatment with an amine. The mechanism proceeds with the formation of a dibromo derivative that converts to a α-bromo-alkene through elimination of bromhydric acid. The conjugate addition of a second molecule of amine, followed by nucleophilic displacement of the bromine, leads to aziridine-carboxylate formation.



The asymmetric version of this reaction has been described using chiral auxiliaries such as camphor sultam [18]. Stereodefined 3-unsubstituted-aziridine-2-carboxylic acid may be prepared starting from acryloyl camphor sultam derivatives and by removal of the chiral auxiliary in a nondestructive manner in the final step. Repetition of aziridination protocol with *N*-crotonyl-camphor sultam resulted in the formation of 1:1 mixtures of easily separable aziridines.



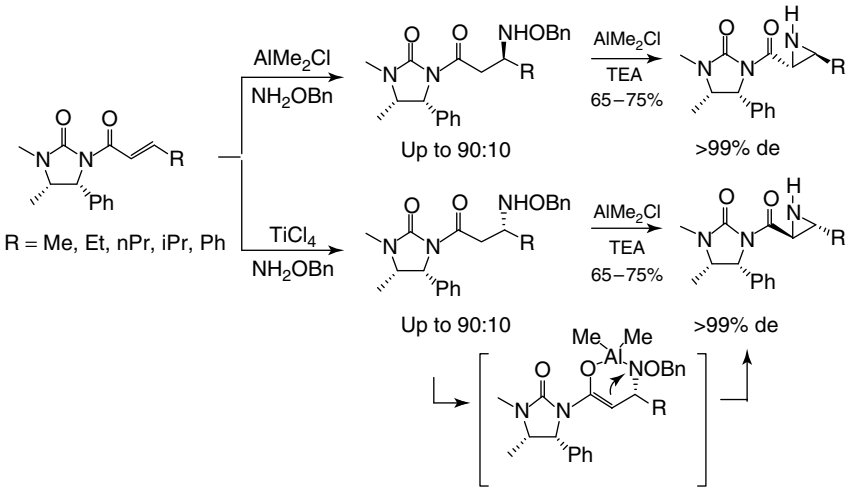
The asymmetric induction controlled by means of ephedrine-derived Helmchen's auxiliary gave better results [19]. Gabriel-Cromwell reaction on chiral imides in DMSO afforded via diastereoselective and high yielding procedure, optically active *trans*-aziridines, easily purified by flash chromatography. The nondestructive cleavage of the chiral auxiliary with lithium benzyloxide gave the corresponding enantiopure benzyl aziridine-2-carboxylates.



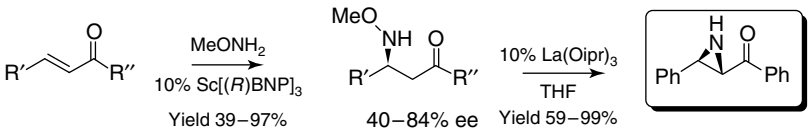
1.1.2.2 **Cyclization of a Stabilized Anion on an Electrophilic N (Pathway B)**

Starting from the unsaturated derivatives reported above, the same authors performed the diastereoselective synthesis of aziridine-2-imides via conjugate addition

of *O*-benzylhydroxylamine followed by cyclization to three-membered rings [20]. This second step was induced through the formation of the stabilized aluminum enolate of the addition product that spontaneously attacked the electrophilic nitrogen bearing the *O*-benzyl leaving group. Removal and recovery of the chiral auxiliary were performed as reported above.

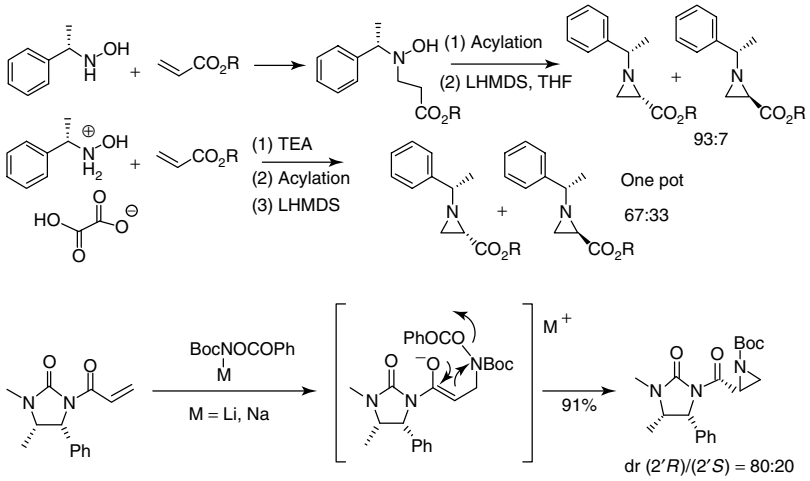


In a similar way, optically active 1H-α-keto aziridines were synthesized from conjugated enones via Sc[(R)-BNP]$_3$-catalyzed enantioselective Michael addition of *O*-methylhydroxylamine, followed by La(OiPr)$_3$-catalyzed ring closure [21].

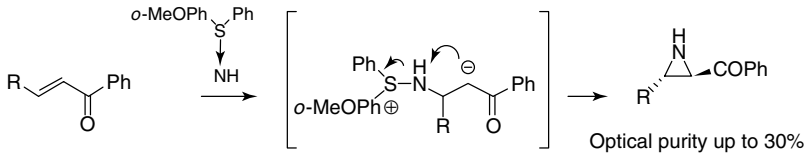


The products obtained by addition of chiral hydroxylamine to acrylates have been transformed into 2- and 2,3-disubstituted-*N*-alkylaziridinecarboxylate through an efficient diastereoselective 3-exo-tet ring closure induced by O-acylation of the diastereomeric adduct followed by enolization. This two-step protocol afforded optically active aziridines with excellent diastereoselectivity (93:7). Attempts to perform a one-pot two-step reaction resulted in a lower stereoselectivity (67:33) [22].

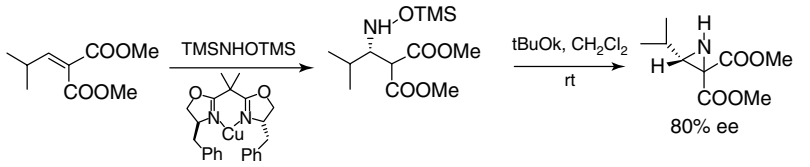
A further development of the same synthetic approach is represented by the synthesis of 3′-unsubstituted-*N*-Boc-aziridines, which has been carried out in one step by conjugate addition of sodium or lithium anion of *N*-Boc-*O*-benzoylhydroxylamine to chiral acryloyl-imides [23].



The Michael-type addition of (+)-(*R*)-*o*-methoxyphenylsulfonylethylsulfimide to unsaturated carbonyl compounds afforded optically active *trans*-acylaziridines with modest stereoselectivity by displacement of the diphenylsulfide group from the intermediate enolates [24].

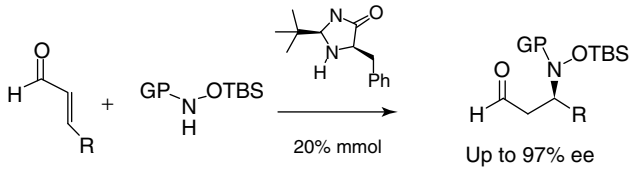


The addition of *N*, *O*-bis(trimethylsilyl)hydroxylamine to alkylidene malonates in the presence of a catalytic amount of $Cu(OTf)_2$ and chiral bisoxazoline as ligand, followed by base-induced cyclization, represents a useful route to enantiomerically enriched aziridine-2,2-dicarboxylates. This two-step protocol afforded the three-membered rings with good yield and enantiomeric excesses up to 80%, depending on the substituent on the alkylidene double bond [25].

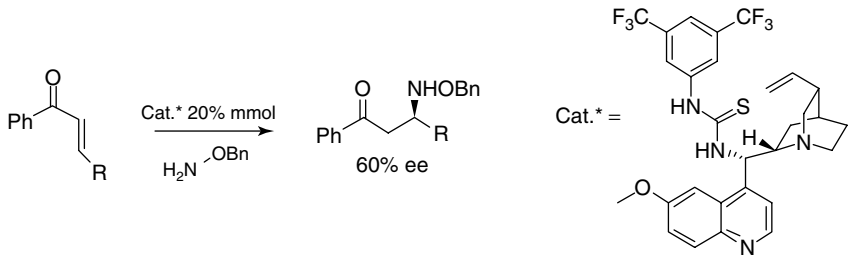


In general, the conjugate addition of hydroxylamines to unsaturated carbonyl derivatives is one of the most convenient methods for the stereoselective synthesis of β-hydroxylamino-carbonyl building blocks, which are useful intermediates in the preparation of enantiopure aziridines. Asymmetric methods dealing with stoichiometric use of chiral auxiliaries in the presence of Lewis acids or with the use of catalytic amount of chiral metal complexes have been exhaustively reviewed [26].

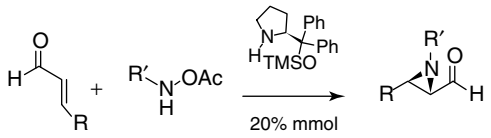
The organocatalytic version of the aza-Michael addition was less explored. MacMillan and coworkers reported the first organocatalytic addition of *N*-silyloxycarbamates to unsaturated aldehydes, giving access to aziridine precursors [27].



In a recent report, the conjugate addition of *O*-benzylhydroxylamine to chalcones was performed in the presence of thiourea-derived catalysts. Although a screening of solvents, O-substituted hydroxylamines, and chiral ligands was performed, moderate enantiomeric excesses up to 60% could be observed [28].



The organocatalysis may be applied to aziridination when the substrate to be transformed is an aldehyde. In fact, the highly chemo- and enantioselective organocatalytic aziridination of a variety of α, β-unsaturated aldehydes with acetyloxy carbamates was developed. The reaction was catalyzed by chiral pyrrolidine derivatives and gave Boc- or Cbz-2-formylaziridines in yields ranging from 60 to 70%, with dr 4:1–19:1 and 84–99% ee [29].



R	R′	Yield	dr	ee
Me	Boc	54%	6:1	94%
Et	Cbz	60%	5:1	97%
nPr	Cbz	62%	10:1	99%
nBu	Cbz	70%	5:1	96%
BzO	Boc	60%	5:1	98%

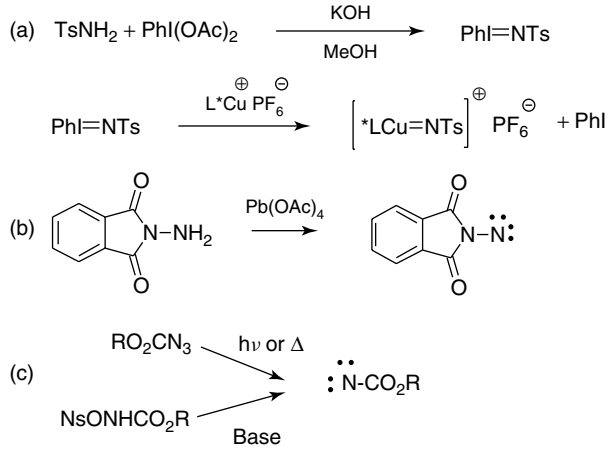
1.1.3
Asymmetric Aziridination via Cycloaddition Methods

1.1.3.1 Addition of Nitrenes to Alkenes

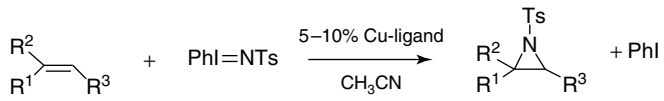
One of the most important pathways to aziridines is the addition of a nitrene to an alkene; however, this reaction may not be well controlled stereochemically owing to the rapid interconversion of the singlet and triplet nitrene states. Anyway,

several methods for nitrene generation have been successfully developed with the aim to obtain stereospecific aziridination. The most common involve photolysis, thermolysis, or chemical modification of nitrogen derivatives.

Many chiral metal catalysts have been used to induce nitrene formation from N-substituted iminoiodinanes, although this method produces stoichiometric amount of iodobenzene and yields N-protected aziridines. The use of azide precursors gives some advantage in terms of atom efficiency and environmental impact since molecular nitrogen is the only side product. Nosyloxycarbamates and *N*-aminophtalimides are also alternative sources of nitrene.

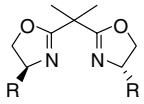
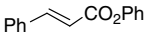
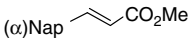
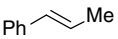
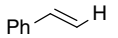
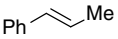
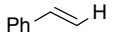
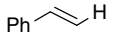
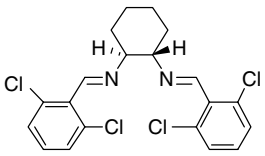
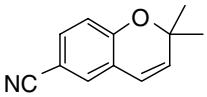
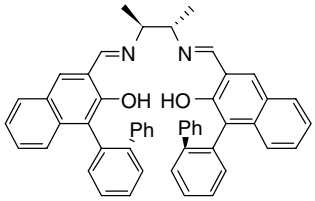
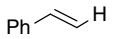


N-(*p*-toluenesulfonyl)iminophenyliodinane (PhI = NTs) [30] (source a) proved to be superior to other imido group donor as precursor and yielded excellent stereoselectivity. In 1991, Evans and coworkers disclosed that low-valent copper complexes catalyze the aziridination of several different olefins by this reagent. Development of the enantioselective process consists in the use of chiral bisoxazoline catalysts. Some selected results are reported in Table 1.1.



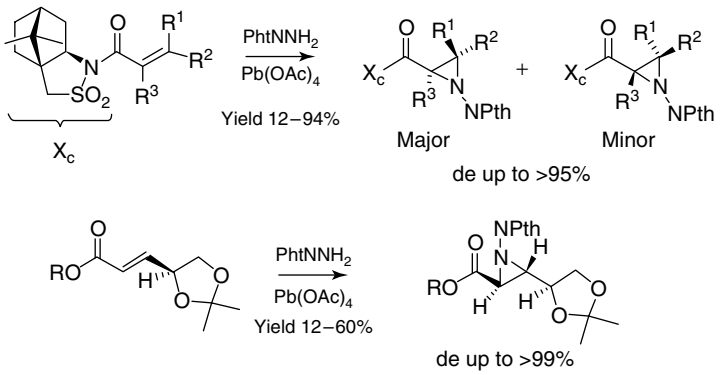
Aryl-substituted olefins have been found as good substrates, which can be efficiently transformed into *N*-tosyl-aziridines with enantioselectivities up to 97% ee (entries 1–4) [31]. The reactions have been carried out with 5% of chiral catalyst derived from copper(I) triflate and bisoxazoline as ligand. Unfortunately, tartrate-derived bisoxazoline gave only low enantiomeric excess (2–49% ee). A complete study on the effect of bisoxazoline substituents and reaction conditions on this reaction has been reported by Page and coworkers [32]. Some improvements of both enantioselectivity and chemical yields were obtained when [*N*-(4-nitrobenzenesulfonyl)imino]phenyliodinane was employed instead of the

Table 1.1 Enantioselective aziridination with *N*-aryliminophenyliodinane and chiral metal complexes

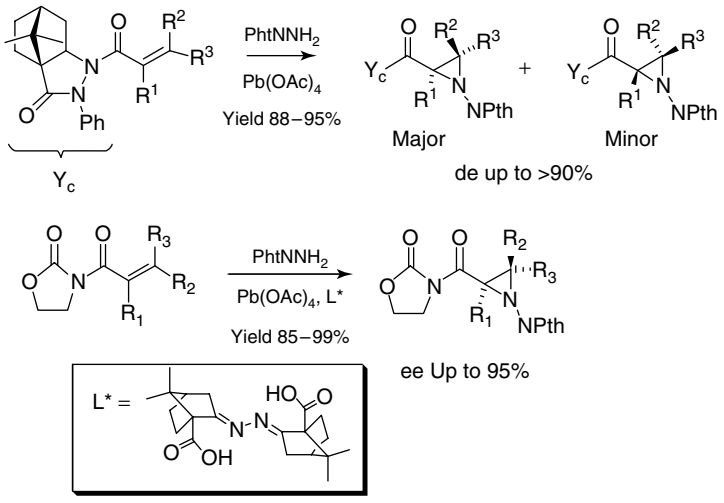
Entry	Chiral ligand	Olefin	Catalyst	Nitrene precursor	Yield	ee
1	 a: R = Ph b: R = CMe_3		a	PhI = NTs	64	97
2			a	PhI = NTs	76	95
3			b	PhI = NTs	62	70
4			b	PhI = NTs	89	63
5			b	*p*-NO_2-PhI = Ts	83	80
6			b	*p*-NO_2-PhI = Ts	94	66
7				PhI = NTs	79	66
8				PhI = NTs	75	>98
9				PhI = NTs	70	87
10			Mn	PhI = NTs	76	94

commonly used *p*-tolyl analog (entries 5–6) [33]. In a similar way, Jacobsen and coworkers [34] obtained excellent results in the aziridination of benzylidene derivatives with chiral copper complexes deriving from bis(benzylidene)imine of 1,2-diaminocyclohexane (entries 7–9). The asymmetric aziridination of styrene derivatives has also been successfully performed with Salen-Mn(III) complexes (entry 10) [35].

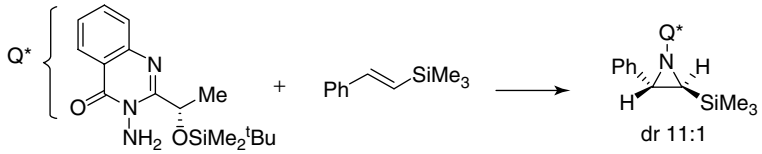
Phtalimidonitrene (source b), generated from *N*-aminophatalimide by oxidation with lead tetraacetate, reacted with *N*-enoylbornane[10,2]sultams (Oppolzer auxiliary) to give the corresponding *N*-phtalimidoaziridine adducts in 12–94% yield and diastereofacial selectivity up to >95% [36]. In a similar way, excellent diastereoselection could be obtained by the addition of phtalimidonitrene to sugar-derived α, β-unsaturated esters [37].



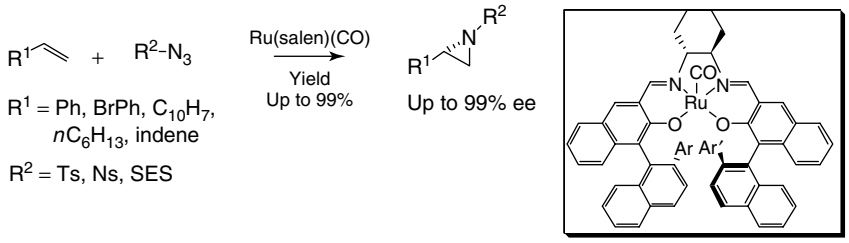
Chen and coworkers applied this methodology to the diastereoselective aziridination of α, β-unsaturated amides linked to a camphor pyrazolidinone-derived chiral auxiliary [38]. The reactions carried out in 5 min afforded excellent yield (86–95%) of diastereomeric aziridines with high selectivity (up to >90% de). In pursuing this work, the same author reported the enantioselective version of this protocol, by performing the lead tetraacetate oxidative addition on *N*-enoyl oxazolidinones in the presence of camphor-derived chiral ligands [39].



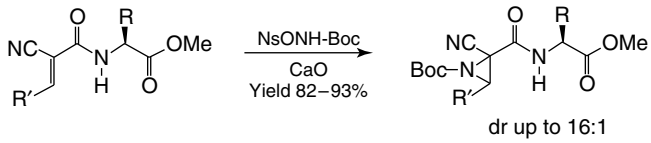
Besides the use of a chiral auxiliary linked to the alkene reagent or of chiral complexes of lead tetraacetate, another possibility is the use of chiral aziridinating agents. Atkinson and coworkers [40] reported that enantiopure 3-acetoxyaminoquinazolinones react with β-trimethylsilylstyrene affording 11:1 ratio of diastereomeric aziridines.



Organic azides (source b) may be considered as ideal sources of nitrenes although they are not very reactive and harsh conditions, such as heating or UV irradiation, are generally needed for molecular nitrogen dissociation. Initial attempts to perform asymmetric aziridination using azides and chiral metal catalysts have been reported by Jacobsen with Cu-diimine complexes and by Müller and co-workers using chiral Rh-complexes. In both cases, the nitrene generation was induced by UV irradiation. On the other hand, excellent yields (up to 99%) and enantioselectivities (up to >99% ee) have been obtained by Katsuki and coworkers in the presence of ruthenium(CO)(salen) complexes and tosyl azide. Under these conditions, neither heating nor irradiation was required for nitrene formation. The method is of general application since it has been successfully applied to a number of different olefins, changing the substituent of the chiral ligand and generating the nitrene reagent starting from different organic azides.



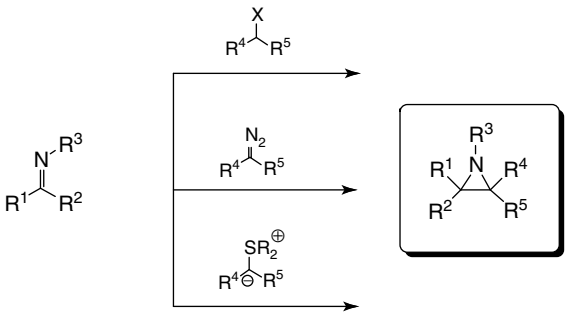
Finally, nitrenes may be formed from *N*-protected nosyloxycarbamate by treatment with a base such as CaO. Pallacani and Tardella applied this method to the synthesis of a variety of substituted N-protected aziridines [41]. Recently, excellent diastereoselectivity was observed in the aziridination of 2-L-α-aminoacyl-(*E*)-acrylonitriles under parallel solution-phase conditions [42].



1.1.3.2 **Reaction between Carbenes and Imines**

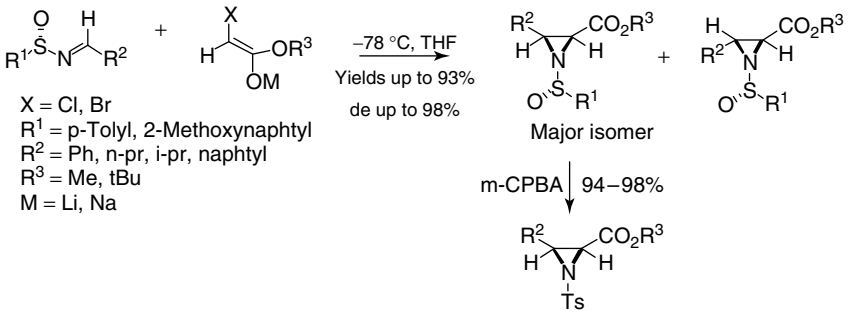
Among several synthetic routes, the classic methods involving imines have been upgraded to their asymmetric version inducing enantiocontrol by the use of chiral imines, chiral nucleophiles, or chiral catalysts. All these approaches share as

common feature the addition of a nucleophile on the electrophilic imine carbon, followed by cyclization to the three-membered heterocycle.



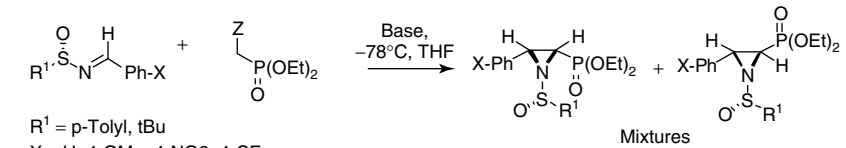
aza-Darzens-Type Reactions Involving α-Haloenolates The aza-Darzens reaction between a α-haloenolate and an imine can be considered a not fully investigated tool for the asymmetric synthesis of aziridines.

Davis and coworkers obtained excellent results in the synthesis of *N*-sulfinyl-aziridine-2-carboxylates by reacting enantiopure chiral sulfinimines with α-bromo-enolates. The method is general for aliphatic, aromatic as well as α, β-unsaturated imines, giving good yields and de up to 98%, *N*-sulfinyl-heterocycles, which are easily transformable into activated *N*-tosyl-aziridines [43].

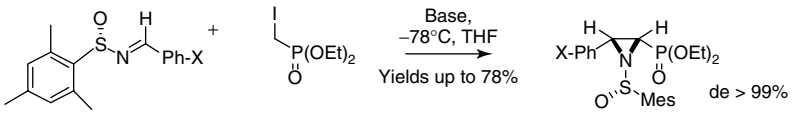


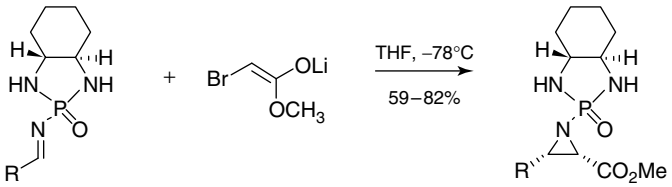
Following the same procedure, enantiopure aziridine-2-phosphonates were obtained from sulfinimines and halomethylphosphonates. A further improvement could be obtained employing *N*(2,4,6-trimethylphenylsulfinyl)imines and lithium diethyliodophosphonate [44].

Despite the excellent results obtained with chiral sulfinimines, development of new chiral imines could overcome shortcomings as sensitivity to oxidative conditions and destructive chiral auxiliary removal. The reaction between chiral *N*-phosphonimines and α-bromo-enolates gave *N*-phosphonylaziridines with excellent yield and high stereocontrol. The electrophilicity of the imine can be controlled by introducing electron-donating or electron-withdrawing groups onto phosphonate chiral auxiliary [45].



R^1 = p-Tolyl, tBu
X = H, 4-OMe, 4-NO2, 4-CF_3
Z = Cl, Br, I

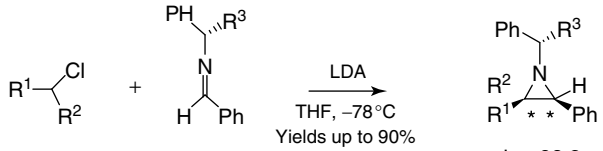




R = Ph, 2-Cl-Ph, 2-Me-Ph, 2-thienyl,
4-halo-Ph, 4-MeO-Ph

de 80 to >99%

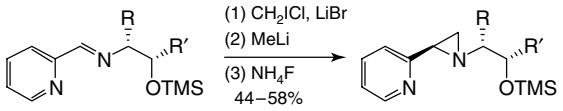
Chiral heterosubstituted aziridines have been obtained by the coupling of lithium enolates derived from (α-chloroalkyl)heterocycles with various enantiopure imines, which are obtained from nonracemic phenylethylamine. The reaction afforded chiral aziridines with complete stereocontrol. The steric hindrance and the coordination power of the alkyl group linked to the iminic nitrogen are responsible for the stereochemistry of the final product [46].

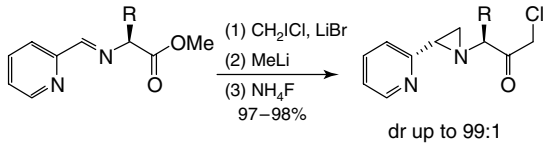


R^1 = thiazolyl, oxazolinyl, pyridyl
R^2 = H, CH_3
R^3 = CH_3, OCH_3

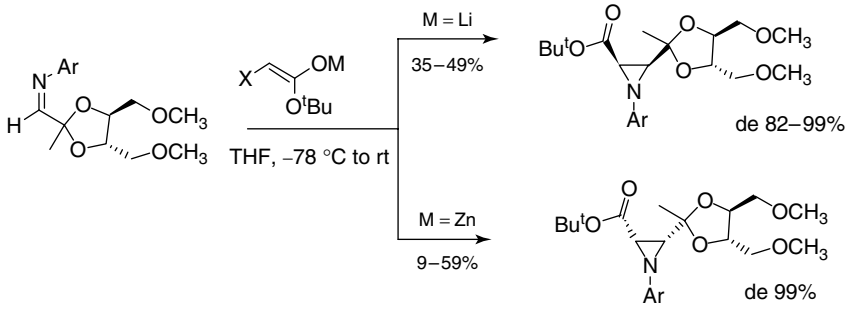
dr > 98:2

In a similar way, the addition of chloromethyllithium to the imine derived from 2-pyridinecarboxaldehyde and chiral aminoalcohol or aminoesters gave disubstituted aziridines with good yields and excellent diastereoselectivity. In the latter case, double addition of the organometallic reagent occurred, affording aziridines having a keto function in the side chain [47].

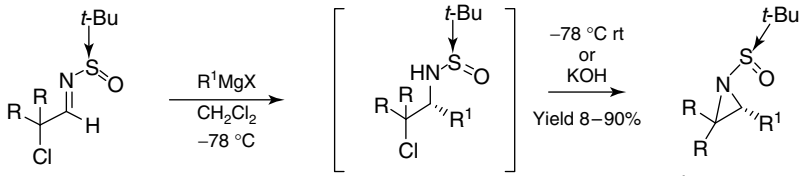




Enantiopure *N*-acylaziridines have been obtained starting from aldimine bearing the chiral auxiliary into the carbon side chain. Under these conditions, complete inversion of diastereocontrol was induced by changing the metal counterion of the bromoenolate from lithium to zinc [48].

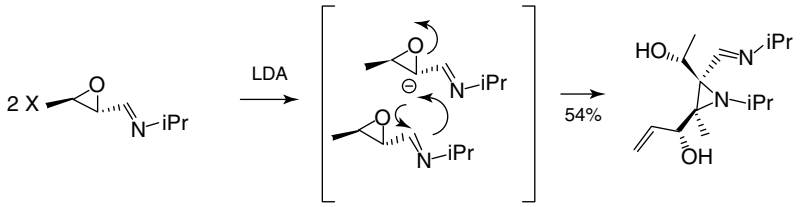


Similarly to aza-Darzens mechanism, the addition of organometallics as Grignards to chiral sulfinylimines bearing a α-halogen leaving group followed by treatment with a base represents a high yielding route to optically active *N*-sulfinylaziridines. In this reaction, spontaneous or base-induced cyclization of the non-isolated intermediate β-halo-*N*-sulfinamides affords the three-membered rings in high yield and excellent diastereomeric ratio [49].



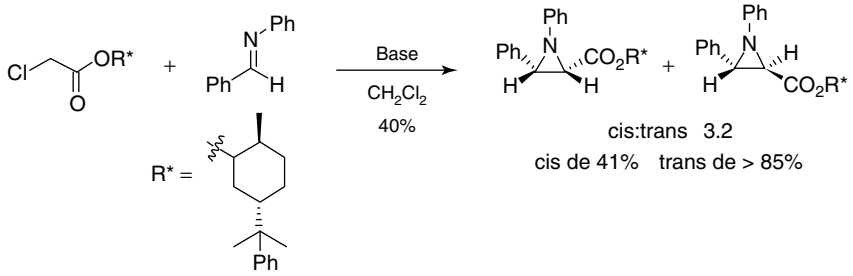
An application of aza-Darzens-type reaction has been performed to obtain polyfunctionalized aziridines through the base-induced dimerization of oxiranylaldimines. This highly diastereoselective process is noteworthy since both nucleophile and electrophile originate from the same precursor. The nucleophilic moiety

is the 1-aza-allylanion having the epoxide at the β carbon and the leaving group is represented by the oxirane oxygen atom [50].

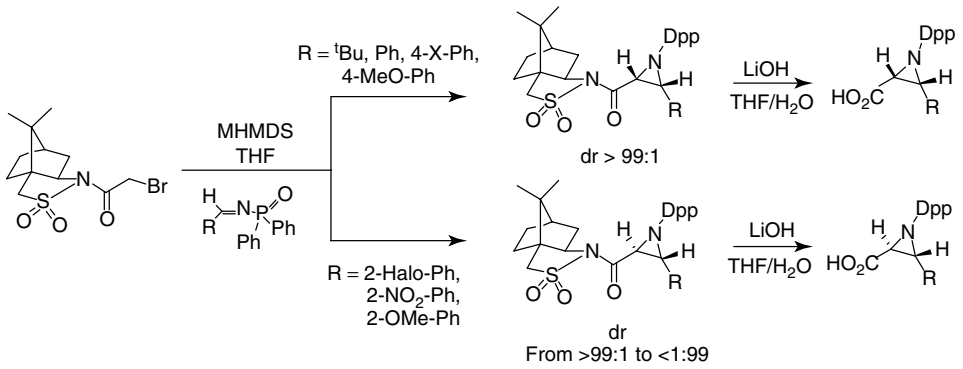


Asymmetric induction in the condensation between imine and haloacetates may be also obtained introducing chiral auxiliaries into the α-haloacetate counterpart.

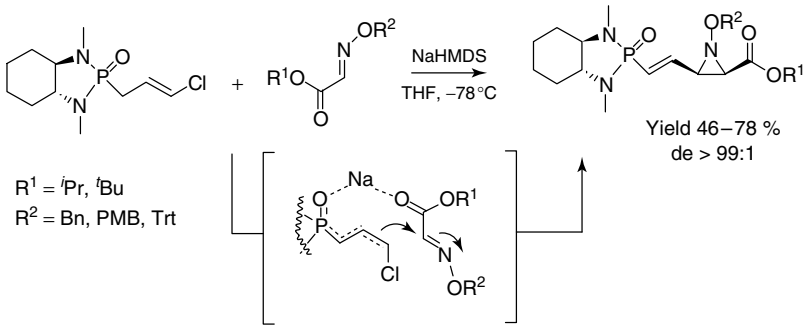
For instance, (+)-8-phenylmenthyl esters gave aziridine-2-carboxylates only in 40% yield and as diastereomeric mixtures of cis/trans heterocycles. Anyway, the diastereomeric excess of the trans isomer reached 85% [51].



On the other hand, camphorsultam-derived α-bromoenolates reacted with *N*-Dpp-imine to afford a single cis diastereoisomer in high yield. Removal of the chiral auxiliary was simply performed with LiOH at room temperature. The method was successfully applied to aromatic, para-substituted aromatic, unsaturated, and aliphatic enolates. The introduction of an ortho substituent into the aromatic ring determined the stereoselectivity inversion, often giving exclusively trans products [52].

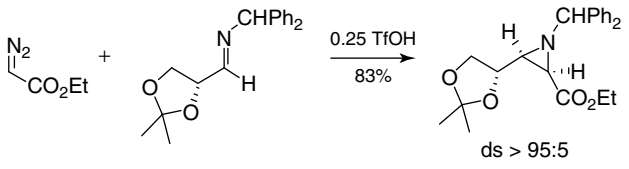


Finally, enantiopure cis *N*-alkoxy-aziridine-carboxylates have been obtained via aza-Darzens like reaction between the anion of optically pure chloroallyl phosphonamide and oximes. The reaction occurred in good to excellent yields through the approach of the oxime on the less hindered left cleft of the phosphonamide anion, giving a single diastereoisomer [53].



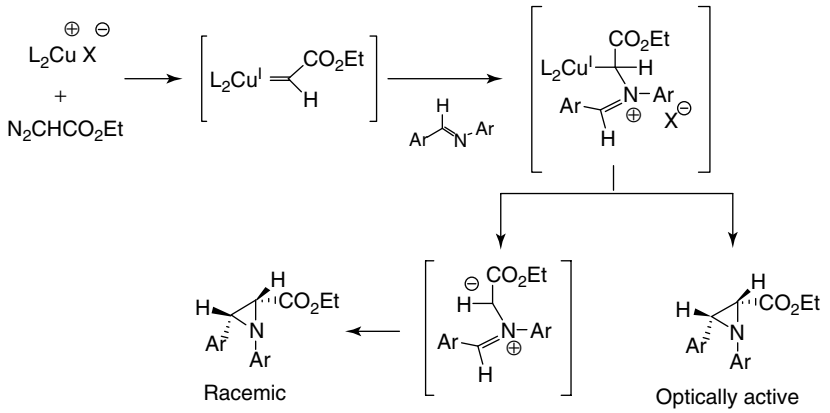
aza-Darzens-Type Reactions Involving Diazo Compounds This methodology, involving the formation of a metal–carbene intermediate complex that adds to an imine, shows several advantages of other synthetic approaches since the reagents are synthetically accessible and highly reactive and the only by-product is represented by molecular nitrogen. The asymmetric version of this reaction has been successfully developed using enantiopure starting materials, stoichiometric amounts of chiral auxiliaries linked to the reagent backbone, or by catalyzing the reaction with chiral Lewis acids.

The protocol recently reported by Johnston and coworkers, based on the Bronsted acid-catalyzed annulation, afforded enantiopure aziridine-2-carboxylates by using glyceraldehyde as chiral auxiliary. The diazocompound reacted as enolate synthon without any decomposition, giving the product in 83% yield and complete diastereoselectivity [54].

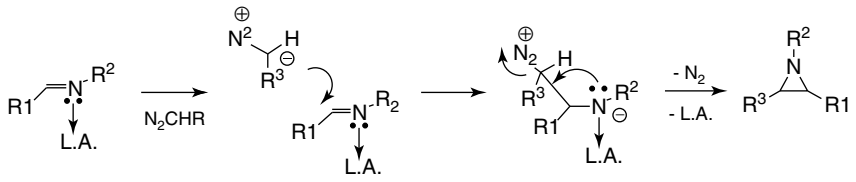


The asymmetric metal-catalyzed transfer of diazocarbonyl-derived carbene to imines represents the most explored approach. To this purpose, Jacobsen and coworkers investigated copper(II) complexes catalyzed aziridination of *N*-benzylidene aniline and diazoacetate [55]. Although *cis*-aziridines were obtained only in modest yields (5–65%) and stereoselectivities (2–67% ee), a deep exploration of the reaction mechanism allowed to suggest the generation of a transient bis(dihydrooxazole)copper carbene complex that reacts with the imine to form a

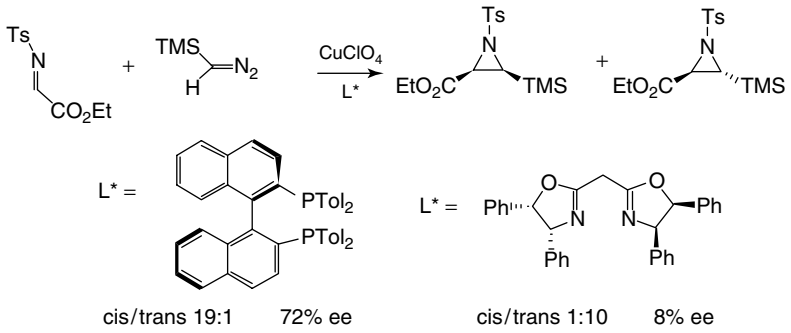
metal-complexed azomethine ylide. This intermediate may undergo intramolecular ring closure to optically active aziridine or it may dissociate to free azomethine ylide, precursor of the formation of racemic aziridine. This investigation outlined the influence of the chiral ligand on the metal-complexed azomethine ylide evolution, thus providing useful information for enantioselectivity enhancement.



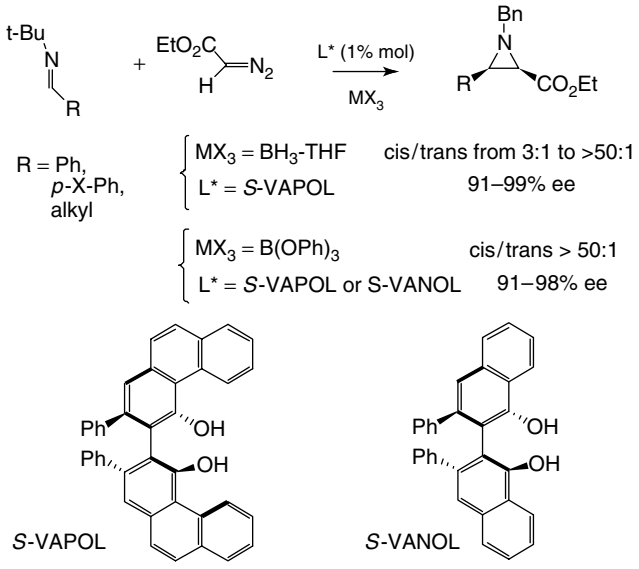
On the other hand, Jørgensen and coworkers explored the reaction of imines with diazoacetate. In the course of this study, they proposed a second possible mechanism involving the coordination of the Lewis acid to the nitrogen atom of the imine, followed by the nucleophilic attack of diazoacetate on the C=N double bond and by the ring closure on the carbon bearing N_2 leaving group [56].



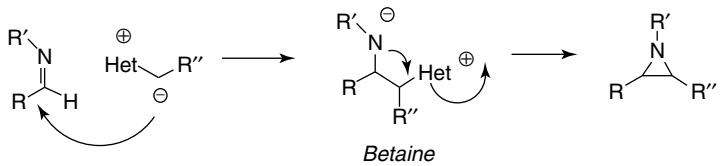
Extension of this approach to the reaction of α-imino esters in the presence of chiral ligands allowed the development of a catalytic diastereo- and enantioselective aziridination of imines derived from α-ethylglyoxylate. Bisoxazolines, phosphinoxazolines, and bis(phosphino)-binaphtyl ligands were tested in combination with $AgSbF_6$ or $CuClO_4$. High diastereoselectivity in *cis*-aziridine formation was observed using (*R*)-Tol-BINAP (cis/trans 19:1) with a good enantiomeric excess (72%), while the trans isomer was obtained as major product in the presence of (4*R*, 5*S*)-Ph-BOX [57].



One of the best generally applicable method for the catalytic asymmetric aziridination was presented by Wulff and Antilla, using a catalyst prepared from VAPOL and borane-tetrahydrofurane. Under these conditions, excellent yields and high asymmetric induction were obtained in the reaction of benzhydrylimines with ethyl diazoacetate using 1% mol of the chiral catalyst [58]. A further enhancement of cis/trans selectivities (up to >50:1), yields (up to 91%), and enantiomeric excesses (90–98%) could be obtained using VAPOL or VANOL ligands in the presence of triphenylborate [59].



Aziridination by Reaction of Imines with Ylides Besides α-halo derivatives and diazo compounds, also ylides were reacted with imines in the asymmetric ring-closure to aziridine. The initial attack of the ylide to the electrophilic imine carbon affords a betaine, which evolves to aziridine via intramolecular ring closure and elimination of ylide heteroatom.

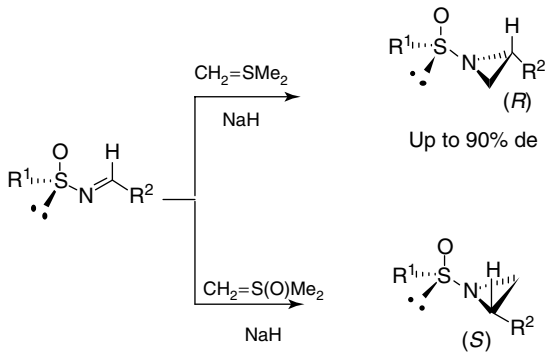


Betaine

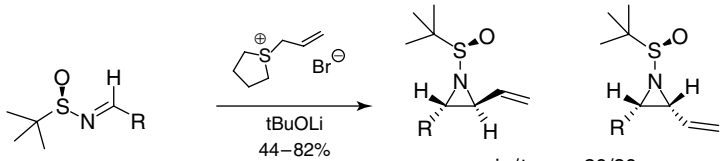
This methodology has been mainly applied to the preparation of enantiopure terminal-, alkyl-, aryl-, propargyl-, and vinyl-substituted heterocycles, by using methylene sulfur ylides as reagents.

The asymmetric induction in this reaction has been obtained introducing a stereocenter on the nitrogen imine side chain or generating sulfur ylides from chiral sulfides.

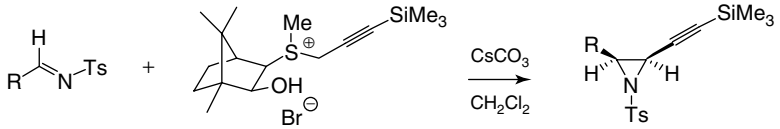
Following the first approach, Garcia Ruano and coworkers performed the reaction between enantiopure *N*-tolylsulfinylimines and dimethyloxosulfonium methylides and dimethylsulfonium methylides [60]. Optically active imines were easily generated by applying the ''*DAG methodology*'', where diacetone-*d*-glucose was used as an inducer of chirality [61]. Under these conditions, the formation of terminal aziridines occurred with good to excellent diastereoselectivities (up to 95:5) and the enhancement of the stereocontrol was obtained by increasing the bulkiness of substituents. The opposite diastereoselectivity observed in the aziridination of dimethyloxosulfonium methylides and dimethylsulfonium methylides was explained by the authors, who suggested a thermodynamic control for the reaction of the first reagent and a kinetic control for the second one.



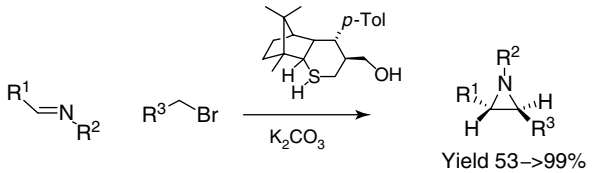
In a similar way, vinyl aziridines were obtained by Stockman and coworkers by treatment of chiral *tert*-butylsulfinylimines with the ylide generated by deprotonation of *S*-allyl tetrahydrothiophenium bromide. Using these methodologies, good yields (44–82%) and satisfactory *cis/trans* selectivities, always around 20/80, could be observed. On the other hand, aziridines were always obtained in excellent diastereoselectivity (up to >95%), thus demonstrating the efficiency of *tert*-butylsulfinyl group as activating and directing group [62].



Dai and coworkers [63] were able to perform the enantioselective synthesis of acetylenylaziridines owing to the introduction of chirality on ylides. Propargylic sulfonium ylides, generated in situ under phase transfer conditions, reacted with *N*-sulfonylimines to give acetylenylaziridines in excellent yields (80–98%). In most cases complete diastereoselectivity could be achieved to give exclusively *cis* heterocycles, although with enantiomeric excesses not higher than 85%.

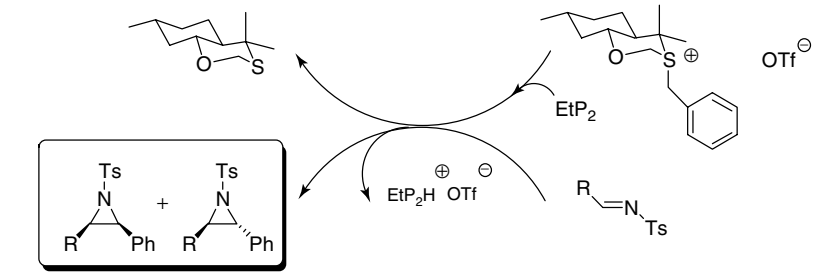


In a similar way, Corey-Chaykovsky reaction between *N*-sulfonylimine, arylmethylbromide, chiral sulfide, and a base by solid–liquid phase transfer conditions allowed Saito and coworkers [64] to synthesize enantiopure aziridines. The reaction occurs via the formation of a sulfonium ylide from the coupling of the sulfide with the halide, followed by deprotonation with the inorganic base. Excellent yields were obtained with imines bearing electron-withdrawing substituents on nitrogen atom.



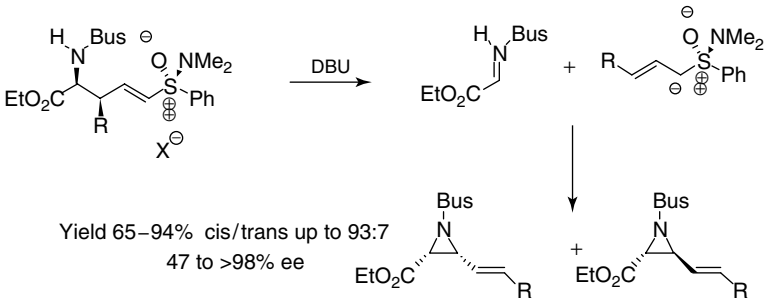
On the basis of the excellent results reported for oxathianes as precursors of enantiopure ylides in asymmetric synthesis, Solladiè-Cavallo and coworkers [65] developed a two-step asymmetric process for the preparation of enantiopure disubstituted *N*-tosyl-aziridines using a phosphazene base to generate the ylide. Although stechiometric amounts of oxathiane are required in this reaction, complete recovery and recycle of this reagent are possible. Furthermore, no unstable or hazardous reagents are involved. Under these conditions, complete conversion of the starting

material into *cis*/*trans* mixtures of aziridines was observed. Both diastereoisomers have exceptionally high enantiomeric purities (98.7–99.9%).



Yield 60–88 % cis/trans up to 100/0
98.7–99.9% ee

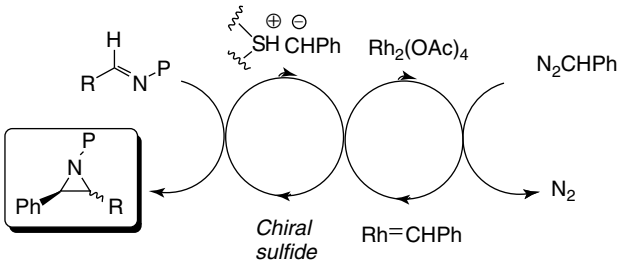
Generation of the two reagents for aziridination was also carried out by treatment of an aminosulfoxonium-substituted β, γ-unsaturated α-amino acid with a base. Fragmentation of the anion indeed affords a conjugated allyl aminosulfonium ylide and an *N-tert*-butylsulfonyl-imino ester. Recombination of these two molecules gave *cis*-vinyl aziridine in almost quantitative yield and excellent diastereoselectivity and enantioselectivity [66].



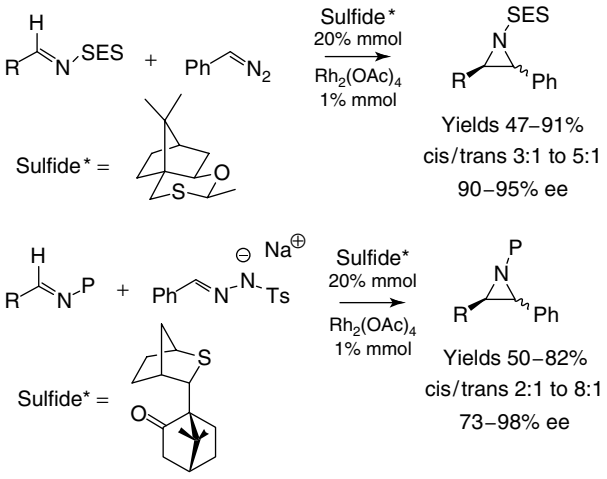
The asymmetric aziridination involving addition of sulfur ylides to imines normally requires stoichiometric amounts of enantiopure reagents. The first catalytic asymmetric application of this reaction was reported by Aggarwal and coworkers, wherein imines bearing an electron-withdrawing group on the nitrogen atom reacted with diazocompounds in the presence of chiral sulfide (20 mol%) and rhodium or copper salts (1 mol) [67].

The reaction proceeds following the catalytic cycle as reported in the figure below, affording optically active aziridines in excellent yields.

A complete study on the relevant factors governing stereocontrol allowed to establish that the origin of diastereoselectivity lies for semistabilized ylides (benzylic) in the nature of transition states leading to betaines, while for stabilized ylides (ester/amide) in the nature of the transition states leading to ring closure [68]. On the other hand, the enantioselectivity is always very high and may be attributed to



both steric and electronic factors in ylide preferred conformation (trimethylsilylethanesulfonyl (SES)). It is noteworthy that the parallel reaction of diazocompounds with imines is very limited and does not significatively affect yield and stereocontrol. Although higher yields could be obtained using stoichiometric amount of chiral sulfide, reduction to catalytic amount did not result in lower stereoselectivity. To overcome potential problems due to hazardousness of large-scale reactions, the diazo compound was generated in situ and a new class of sulfides, compatible with reaction conditions, was developed [69].

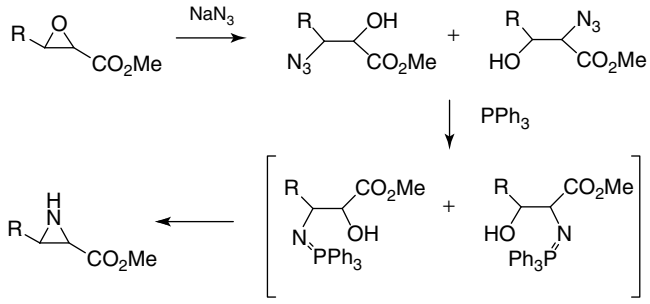


1.1.4
Ring Transformation Methods

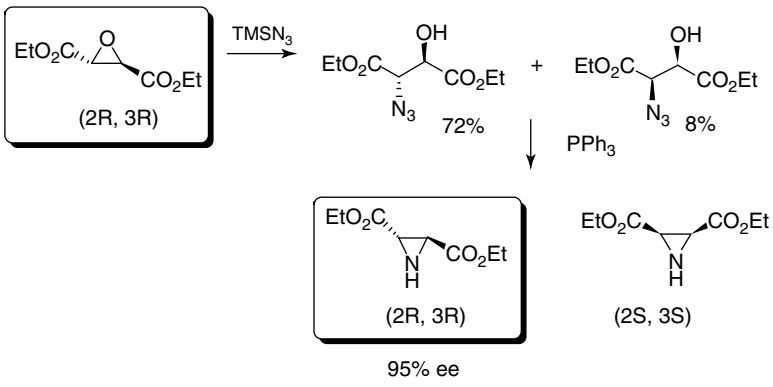
1.1.4.1 **Aziridines from Epoxides**

The transformation of oxiranes to aziridines through a Staudinger-type reaction [70] represents a useful and well-known method for synthesis of these nitrogen-containing heterocycles.

The reaction occurs via the regioselective ring opening of the oxirane moiety by means of an azide followed by closure to aziridine by treatment with triphenylphosphine. Overall, both carbons of the initial epoxide are inverted.



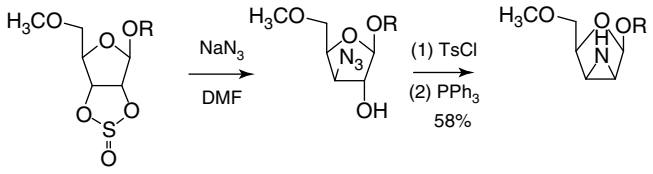
The absolute stereocontrol of this methodology suggests that starting from enantiopure oxiranes, enantiopure aziridines can be obtained. In particular, epoxides deriving from allylic alcohols, which are readily available in optically active form employing Sharpless epoxidation technique, can be considered excellent starting materials. The initial introduction of chirality may be guided by simple variation of the starting allylic alcohol (*Z* or *E*) and tartrate (D or L) geometries. The excellent regio- and stereospecificity of the following Staudinger reaction allows to obtain only one enantiomer of the aziridine by choosing the proper precursors. This methodology has been successfully applied to the preparation of aziridine-2-carboxylates [71], which represent an interesting class of compounds for their potential application as mimetics and precursors of both α- and β-amino acids. In a similar way, the same authors applied this methodology to the preparation of enantiopure 2,3-dicarboxylic acid, the only example of naturally occurring aziridine-carboxylic acid, isolated as metabolite of Streptomyces MD398-A1 [72].



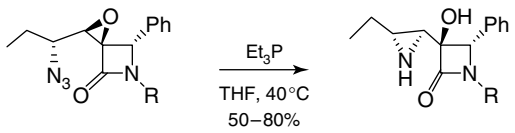
This methodology has been successfully applied to the preparation of building blocks for the synthesis of bioactive derivatives as carbapenems [73] or lipooxygenase pathway intermediates [74].

Enantiopure azides, useful starting material for the preparation of bicyclic analog of aziridine-2-carboxylates, have been obtained using readily available carbohydrates as a source of chirality. Thus, ring opening of 2,3-sulfite-furanoside by an azide group, followed by tosylation of the resulting hydroxyl moiety, gave

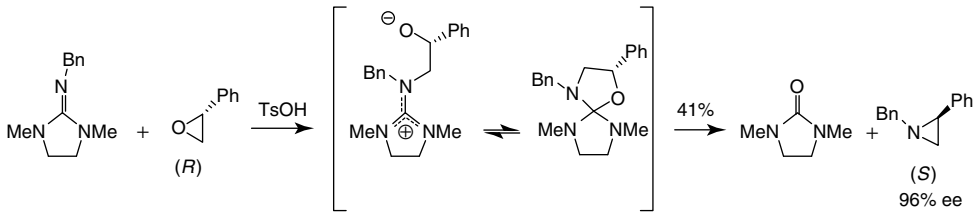
a reactive substrate for a Staudinger-type reaction, leading to carbohydrate-fused aziridines [75].



In general, the presence of an azido moiety vicinal to a good oxygenated leaving group is a sufficient requirement for the synthesis of aziridine rings via Staudinger-type mechanism. Recently, the preparation of polyfunctionalized azetidin-2-ones, bearing an aziridine ring and an hydroxyl moiety on the side chain, has been reported via aza-Payne displacement induced by triethylphosphine [76].

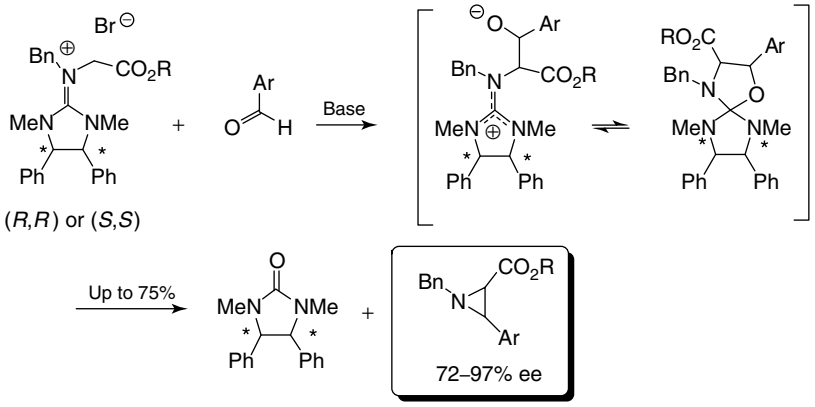


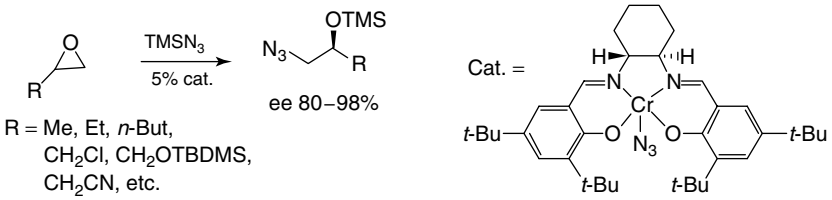
The direct conversion of chiral epoxides to aziridines can be also performed using a cyclic guanidine derivative as nitrogen source. The reaction involves the formation of a spiro intermediate, which undergoes acid catalysis fragmentation to aziridine and urea. Application of this procedure to (*R*)-styrene oxide gave (*S*)-aziridine in 41% yield [77].



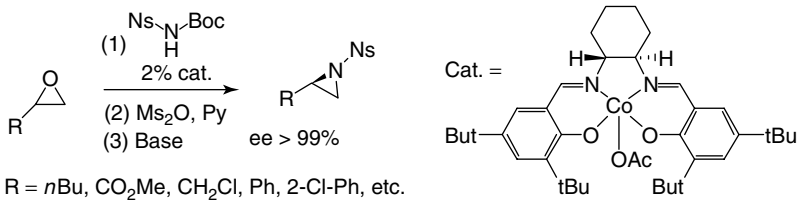
Following a very close mechanism, aziridine-2-esters have been obtained from enantiopure guanidine ylides and a variety of aryl aldehydes. This method afforded *trans*-aziridines as major diastereoisomers in excellent yields (up to 95%) and high enantiomeric excess (72–97%).

An efficient and practical route to enantiopure aminoalcohols starting from racemic terminal oxiranes via enantioselective ring opening with trimethylsilylazide in the presence of chromium-salen was presented by Jacobsen and coworkers. This kinetic resolution allowed the preparation of azido-alcohols with excellent enantiomeric excesses (80–98% ee) [78].





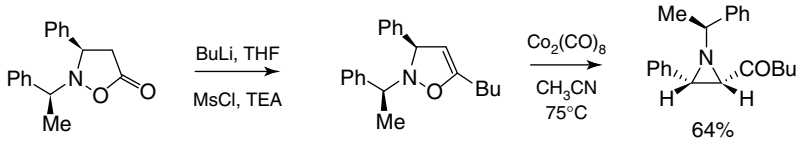
The same group explored the possibility to identify alternative nitrogen sources to overcome azide practical concerns and reported a general catalytic method for the preparation of enantiomerically enriched aziridines starting from racemic epoxides and *N*-Boc-2-nitrobenzenesulfonamide. The reaction, promoted by (*S*,*S*)-[(salen)Co-Ac], provided in few steps enantiopure *N*-nosylaziridines in yields ranging from 58 to 86% and enantiomeric excesses always higher than 99%. Moreover, the presence of the *N*-nosyl protecting group imparts to the heterocycle a particular reactivity toward nucleophilic addition [79].



1.1.4.2 **Aziridines from Other Heterocycles**

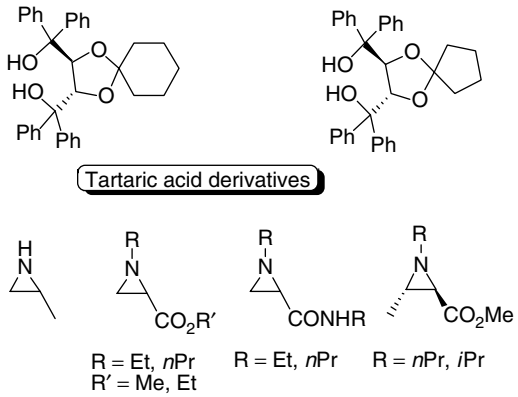
4-Isoxazolines are useful sinthons for the preparation of 2-acylaziridines through thermal rearrangement. This transformation was first reported by Baldwin and coworkers but its application to asymmetric synthetic purposes was scarcely developed. In order to accelerate this rearrangement, catalysts for N–O bond cleavage have been tested and $CO_2(CO)_8$ in anhydrous acetonitrile gave excellent

results. The transformation proceeds with complete diastereoselectivity when a stereogenic center is present in the substituent on the N atom [80].

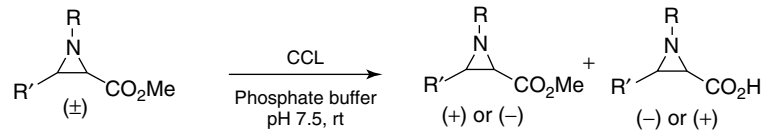


1.1.5
Racemate Resolution

Starting from racemic mixtures, mono- and disubstituted enantiomerically pure aziridines can be obtained by chemical or enzymatic resolution. Concerning chemical methods, an efficient resolution of *N*-alkyl-aziridine-2-carboxylates has been carried out by host–guest molecular association with optically active host compounds derived from tartaric acid [81].

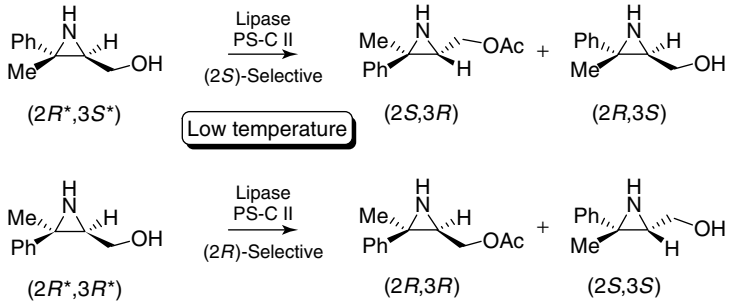


Efficient methods for the kinetic resolution of aziridines have also been obtained with the use of biocatalysts. Racemic substituted aziridine-methanol, aziridine-carboxylate, and aziridine-carboxamide derivatives have been easily separated. Enzymatic hydrolysis catalyzed by *Candida Cylindracea Lipase* (CCL) [82] has been performed both on *N*-unsubstituted aziridine-carboxylates and on more reactive *N*-chloro, *N*-acyl, or *N*-sulfonyl derivatives.

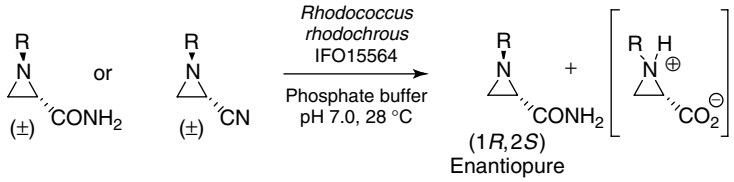


R′ = H, CO_2Me
R = H, Cl, Ac, COPr
SO_2Me, SO_2Tol-*p*

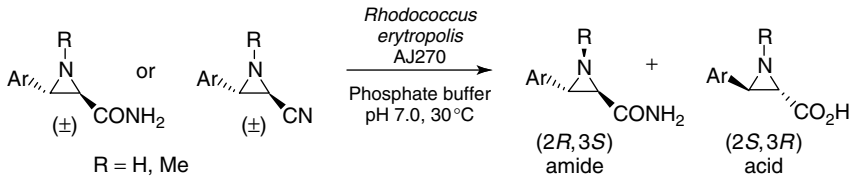
In a similar way Lipase PS-C II, immobilized on porous ceramic particles, has been reported to catalyze the resolution of (2*R**,3*S**) and (2*R**,3*R**)-3-methyl-3-phenyl-2-aziridinemethanol [83]. The temperature control on alcohol acetylation by means of vinylacetate suggests that enantioselectivity of this lipase-catalyzed kinetic resolution is favored by low temperature [84].



Biotransformation of racemic 1,2-*trans*-*N*-substituted-aziridine-2-carboxamides were carried out with a standard cell concentration of *Rhodococcus rhodochrous* IFO15564, an amidase-containing commercially available bacterium. Owing to the concomitant presence of a nitrile hydratase in these bacterial strains, the biotransformation was also successfully performed on *trans*-*N*-substituted-aziridine-2-carbonitriles [85].



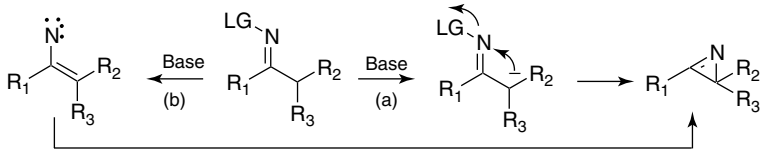
In a similar way, enantiopure (2*R*,3*S*)-3-aryl-aziridine-2-carboxamides were obtained from racemic 2,3-*trans*-aziridine-2-carbonitriles and amides under the catalysis of *Rhodococcus erythropolis* AJ270 whole cells. This highly efficient and enantioselective hydrolysis occurred under very mild conditions in aqueous phosphate buffer at pH 7.0 at 30 °C [86].



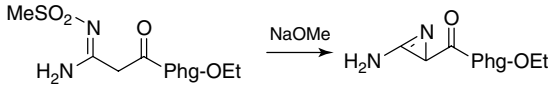
1.1.6
Asymmetric Synthesis of Azirines

1.1.6.1 The Neber Reaction

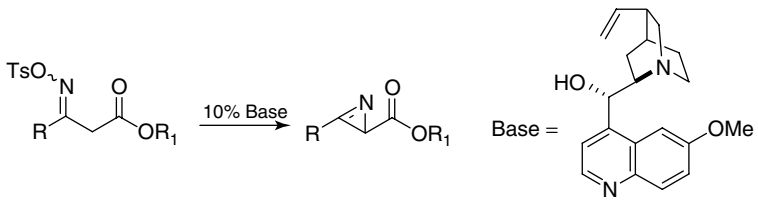
2*H*-Azirines have been first reported by Neber *et al*. in 1932 [87]. The Neber reaction possibly occurs either through an internal concerted nucleophilic displacement (route a) or via a electrocyclization of a vinylnitrene (route b), a reactive species formed by base-promoted loss of the leaving group on the nitrogen atom of oxime sulfonates and hydrazonium halides [88].



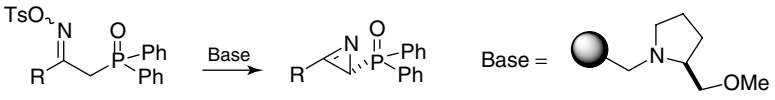
The first optically active 2H-azirine was synthesized by Neber reaction starting from the *O*-mesyl amidoxime derivative carrying a chiral phenylglycine (Phg) ester as a chiral auxiliary. Treatment of this derivative with base gave the 3-amino-2H-azirine in good yield and 96:4 stereoselectivity [89].



A remarkable asymmetric synthesis of azirine 2-carboxylates has been performed with a stoichiometric amount of dihydroquinidine or quinine as chiral tertiary base. The enantiomeric excess obtained ranged between 44 and 82%. Good results were also obtained when a catalytic amount (10 mol%) of quinidine was used. The hydroxy group of the base proved to be fundamental for a good stereoselectivity. Indeed, other chiral tertiary bases deprived of such hydroxy group, sparteine, brucine, and strychnine, did not provide any optically active azirine [90]. Later, this strategy has also been applied to the first synthesis of enantiomerically enriched 2-phosphinyl-2H-azirines [91].

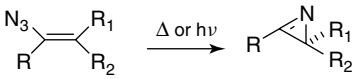


Finally, optically active 2H-azirines substituted in the 3-position with a phosphine oxide group or a phosphonate in the 2-position have been obtained with moderate enantiomeric excess by Neber reaction, starting from easily available oximes, and using chiral polymer-bound amines [92].

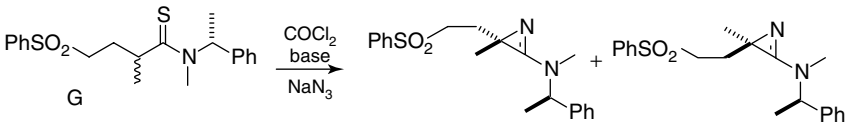


1.1.6.2 **Thermal or Photochemical Treatment of Vinyl Azides**

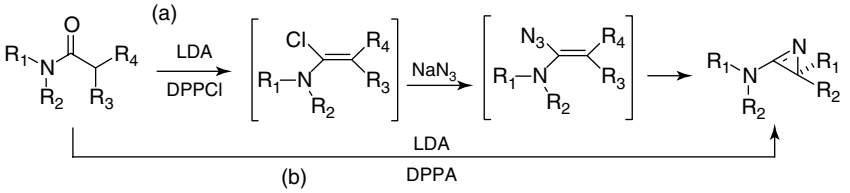
The thermal and/or photochemical treatment of vinyl azides has become a general method for the synthesis of 2H-azirines. In a similar way as for the Neber reaction, 4π-electron vinylnitrenes are thought to be the intermediates, which would then undergo electrocyclization to 2H-azirines.



Optically active 3-amino 2H-azirines can be obtained starting from mono- or disubstituted thioamides with a chiral substituent at the amino group, by treatment with phosgene/triethylamine and sodium azide [93]. This reaction is based on a previously reported synthetic protocol that likely proceeds through α-chloro enamine and vinyl azide intermediates, which are not isolated [94].

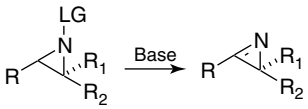


The highly toxic phosgene can be substituted by diphenyl phosphorochloridate (DPPCl), (route a) [95]. Further, diphenyl phosphorazidate (DPPA) has been used as an alternative azide source allowing to obtain the azirines in a single step with very good yields (route b) [96].

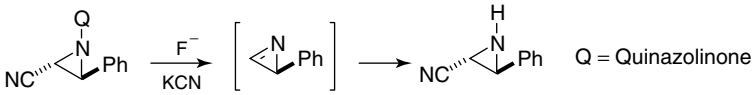


1.1.6.3 **Elimination from Aziridines**

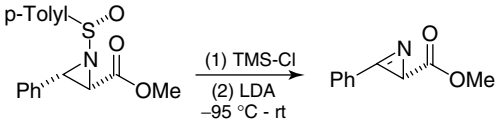
Aziridines carrying a leaving group at the nitrogen (*N*-chloro, *N*-sulfonyl, and *N*-acyl groups) are prone to elimination when treated with a base, giving 2H-azirines. This strategy has also been used for the asymmetric synthesis of azirine-carboxylates by the elimination of *N*-haloaziridines [97].



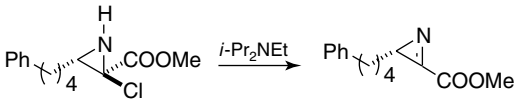
An alternative approach was based on the elimination of the $SiMe_3$ and the *N*-quinazolinone substituents from a chiral aziridine promoted by cesium fluoride. The resulting optically active azirines were not isolated, but directly treated with nucleophiles to yield aziridines in high enantiomeric excess.



On the other hand, the treatment of chiral *N*-sulfinylaziridines with TMSCl followed by LDA gave 2H-azirine-2-carboxylates under complete regioselectivity. This procedure has been applied to the first asymmetric synthesis of the marine cytotoxic antibiotic (*R*)-(−)-dysidazirine and its (*S*)-(+) epimer [98].

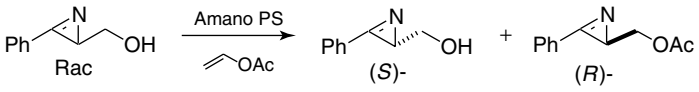


Most methods developed for the preparation of azirines cannot be utilized for the asymmetric synthesis of 2H-azirine-3-carboxylates. On the contrary, the dehydrochlorination of methyl 2-chloroaziridine 2-carboxylates provided the first examples of enantiopure 2-substituted 2H-azirine 3-carboxylates [99].



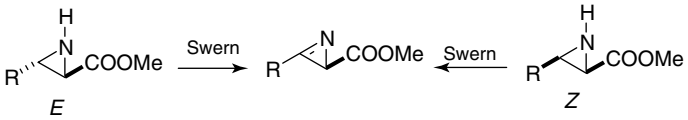
1.1.6.4 **Resolution of Racemic Azirines**

Enantiomerically, pure 2H-azirines have been recently obtained by enzymatic methods. Thus, the kinetic resolution of the racemic 2H-azirinemethanol with Amano lipase at low temperature gave optically pure (*S*)-(1)-phenyl-2H-azirine-2-methanol and the (*R*)-(2)-acetate derivative [100].

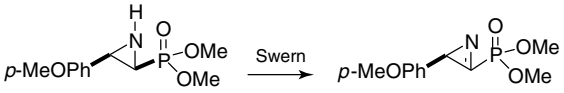


1.1.6.5 Oxidation of Aziridines

One of the first asymmetric syntheses of 2H-azirine-2-carboxylates described in the literature is the Swern oxidation of 3-alkylaziridine-2-carboxylates to the corresponding 2H-azirines. The oxidation of either the (*Z*) or the (*E*) isomers with $COCl_2$/DMSO, followed by NEt_3, proceeded with complete regioselectivity, in good yields and with retention of configuration of the surviving stereogenic center [101].



The Swern oxidation has been later utilized for the efficient synthesis of (+)-2H-azirine 3-phosphonate. This compound represents a new kind of chiral iminodienophile that on reaction with dienes such as trans-piperylene affords bicyclic aziridine adducts [102].

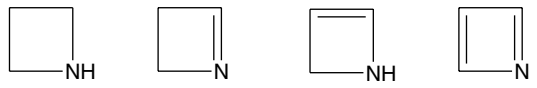


1.2 Substituted Monocyclic Azetidines and Carbocyclic-Fused systems

1.2.1 Generalities

Azetidines are four-membered nitrogen-containing analogs of cyclobutane whose nonplanar cyclic structure has been elucidated by electron diffraction and X-ray christallographic studies.

Unsaturated derivatives of azetidine are also known as *1-azetines, 2-azetines, and azetes*. Considerable attention has been paid in particular to the well-known amide derivatives azetidin-2-ones (β-lactams) that constitute systems of central importance due to their antibacterial properties. They have been the subject of many exhaustive reviews and books of bioorganic and medicinal chemistry owing to the widespread interest shown by scientists [103]. For this reason, in this chapter, their asymmetric synthesis are not treated. On the other hand, some azetidinones have been reported as starting materials for the preparation of enantiopure azetidines.

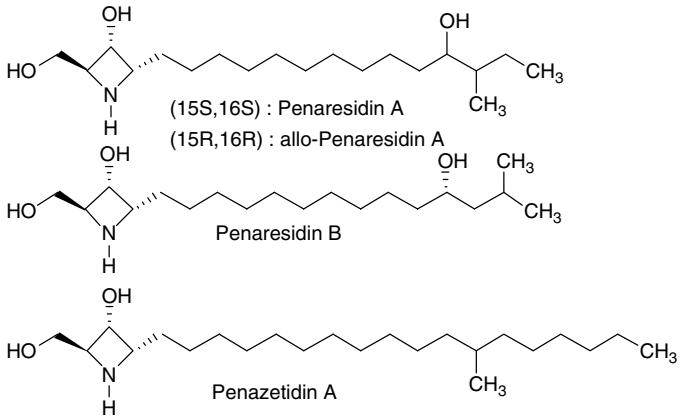


In comparison with strained highly reactive three-membered aziridines, the four-membered rings are more stable, unreactive toward reduction and susceptible of ring cleavage only at high temperature.

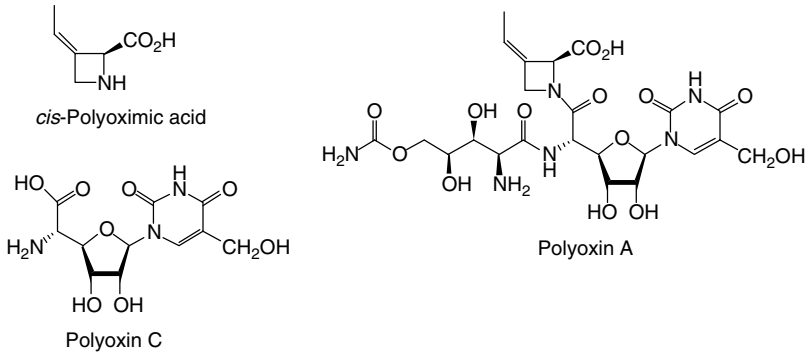
Nevertheless, azetidines are unstable toward mineral acids and ring cleavage by nucleophiles may be performed on protonated rings or in the presence of Lewis acid activation.

Azetidines are typical cyclic amines, appreciably more basic than both smaller and larger rings, showing in aqueous solution a $pK_a = 11.29$.

Naturally occurring azetidine derivatives are rare, and only in 1991 biologically active sphingosine-like compounds from marine origins, penaresidin A and B, were isolated as mixture of isomers. Tested as the mixture, they induced activation of myofibrils from rabbit skeletal muscle elevating the ATPase activity. After few years, a related compound, penazetidine A, was isolated from Indopacific marine sponge *Penares sollasi*, which possesses potent protein kinase C inhibitory activity.



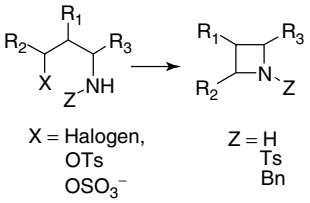
The isolation and characterization of the polyoxin group nucleosides have been reported by Isono and coworkers [104]. Nucleoside polyoxins A, F, H, and K represent a class of antifungal antibiotics. An unusual common feature is the presence of an unsaturated azetidine-containing amino acid peptidically linked to polyoxin C.

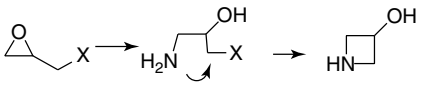


Finally, azetidine 2-carboxylic acids and 2-phosphonic acids have been recently proposed as conformationally constrained analogs of α–amino acids in peptide chemistry [105]. Moreover, chiral C_2-symmetric 2,4-disubstituted azetidine derivatives showed excellent catalytic ability in the asymmetric addition of organozinc to carbonyl compounds.

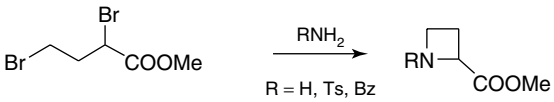
1.2.2
Cyclization Methods: Introduction

General synthetic methods for the preparation of azetidine ring are based on intramolecular displacement of a leaving group on carbon by a γ-amino function. Aminoalcohols and aminohalo-derivatives are among the most important classes of starting materials for heterocycle formation. Halo-alkyloxiranes have also been converted to 3-hydroxy-azetidines via epoxide ring opening by an amine followed by intramolecular nucleophilic displacement.





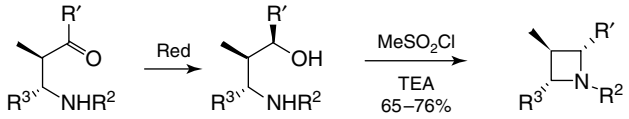
In a similar way, reaction of an amine or a sulfonamide with a 1,3-dihalogeno derivative results in the dialkylation of the nitrogen atom, providing a useful method for the preparation of NH, *N*-alkyl, or *N*-tosyl azetidines.



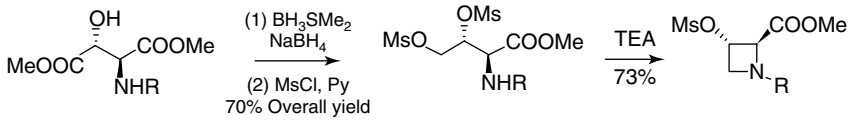
A general enantioselective synthesis of this class of four-membered rings is still lacking and the stereoselective methodologies presented so far suffer from indirect and lengthy procedures such as reduction of enatiopure β-lactams, bis-alkylation of 1,3-sulfonates with primary amines, or intramolecular N-alkylation involving 1,3-amino alcohols. Anyway, the transformation of these methodologies into asymmetric procedures has been performed mainly by cyclization of optically active precursors or by resolution of racemic azetidine mixtures. In the following sections, some selected examples are reported.

1.2.2.1 Cyclization methods: Enantiopure Azetidines via Formation of C–N Bond

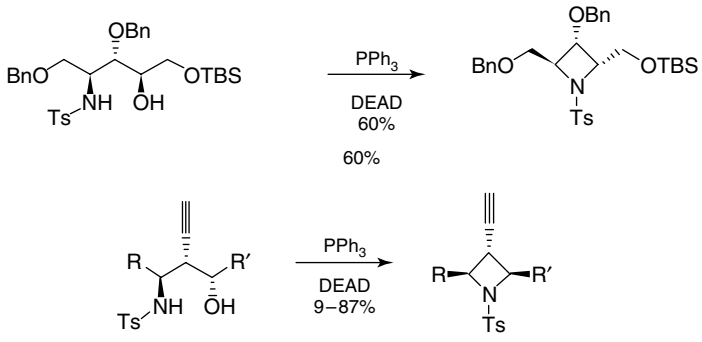
The most important and easy synthetic pathway to azetidines involves the ring closure of aminoalcohols induced by transformation of the hydroxyl moiety into a good leaving group. Many optically active amino alcohols are commercially available; nevertheless, they can also be easily obtained by asymmetric reduction of β-aminoketones or β-amino acids [106]. This approach has also been applied to the synthesis of bioactive alkaloids core and fused-azetidine rings present in bridged nucleosides [107].



When the reacting hydroxy derivative was obtained by reduction of hydroxyaspartate [108], the presence of two possible leaving groups generated a competition between three-membered and four-membered rings. A strong effect of the starting aminoalcohol stereochemistry on the regioselectivity of the process was demonstrated.

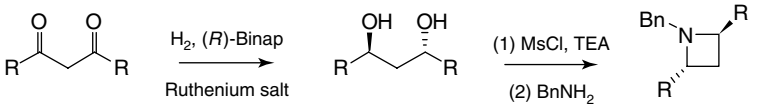


On polyfunctionalized amino alcohols, precursors of sphingosine-derived alkaloids named penaresidins, crucial cyclization has been induced under mild Mitsunobu conditions to yield enantiopure azetidines [109]. Under the same conditions, enantiopure ethynylazetidines were obtained in high yields from 2-ethynyl-1,3-aminoalcohols [110].

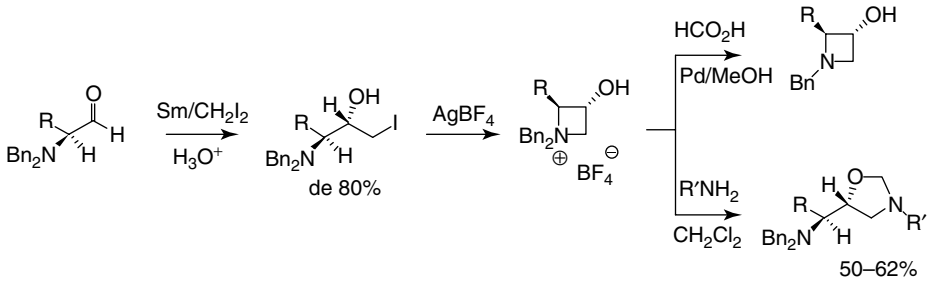


Enantiopure 1,3-diols, obtained by hydrogenation of 1,3-diketones in the presence of chiral ligands, have been successfully used as 2,4-disubstituted azetidine precursors. Treatment with methanesulfonyl chloride followed by reaction with an

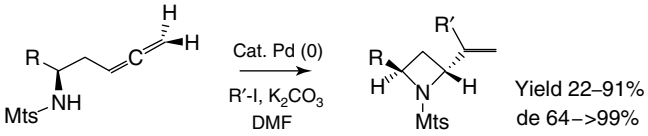
excess of benzylamine afforded *N*-benzyl heterocycles in yields ranging form 60 to 85% [111].



Iodomethylation of enantiopure α-(dibenzyl)aminoaldehydes by means of samarium/diiodomethane under mild conditions gave optically active aminoiodohydrins, as precursors of azetidinium tetrafluroborate salts. These salts are versatile building blocks that can be transformed into aminoepoxides, 1,3-oxazolidines, or turned into *N*-benzyl-hydroxyazetidines by simple hydrogenolysis [112].



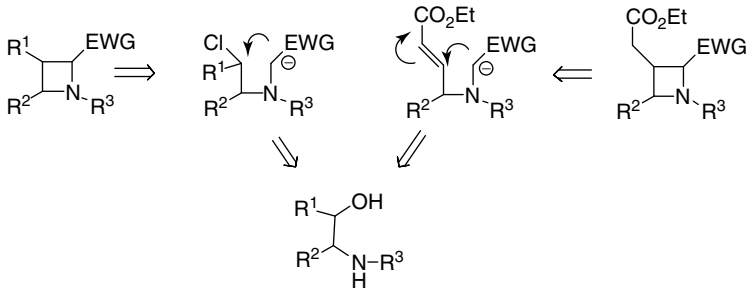
Ring closure of aminoallenes has attracted much attention in the development of stereoselective processes to five- or six-membered nitrogen-containing heterocycles. In a similar way, allenes bearing shorter carbon chain may lead to small size rings. Treatment of β-aminoallene and iodobenzene in the presence of palladium afforded exclusively 2,4-cis-azetidines in excellent yield [113].

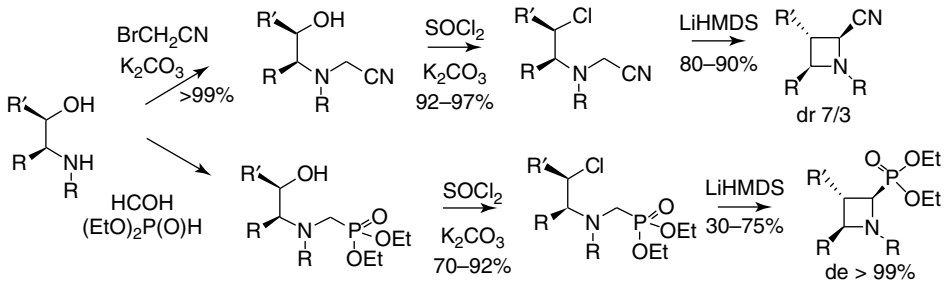


1.2.2.2 **Cyclization Methods: Enantiopure Azetidines via Formation of C–C Bond**

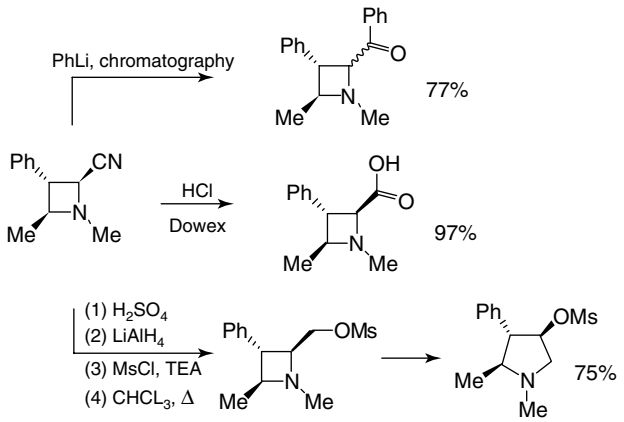
Considerable attention has been paid to the synthesis of enantiopure azetidines bearing a nitrile or a phosphonic acid linked to the α position of the ring, owing to the potential application of these molecules as precursors or mimics of cyclic amino acids. To this purpose, Couty and coworkers [114] developed an easy three-step methodology starting from readily available β-amino alcohols.

N-cyanomethylation or *N*-phosphomethylation of the starting material was followed by substitution of the alcoholic moiety by thionyl chloride. Stereoselective 4-exo-tet ring closure through intramolecular alkylation of the methylene group gave enantiopure azetidines.

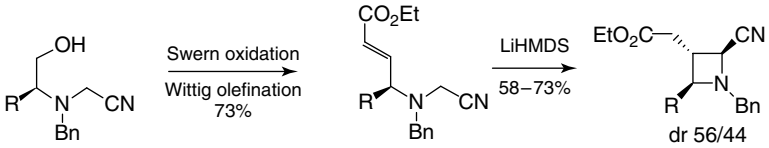




2-Cyano azetidines are versatile building blocks that can be easily transformed into functionalized heterocycles. In fact, treatment of cyano azetidines with phenyllithium cleanly afforded 2-acyl azetidines. Unfortunately, under these conditions, complete epimerization at C2 could not be avoided. On the other hand, hydrolysis of the cyano derivatives into carboxylic acids required harsh conditions, and prolonged heating in concentrated acid was necessary to completely hydrolyze the intermediate amide. Although drastic conditions were applied, neither ring opening nor epimerization was observed. These derivatives were successfully introduced into peptidic sequences as constrained mimetics of natural amino acids. Finally, reduction of the nitrile to alcohol followed by mesylation allowed the expansion of enantiopure azetidines to 3-mesyloxy pyrrolidines.



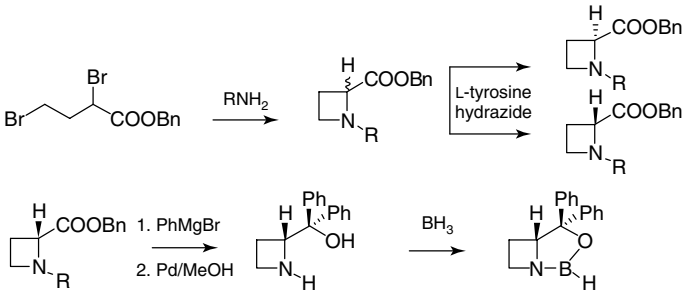
Starting from the same *N*-cyanomethylated intermediates, the same authors reported the preparation of a new class of functionalized heterocycles via Wittig olefination of a transient amino-aldehyde followed by intramolecular Michael addition of the deprotonated methylene position. Unfortunately, low diastereoselectivity could be observed because of the base-catalyzed equilibration between stereoisomers [115].



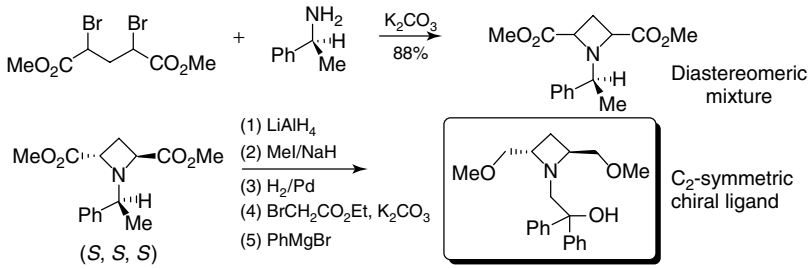
1.2.3
Azetidines by Resolution of Racemates

Azetidines can be obtained in enantiomerically pure form through enzymatic or chemical resolution of racemic mixtures.

Starting from the Baldwin's adaptation of Cromwell general method of preparation of azetidine from 1,3-dihalogeno compounds, racemic azetidine-2-carboxylates were obtained in 96% by reaction with benzhydrylamine under microwave irradiation in CH_3CN. The resolution [116] was conveniently carried out by using L-tyrosine hydrazide as a resolving agent. Enantiomerically pure azetidines have been converted into (*R*)- or (*S*)-oxazaborolines, useful for the enantioselective reduction of prochiral ketones.

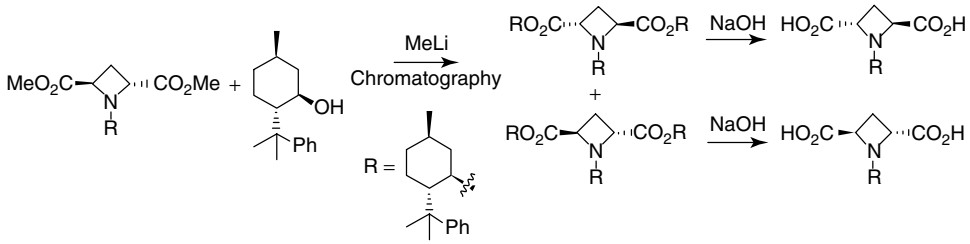


(*S*)-1-Phenylethylamine has been used as a chiral auxiliary as well as a nitrogen atom donor in the synthesis of an enantiomeric pair of azetidine-2,4-dicarboxylic acids from racemic dibromoderivatives; the absolute configuration of one of which has been assigned on the basis of the X-ray structure and the known absolute configuration of the (*S*)-1-phenylethylamine moiety [117]. These C_2-symmetric disubstituted heterocycles have been successfully exploited as rigid core for the preparation of chiral ligands in the asymmetric addition of diethylzinc to aldehydes.

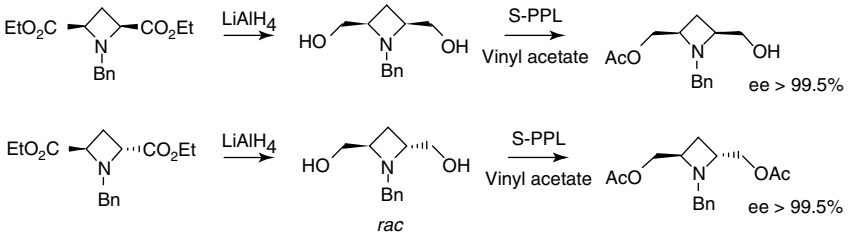


The application of hydroxy-azetidines as chiral ligands for zinc-catalyzed enantioselective additions was also previously reported by Martens and coworkers. Starting form (*S*)-azetidinecarboxylic acid, a constituent of the natural mugineic acid and one of the few commercially available azetidines, the chiral catalyst was prepared by enantioselective catalytic reduction of ketone moiety in the presence of oxazaborolidines [118].

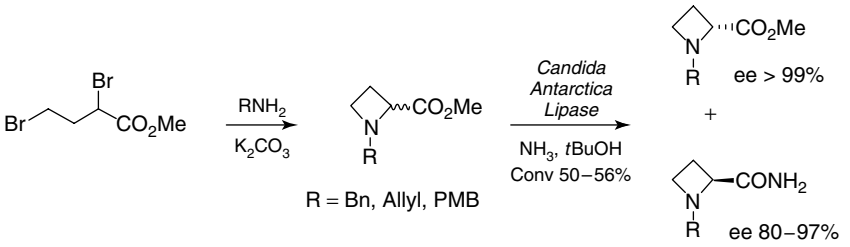
Resolution of racemic *trans*-azetidine-2,4-dicarboxylic acids, synthesized following the same procedure, was achieved by transesterification of N-substituted dimethylesters with (-)-8-phenylmenthol and chromatographic separation of the resulting diastereoisomers [119].



Starting from dicarboxylic derivatives, *cis*- and *trans*-dihydroxy-substituted heterocycles were obtained by reduction with $LiAlH_4$, followed by treatment with benzylamine. The dihydroxy-meso compound was desymmetrized and transformed into monoacetate by the immobilized mammalian lipase from *Porcine pancreas* (S-PPL). The best results were obtained when diisopropylether was used as co-solvent in the presence of vinyl acetate. Optimized procedure allowed to obtain enantiomeric excess higher than 98% by stopping the reaction at conversion around 55%. Longer reaction times showed the formation of a significative amount of *meso*-diacetate derivative. Using the same enzyme, the trans isomer was resolved by a double kinetic resolution, stopping the reaction at moderate degree of conversion. In this case, the diacetate was isolated by the higher enantiomeric excess, while the starting dihydroxyderivative was isolated with 94.5% ee after recrystallization [120].

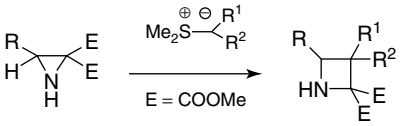


Enzymatic resolution of *N*-alkyl-azetidine-2-carboxylates could be accomplished via transacylation of ammonia catalyzed by *Candida Antarctica* lipase. Treatment of racemic azetidine-esters with an alcoholic saturated solution of ammonia afforded enantiopure unreacted (*R*)-esters and highly enriched (*S*) amides [121].

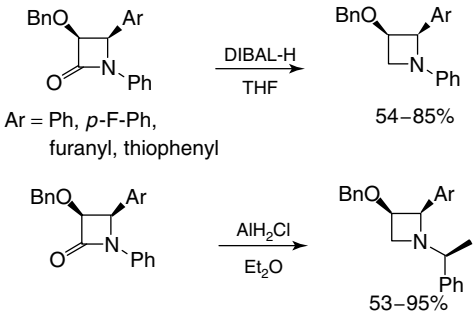


1.2.4
Azetidines by Ring Transformation

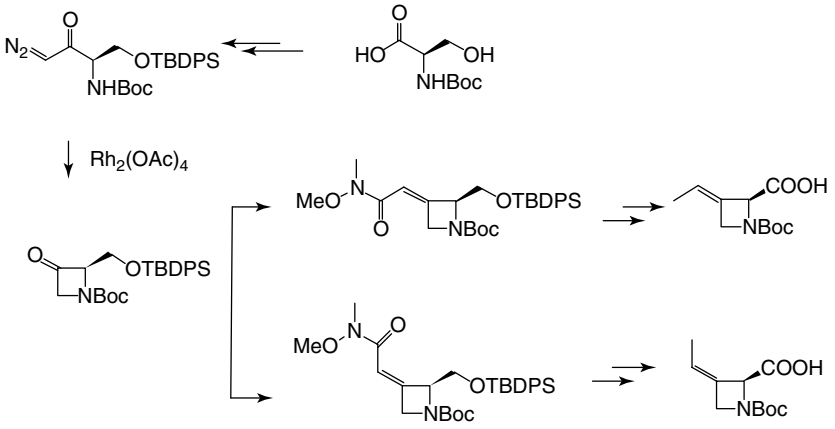
Transformation of heterocyclic precursors represents a further possibility for the synthesis of this class of compounds. One of the most important features is the ring expansion of activated aziridines.



Azetidine derivatives carrying a carbonyl group on the ring backbone occupy a special place in heterocyclic chemistry. Besides the well-known natural and synthetic azetidin-2-one derivatives, whose asymmetric synthesis has been extensively reviewed in the past, much less attention has been paid to azetidin-3-ones. Recently, a useful protocol for the synthesis of these heterocycles has been reported by De Kimpe and coworkers [122], starting from readily accessible *N*-alkylidene-tribromopropylamines. Anyway, both classes of compounds represent starting materials for the preparation of azetidine derivatives. Optimization of the conditions for chiral nonracemic azetidinones reduction with metal hydrides allowed to identify DIBAL-H or AlH_2Cl as the reagents of choice [123].



Natural-cis and unnatural-trans polyoximic acids have been synthesized starting from D-serine through L-3-azetidinone-2-hydroxymethyl chiron using a rhodium-mediated diazoketene insertion reaction. By choosing the proper reagents, the following Horner-Wadsworth-Emmons and Wittig reactions were suited to exclusively obtain the cis or the trans isomer [124].



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