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Recent developments in asymmetric aziridination

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Abbreviations: Ac, acetyl; Anth, anthryl; Ar, aryl; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Box, bisoxazoline; Bs, benzenesulfonic; Bu, butyl; Bz, benzoyl; Cat, catalyst; Cbz, benzyloxycarbonyl; Cy, cyclohexyl; DAP, diaminopimelic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; de, diastereomeric excess; DEAD, diethyl azodicarboxylate; Dec, decyl; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; DMSO, dimethylsulfoxide; DNA, desoxyribonucleic acid; DPPA, diphenylphosphoryl azide; E, electrophile; ee, enantiomeric excess; Esp, α,α,α′,α′-tetramethyl-1,3-benzenedipropionate; Et, ethyl; EWG, electron-withdrawing group; Fu, furyl; Hept, heptyl; Hex, hexyl; HMDS, hexamethyldisilazide; HMPA, hexamethylphosphoramide; L, ligand; LDA, lithium diisopropylamide; M, metal; MCPBA, 3-chloroperoxybenzoic acid; Me, methyl; MEM, methoxyethoxymethyl; MEOX, methyl-1-oxo-(2-oxazolidine)-4-carboxylate; MEPY, methyl-2-oxopyrrolidine-5-carboxylate; MIRC, Michael-initiated ring closurep; MOM, methoxymethyl; Ms, mesyl; MSH, *O*-mesitylenesulfonylhydroxylamine; Mts, 2,4,6-trimethylphenylsulfonyl; Naph, naphthyl; NBS, *N*-bromosuccinimide; NOBIN, 1-amino-1′-hydroxylbinaphthyl; Non, nonyl; Ns, nosyl; Nttl, 1,8-naphthanoyl-*tert*-leucine; Nu, nucleophile; Oct, octyl; Pent, pentyl; Pf, phenylfluorenyl; Pfm, perfluorobutyramide; PG, protecting group; Ph, phenyl; Phth, phthalimido; Phen, phenanthryl; Piv, pivalate; PMP, *p*-methoxyphenyl; Pr, propyl; PTAB, phenyltrimethylammonium tribromide; PTC, phase-transfer catalyst; Py, pyridyl; Salen, 1,2-bis(salicylidenamino)ethane; Ses, trimethylsilylethanesulfonyl; TADDOL, α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TASF, tris(dimethylamino)sulfonium difluorotrimethylsilicate; TBDPS, *tert*-butyldiphenylsilyl; TBME, *tert*-butyl methyl ether; TBS, *tert*-butyldimethylsilyl; TCPTTL, *N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate; TEA, triethylamine; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Thio, thiophene; TMEDA, tetramethylethylenediamine; TMG, 1,1,3,3-tetramethylguanidine; TMS, trimethylsilyl; Tol, tolyl; Tr, trityl; Ts, 4-toluenesulfonyl (tosyl).

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1. Introduction

Aziridines are saturated three-membered heterocycles containing one nitrogen atom. These compounds are among the most fascinating intermediates in organic synthesis, acting as precursors of many complex molecules due to the strain incorporated in their skeletons. Indeed, aziridines have attracted considerable attention owing to their striking chemical properties. The high strain energy associated with the aziridine ring enables easy cleavage of the C–N bond. Therefore, aziridines can either undergo ring-cleavage reactions with a range of nucleophiles or cycloaddition reactions with dipolarophiles. Transformations of this stable but strain-loaded (27 kcal mol^{-1}), three-membered ring allow regio- and stereoselective installation of a wide range of functional groups in a 1,2-relationship to nitrogen. Aziridines, which are extremely important synthetic building blocks, are nitrogen equivalents of epoxides, and can be similarly opened in a stereocontrolled manner with various nucleophiles, providing access to a wide range of important nitrogen-containing products.[1] However, they are less widely used in synthesis than their oxygen counterparts, partly because there are fewer efficient methods for aziridination relative to epoxidation. This is particularly true when enantioselective methods are considered. Besides their importance as reactive intermediates, many biologically active compounds also contain these three-membered rings. Thus, obtaining aziridines, especially optically active aziridines, has become of great importance in organic chemistry. In particular, the antitumour and antibiotic properties of a great number of aziridine-containing compounds are of high significance among other biological properties, which make them attractive synthetic targets in their own right.[2] As powerful alkylating agents, aziridines have an inherent in vivo potency by their ability to act as DNA cross-linking agents via nucleophilic ring opening of the aziridine moiety. Structure–activity relationships have identified the aziridine ring as being essential for the antitumour activity, and a vast amount of work has concentrated on synthesising derivatives of these natural products with increased potency. Various antitumour agents related to mitosanes and mitomycins, for example, have been synthesised and demonstrated to possess activity against a variety of cancers. A number of other synthetic chiral aziridines have also been shown to exhibit other useful biological properties such as enzyme-inhibitory activities.

Indeed, aziridines have attracted great interest to chemists for years because of their easy transformation into pharmacologically and biologically active compounds, their appearance as structural subunits in naturally occurring substances, their antitumour and antibiotic activities, their use as precursors for chiral ligands and their application as chiral building blocks for the construction of various chiral nitrogen compounds, such as chiral amines, amino acids, β-aminosulfonic acids, amino alcohols, alkaloids, β-lactam antibiotics, etc.

Since the first synthesis of an aziridine reported by Gabriel in 1888,[3] the synthetic scope of aziridine chemistry has blossomed in recent years. Chiral aziridines can be prepared by either asymmetric catalytic methods or from chiral auxiliaries. The main approaches to the synthesis of chiral aziridines can be classified as transfer of nitrogen to olefins, transfer of carbon to imines, cyclisation reactions, addition across the carbon–nitrogen double bond of azirines, reactions of ylides, aza-Darzens approaches and miscellaneous reactions such as ring contraction.

Asymmetric aziridination based on the use of chiral catalysts was previously reviewed by Müller and Fruit in 2003,[4] and by Mössner and Bolm in 2004,[5] covering the literature until the end of 2002. On the other hand, asymmetric aziridination based on the use of chiral auxiliaries was reviewed by Tanner in 1994,[1b] and by Sweeney et al. in 1997.[6] It must be noted that more general reviews dealing with aziridination, not especially asymmetric, and sometimes concomitantly with epoxidation or application of aziridines in organic synthesis, have also incorporated literature about asymmetric aziridinations.[7] In addition, it must also be mentioned that De Kimpe et al. have reviewed the synthesis and reactivity of particular *C*-heteroatom-substituted aziridines, in 2007.[8] It was therefore decided to review both methods to obtain asymmetric aziridination, namely that based on the use of chiral auxiliaries in the first section, and that based on the use of chiral catalysts in the second section, since 2003.

2. Aziridination based on use of chiral auxiliaries

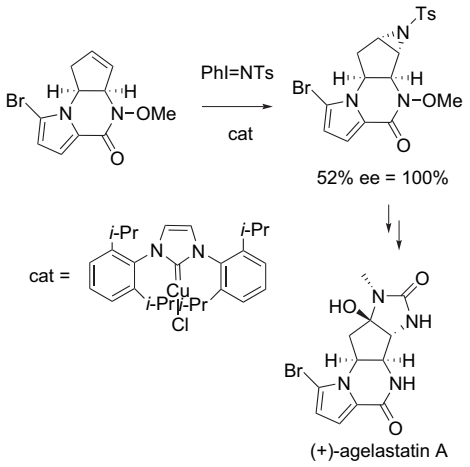
2.1. Addition to alkenes

Nitrogen-atom transfer to alkenes is a particularly appealing strategy for the generation of aziridines because of the ready availability of olefinic starting materials and the direct nature of such a process. There are two general methods for the addition of nitrenes and nitrenoids to alkenes, involving a one- or a two-step mechanism. Nitrenes and metallonitrenes add to alkenes by a direct aziridination reaction, whereas non-metallic nitrenoids usually react through an addition–elimination process.

2.1.1. Aziridination via nitrene transfer to alkenes. The aziridination of olefins is typically accomplished by using a nitrene-transfer reagent. The nitrene source for this reaction, a nitrene or a nitrenoid, can be generated from various methodologies, such as the metal-catalysed reaction of [*N*-(*p*-toluenesulfonyl)imino]aryliodinanes,[9] the oxidation of primary amines, the α-elimination of HX from an amine or amide with an electronegative atom X (X=halogen or oxygen) attached to the NH group, the thermolytic or photolytic decomposition of organyl azides and the α-elimination of metal halides from metal *N*-arenesulfonyl-*N*-haloamines.

In 1993, Evans et al. and Jacobsen et al. independently reported the copper-catalysed asymmetric alkene aziridination using [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) as the nitrene source.[10] This process had been successfully applied to the total synthesis of several natural or biologically active

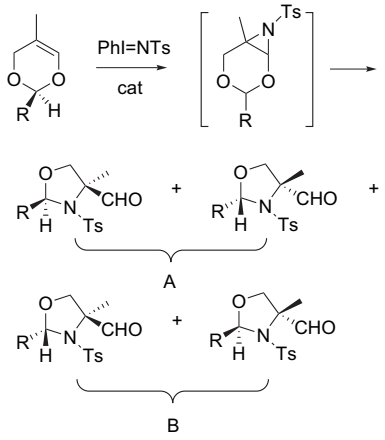
products, such as (+)-agelastatin A, possessing nanomolar activity against several cancer cell lines. Furthermore, this natural product inhibits glycogen synthase kinase-3β, a behaviour that might provide an approach for the treatment of Alzheimer's disease. In 2006, Trost and Dong reported a total synthesis of (+)-agelastatin A based on the aziridination of a chiral piperazinone depicted in Scheme 1.[11] This reaction was performed in the presence of PhI=NTs as the nitrene source and a catalytic amount of a novel copper *N*-heterocyclic carbene complex, providing the corresponding enantiomerically pure aziridine in moderate yield. This chiral aziridine was further converted into the expected (+)-agelastatin A in four steps.



Scheme 1. Synthesis of (+)-agelastatin A by Cu-catalysed aziridination of chiral piperazinone using PhI=NTs.

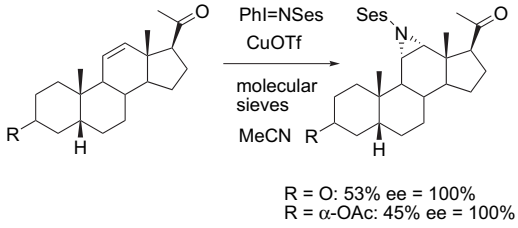
In 2007, Flock and Frauenrath applied this methodology to the aziridination of chiral dioxins.[12] Unexpectedly, the Cu-catalysed reaction of chiral 5-methyl-4*H*-1,3-dioxins with the nitrene generated from PhI=NTs led to the corresponding 4-methyl-1,3-oxazolidine-4-carbaldehydes according to an aziridination–rearrangement process with diastereoselectivities of up to 73% de (Scheme 2). These authors assumed that the aziridination of chiral dioxins intermediately afforded the corresponding aziridines, which immediately rearranged via ring opening/ring contraction to give the corresponding diastereomeric oxazolidinecarbaldehydes. When the reaction was carried out in solvents other than TBME, such as acetonitrile, acetone or dichloromethane, a mixture of similar diastereomers was obtained, but with respect to the diastereoselectivity of the intermediate nitrogen-transfer step, the reaction proved to be unselective (Scheme 2).

A disadvantage of this methodology, however, is the often troublesome removal of the stable *N*-arylsulfonyl group, both in the intact aziridine as well as in the products of subsequent nucleophilic aziridine ring opening. It was for this reason that Dauban and Dodd developed, as an alternative, the trimethylsilylethanesulfonyl (PhI=NSes) version of these hypervalent iodine reagents, [*N*-(arenesulfonyl)imino]aryliodinanes, in order to allow facile removal of the alkylsulfonyl group using a source of fluoride anion.[13] In 2003, these workers applied the Ses iminoiodane to the Cu-catalysed aziridination of 11-pregnane derivatives in order to prepare a chiral 11,12-aziridino analogue of neuroactive steroids.[14] Using this method, the reaction of chiral 11-pregnene-3,20-dione or 3-α-acetoxy-11-pregnen-20-one with PhI=NSes in the presence of copper(I) triflate provided the corresponding α,α-11,12-aziridino steroids in moderate



Scheme 2. Cu-catalysed aziridination of chiral 5-methyl-4*H*-1,3-dioxins using PhI=NTs.

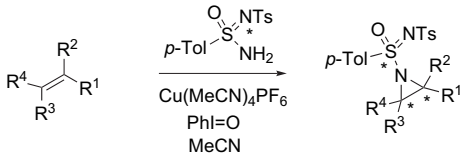
yields, as shown in Scheme 3. The 3α-acetoxy-11-pregnen-20-one derivative was further converted via TASF-mediated removal of the *N*-Ses blocking group into *N*-methyl-11,12-aziridino-3α-hydroxy-5β-pregnan-20-one, a conformationally constrained analogue of the



Scheme 3. Cu-catalysed aziridination of chiral 11-pregnene derivatives using PhI=NSes.

endogenous neurosteroid, pregnanolone and a structural analogue of the synthetic general anaesthetic, minaxolone.

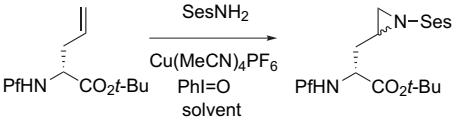
One of the drawbacks of the methods described above is the need to isolate the nitrene precursors (PhI=NR), some of which were reported to be unstable and explosive.[15] In order to simplify the procedure for the preparation of the nitrene precursor, Dauban and Dodd have reported a modified procedure for the copper-catalysed asymmetric alkene aziridination.[16] In their procedures, PhI=NR was generated in situ by treating sulfonamides with iodosylbenzene (PhI=O).[16a] These processes greatly simplified the troublesome handling of iminoiodanes, but, more importantly, enhanced the variety of nitrogenous compounds that could be transformed into the hypervalent iodine(III) reagents. In this context, Dauban et al. reported, in 2004, that chiral *N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide reacted with iodosylbenzene to afford an in situ chiral iminoiodane, which gave, in the presence of a copper(I) catalyst, a nitrene that was very efficiently transferred under stoichiometric conditions to a wide range of alkenes with diastereoselectivities of up to 60% de[17] As shown in Scheme 4, the corresponding chiral aziridines were isolated in good-to-excellent yields, particularly in the case of the poorly reactive α,β-unsaturated esters.



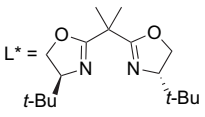
R^1 = CO_2Me, R^2 = R^3 = R^4 = H: 93% de = 55%
R^1 = CO_2Me, R^2 = Me, R^3 = R^4 = H: 96% de = 41%
R^1 = CO_2Me, R^2 = R^3 = H, R^4 = Me: 63% de = 60%
R^1 = CO_2Me, R^2 = R^4 = Me, R^3 = H: 90% de = 40%
R^1 = *n*-Pent, R^2 = R^3 = R^4 = H: 78% de = 10%
R^1 = R^4 = H, R^2 = Me, R^3 = *n*-Pr: 73% de < 10%
R^1 = Me, R^2 = R^4 = H, R^3 = *n*-Pr: 79% de < 10%
R^1,R^3 = $(CH_2)_4$, R^2 = R^4 = H: 89% de = 0%
R^1,R^3 = $(CH_2)_3$, R^2 = R^4 = H: 91% de = 0%
R^1 = Ph, R^2 = R^3 = R^4 = H: 96% de < 10%

Scheme 4. Cu-catalysed aziridination of alkenes using chiral sulfonimidamide and PhI=O.

The combination of sulfonamide $SesNH_2$ with PhI=O was employed by these authors to achieve the copper-catalysed aziridination of a chiral *N*-phenylfluorenyl(Pf)-protected α-allylglycine derivative.[18] This reaction constituted the key step of a novel strategy to prepare new chiral rigid analogues of arginine. Several attempts were made to improve the yield and/or the diastereoselectivity of the aziridination, but these all proved to be somewhat unsatisfactory. Thus, while using benzene or dichloromethane instead of acetonitrile as the reaction solvent allowed moderately higher diastereoselectivities to be obtained, this was at the detriment of the yields, as shown in Scheme 5. Moreover, no substantial changes in both the yields and the diastereoselectivities were observed when the reaction was performed at lower (5 °C) or higher (45 °C) temperatures than room temperature. Even doubling the quantity of the copper catalyst led to a slightly decreased aziridine



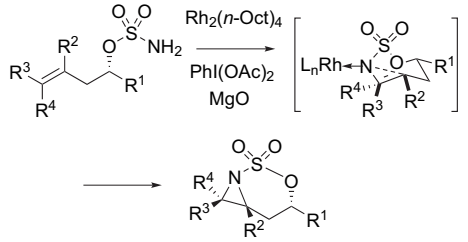
solvent = MeCN: 32% de = 30%
solvent = C_6H_6: 26% de = 34%
solvent = CH_2Cl_2: 24% de = 40%
solvent = MeCN with 35 mol% of L*: 16% de = 50%



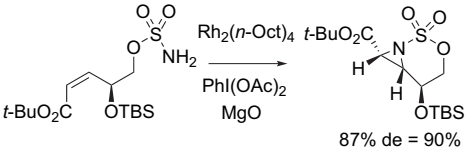
Scheme 5. Cu-catalysed aziridination of chiral α-allylglycine derivative using $SesNH_2$ and PhI=O.

yield. Finally, the best diastereoselectivity (50% de), albeit with a low yield (16%), was obtained when the reaction was carried out in the presence of a chiral bisoxazoline ligand, as shown in Scheme 5.

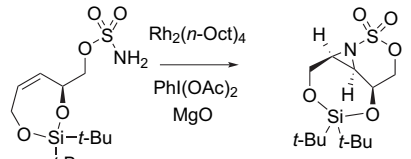
In 2000, Che et al. demonstrated that PhI=NR could also be simply generated by treating sulfonamides with a commercially available reagent, iodobenzene diacetate ($PhI(OAc)_2$).[19] In this context, Du Bois et al. have developed the asymmetric intramolecular aziridination of chiral homoallyl sulfamates performed in the presence of a rhodium catalyst, MgO and $PhI(OAc)_2$.[20] This Rh-catalysed alkene oxidation process allowed the corresponding bicyclic chiral aziridines to be obtained in high yields and diastereoselectivities of up to 90% de (Scheme 6). It must be noted that these stable, heteroatom-substituted aziridines constituted rather unusual structural motifs, access to which was not readily apparent in the absence of this novel method. A number of differently configured chiral unsaturated sulfamates have been tested to map the scope of this new aziridination process. While only moderate stereocontrol was noted for sulfamates derived from secondary alcohols, a sharp increase in diastereoselectivity was recorded for substrates containing a stereo-genic element at the β-site. These results have led these authors to propose a stereochemical model to account for the observed sense of induction. It was consistent with an aziridination event proceeding through a chair-like transition state (Scheme 6),



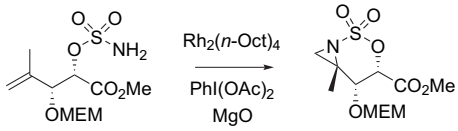
R^1 = Me, R^2 = R^4 = H, R^3 = CH_2Bn: 88% de = 42%
R^1 = Me, R^2 = R^3 = H, R^4 = *n*-Oct: 84% de = 82%
R^1 = Me, R^2 = R^3 = R^4 = H: 84% de = 60%
R^1 = CO_2Et, R^2 = Me, R^3 = R^4 = H: 92% de = 60%
R^1 = CH_2OTBS, R^2 = R^3 = H, R^4 = TMS: 69% de = 88%



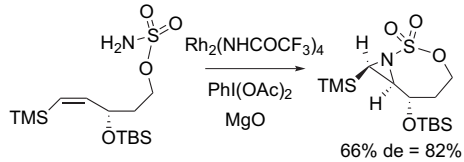
87% de = 90%



61% de = 90%



82% de = 90%

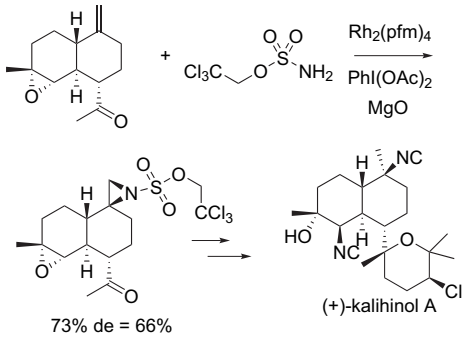


66% de = 82%

Scheme 6. Rh-catalysed intramolecular aziridinations of chiral homoallyl sulfamates using $PhI(OAc)_2$.

which minimized *gauche* and $A_{1,3}$-type interactions. It is interesting to note that even seven-membered ring oxathiazepane-fused aziridines could also be generated with useful levels of diastereocontrol (Scheme 6).

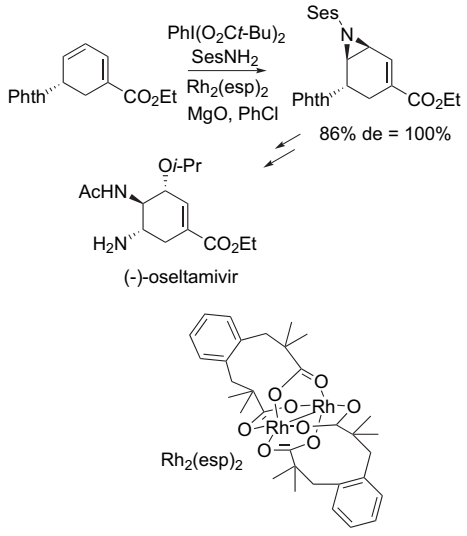
As an alternative to the use of $Rh_2(NHCOCF_3)_4$ as the catalyst, which proved both tedious to prepare and difficult to isolate in high purity, Wood and Keaney have explored the use of rhodium perfluorobutyramide ($Rh_2(pfm)_4$) for the aziridination of olefins.[21] Thus, the treatment of a chiral olefin depicted in Scheme 7 by trichloroethylsulfamate ester in the presence of a combination of $Rh_2(pfm)_4$ with $PhI(OAc)_2$ provided the expected trichloroethoxysulfonylaziridine in good yield and moderate



Scheme 7. Synthesis of (+)-kalihinol A.

diastereoselectivity. This compound was a potent intermediate for the synthesis of (+)-kalihinol A.

With the aim of developing a synthesis of the orally active neuraminidase inhibitor, (−)-oseltamivir, Trost and Zhang have recently studied the asymmetric aziridination of a chiral diene depicted in Scheme 8.[22] In this case, the best result for the aziridination was obtained when the reaction was performed in the presence of $SesNH_2$ as the nitrene source, $PhI(O_2Ct\text{-}Bu)_2$ as the oxidant, bis-[rhodium(α,α,α′,α′-tetramethyl)-1,3-benzenedipropionate] [$Rh_2(esp)_2$] as the catalyst and chlorobenzene as the solvent, as shown in Scheme 8. Indeed, the corresponding enantiopure γ,δ-aziridine was most satisfyingly isolated as the sole product of the reaction. This product was further converted into the desired (−)-oseltamivir, which was finally synthesised in only eight steps

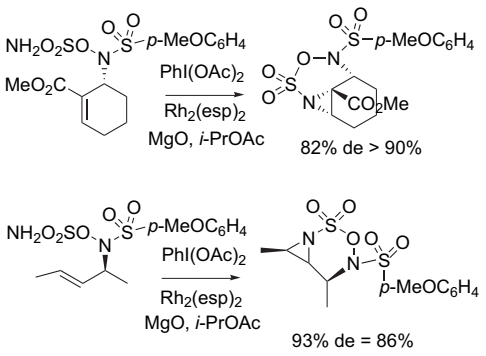


Scheme 8. Synthesis of (−)-oseltamivir.

from commercially available starting materials with an overall yield of 30%.

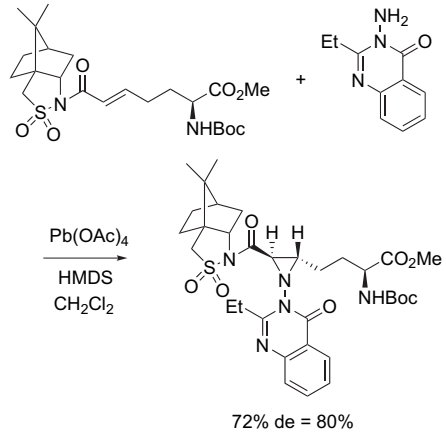
In 2009, Du Bois et al. reported the asymmetric synthesis of chiral *N*-allyl hydroxylamine-*O*-sulfamates through enantioselective palladium-catalysed allylic aminations.[23] These products could be readily transformed into the corresponding enantiopure amino aziridines via diastereoselective oxidative cyclisation upon treatment with [$Rh_2(esp)_2$] as catalyst, $PhI(OAc)_2$ and MgO. As shown in Scheme 9, both cyclic and acyclic olefins underwent the oxidative cyclisation, providing the corresponding tricyclic or bicyclic aziridines, both in high yields and diastereoselectivities.

Another methodology to generate nitrenes consists of the in situ oxidation of hydrazine derivatives in the presence of lead



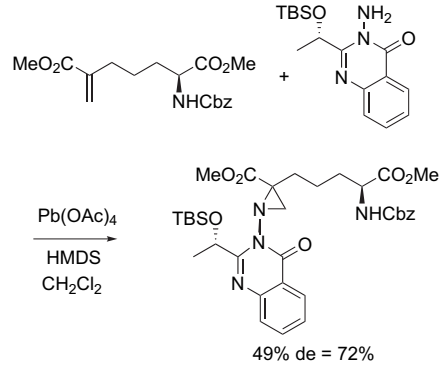
Scheme 9. Rh-catalysed intramolecular aziridinations of chiral *N*-allyl hydroxylamine-*O*-sulfamates using $PhI(OAc)_2$.

tetraacetate. In 2005, Vederas et al. successfully applied this methodology to the asymmetric aziridination of a camphor derivative in the presence of 3-amino-2-ethyl-3,4-dihydroquinazolin-4-one combined with $Pb(OAc)_4$ and HMDS.[24] Thus, the oxidative addition of this aminoquinazolinone mediated by $Pb(OAc)_4$ produced the corresponding aziridine in good yield and with a diastereoselectivity of 80% de, as shown in Scheme 10.



Scheme 10. Aziridination of camphor derivative with 3-amino-2-ethyl-3,4-dihydroquinazolin-4-one combined with $Pb(OAc)_4$.

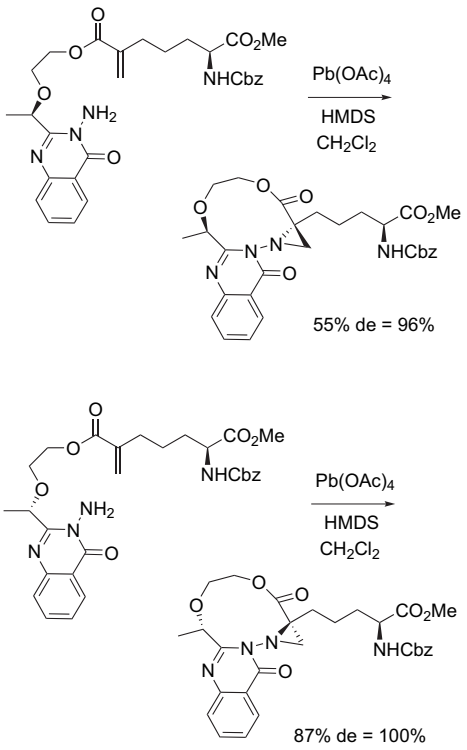
As an extension of this methodology, these workers have investigated the use of chiral 3-acetoxyaminoquinazolinones for the aziridination of an unsaturated α-aminopimelic ester in order to prepare aziridine analogues of diaminopimelic acid (DAP), which is an inhibitor of DAP epimerase.[24] Thus, the aziridination of this chiral alkene performed in the presence of the chiral aminoquinazolinone depicted in Scheme 11 and $Pb(OAc)_4$ provided the



Scheme 11. Aziridination of unsaturated α-aminopimelic ester with chiral aminoquinazolinone and $Pb(OAc)_4$.

expected corresponding aziridine in moderate yield and with a diastereoselectivity of 72% de.

Moreover, an asymmetric intramolecular version of this methodology was developed by the same authors, providing the corresponding 10-membered polycyclic aziridines with almost complete diastereoselectivity, as shown in Scheme 12.[24]

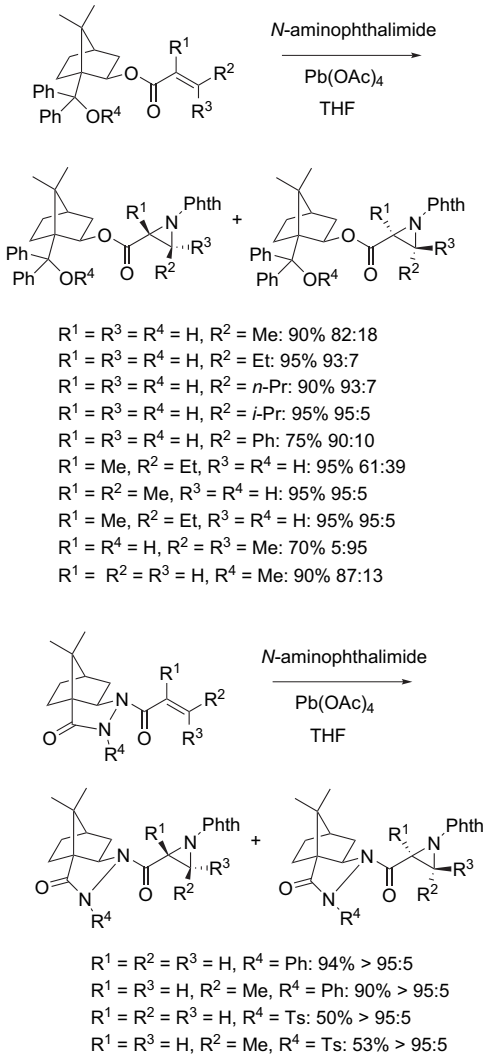


Scheme 12. Intramolecular aziridinations of chiral unsaturated aminoquinazolinones with $Pb(OAc)_4$.

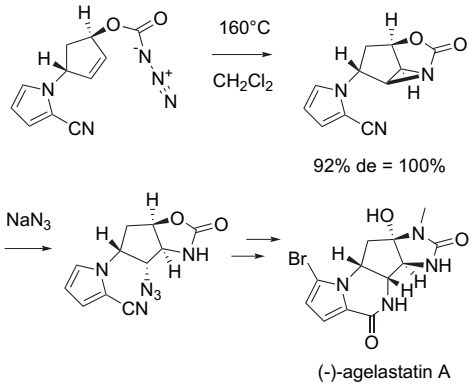
More recently, Chen et al. have studied the treatment of a range of *N*- and *O*-enones derived from various camphor-based chiral auxiliaries with *N*-aminophthalimide in the presence of $Pb(OAc)_4$.[25] In general, both high diastereoselectivities of up to 98% de and high yields of up to 95% were obtained for the formed chiral *N*-phthalimidoaziridines, as shown in Scheme 13.

Another methodology to prepare aziridines is constituted by the thermolytic or photolytic decomposition or organyl azides.[26] In 2008, Tanaka et al. employed this method for the key step of a total synthesis of (−)-agelastatin A, a potent antineoplastic agent.[27] Thus, the requisite nitrogen functionality of the agelastatin core was installed by thermolytic intramolecular aziridination of a chiral azidoformate. The formed enantiopure tricyclic aziridine was further submitted to a regioselective azidation, leading to trans-diamination of the double bond. The obtained chiral azide was subsequently converted into the expected (−)-agelastatin A (Scheme 14).

In 2006, Lowary et al. reported the synthesis of L-daunosamine and L-ristosamine glycosides on the basis of photoinduced intramolecular aziridinations of acylnitrenes derived from L-rhamnose.[28] As shown in Scheme 15, a chiral acyl azide allowed, upon exposure to UV light (254 nm), the corresponding aziridine to be obtained by generation of a presumed acylnitrene intermediate in good yield (79%) and total diastereoselectivity. This aziridine was further converted into a glycoside L-daunosamine derivative. Similarly, the irradiation of a 2:1 α:β anomeric mixture of an acyl azide of an L-*erythro*-hex-2-enopyranoside derivative provided a mixture of the corresponding aziridines in 91% yield (Scheme 15). These products were further separated



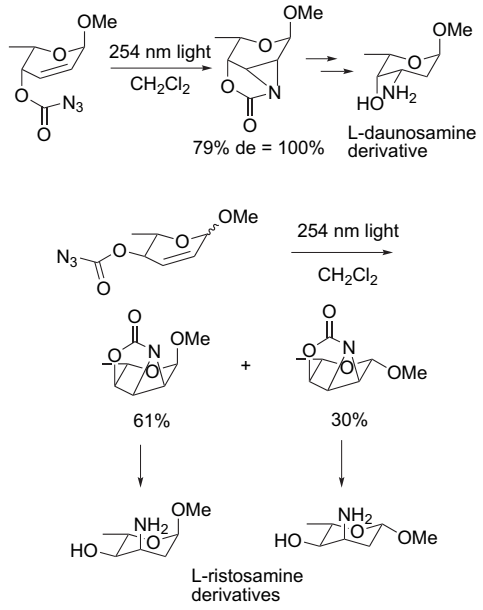
Scheme 13. Aziridinations of camphor-derived *N*- and *O*-enones with *N*-aminophthalimide combined with $Pb(OAc)_4$.



Scheme 14. Synthesis of (−)-agelastatin A by intramolecular aziridination of a chiral azidoformate.

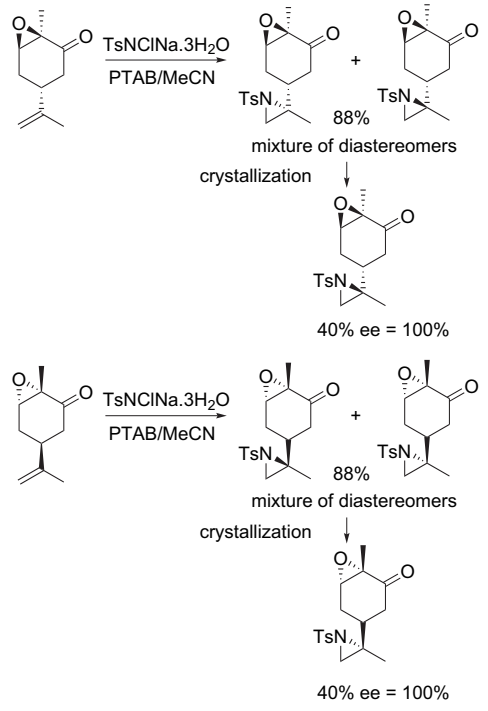
by chromatography and then converted into glycoside L-ristosamine derivatives.

The aziridination of alkenes can also be achieved by using chloramine T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) as the nitrene source. This methodology was recently applied by Chandrasekaran et al. for the synthesis of both enantiomers of *cis*-aziridino epoxides from (*R*)-(−)- and (*S*)-(+)-carvones.[29] Thus, treatment of



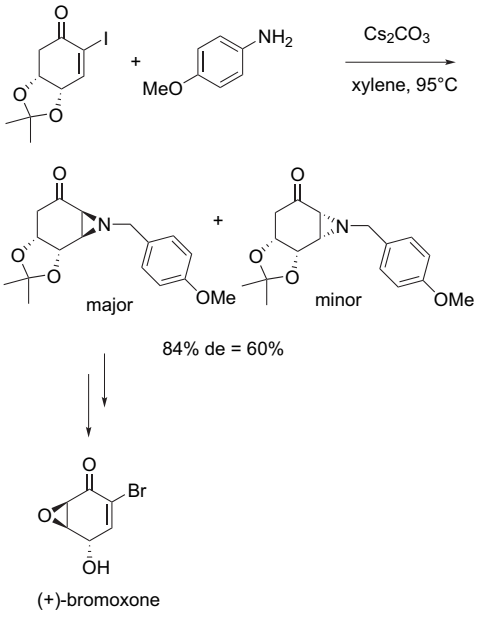
Scheme 15. Syntheses of L-daunosamine and L-ristosamine glycosides via intramolecular photoinduced aziridinations of chiral acyl azides.

enantiopure epoxycarvones by chloramine T in combination with phenyltrimethylammonium tribromide (PTAB) provided, for each enantiomer, a diasteromeric mixture of the corresponding aziridino epoxides in high yield, as shown in Scheme 16. Unfortunately, these authors did not mention the diastereoselectivity of the reactions, but only the yields of the required enantiopure *cis*-aziridino epoxides, which were further purified by crystallisation.



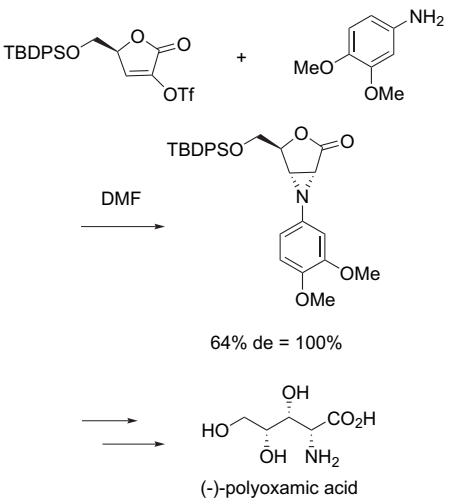
Scheme 16. Syntheses of *cis*-aziridino epoxides derived from (*R*)-(−)- and (*S*)-(+)-carvones by using chloramine T.

2.1.2. Aziridination via addition–elimination processes. The Gabriel–Cromwell aziridine synthesis involves a nucleophilic addition of a formal nitrene equivalent to a 2-haloacrylate or similar reagent. Thus, there is an initial Michael addition, followed by protonation and 3-*exo*-tet ring closure. In 2003, Maycock et al. reported the Gabriel–Cromwell reaction of a chiral α-iodocyclohexenone derived from (−)-quinic acid.[30] The aziridination performed in the presence of 4-methoxybenzylamine and Cs_2CO_3 as a base afforded the corresponding aziridine in good yield as an 80:20 mixture of diastereomers, as shown in Scheme 17. This reaction constituted the key step of a short route to (+)-bromoxone, the acetate of which showed potent antitumour activity.



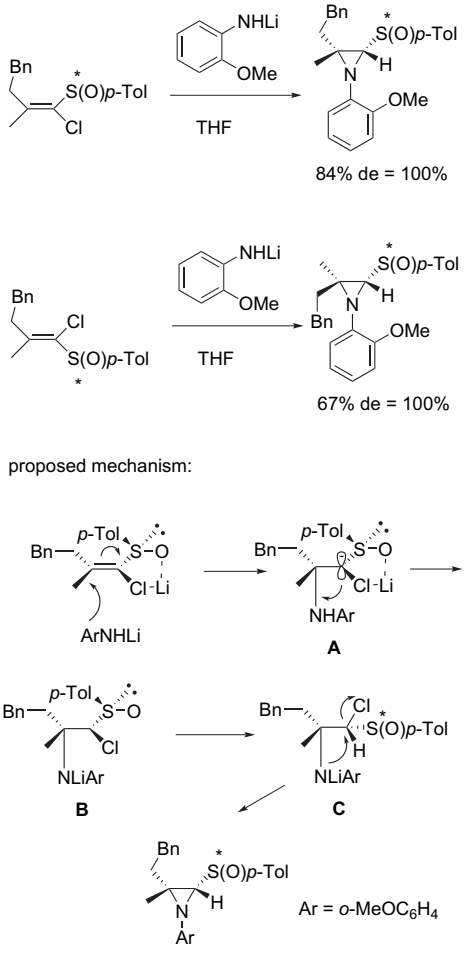
Scheme 17. Synthesis of (+)-bromoxone by Gabriel–Cromwell reaction.

In the same context, Dodd et al. have developed a total synthesis of the non-natural enantiomer of polyoxamic acid on the basis of a tandem Michael-type addition–elimination involving a chiral triflate derived from D-ribonolactone.[31] As shown in Scheme 18, this triflate reacted with 3,4-dimethoxybenzylamine to provide the corresponding aziridine as a single diastereomer in good yield. The diasteroselectivity of the reaction was explained as a result of a Michael-type addition of 3,4-dimethoxybenzylamine to the face opposite to that of the bulky silyl group at C-5. This aziridine was further converted in six steps into the expected (−)-polyoxamic acid with an overall yield of 10%.



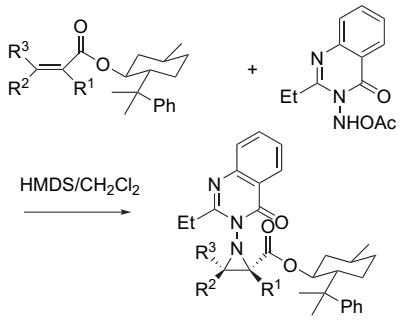
Scheme 18. Synthesis of (−)-polyoxamic acid by Gabriel–Cromwell reaction.

On the other hand, Satoh et al. have recently demonstrated that the treatment of chiral α-chlorovinylsulfoxides with *N*-lithio *o*-anisidine led to the formation of the corresponding sulfinylaziridines in good yields.[32] The reaction of either (*E*)-vinylsulfoxide or (*Z*)-vinylsulfoxide provided the corresponding aziridine as a single diastereomer (Scheme 19). These authors proposed the reaction mechanism depicted in Scheme 19 in order to explain the chiral induction of the reaction of (*E*)-vinylsulfoxide with *N*-lithio *o*-anisidine. Thus, the lithium cation formed a five-membered chelate between the oxygen of the sulfoxide and the chlorine atom.[33] The nitrogen nucleophile attacked from the less hindered *Re*-face to give the intermediate **A**. The intramolecular proton transfer from the nitrogen to the anionic carbon then took place to give intermediate **B**. The rotation of the carbon–carbon bond at 60° to afford conformer **C** occurred, in which the nitrogen attacked the carbon bearing a chlorine atom, resulting in the formation of the corresponding optically active sulfinylaziridine. This process constituted a novel method for the synthesis of chiral α-quaternary α-amino aldehydes by treatment of the formed sulfinylaziridines with *N*-lithio aniline.



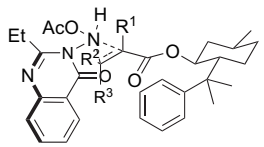
Scheme 19. Aziridinations of chiral α-chlorovinylsulfoxides with *N*-lithio *o*-anisidine.

In 2005, Ulukanli et al. reported the asymmetric aziridination of 8-phenylmenthol-derived α,β-unsaturated esters by using 3-acetoxyamino-2-ethylquinazolinone, which provided in good yields the corresponding aziridines as a single diastereomer for each substrate.[34] The proposed mechanism involved a Michael addition of the exocyclic nitrogen onto the β-position of the α,β-unsaturated ester followed by an S_N2 type displacement of the acetoxy group by the developing partially negative charge at Cα. The high diastereoselectivity of the process could be ascribed to the π-stacking effect[35] between the phenyl group and/or the double bond of the alkene in the unsaturated ester. This blocked one face of the alkene directing the exocyclic nitrogen in 3-acetoxyamino-2-ethylquinazolinone to attack the other face, as shown in Scheme 20. Moreover, these authors observed that the yields of these reactions were greatly improved in the presence of hexamethyldisilazane.



$R^1 = R^2 = R^3 = H$: 72% de > 96%
$R^1 = R^3 = H$, $R^2 = Me$: 79% de > 96%
$R^1 = Me$, $R^2 = R^3 = H$: 73% de > 96%
$R^1 = R^3 = H$, $R^2 = Et$: 71% de > 96%
$R^1 = R^3 = H$, $R^2 = Ph$: 66% de > 96%

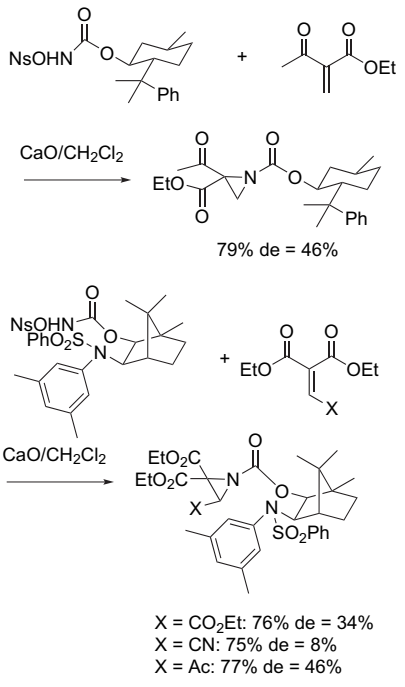
proposed transition state:



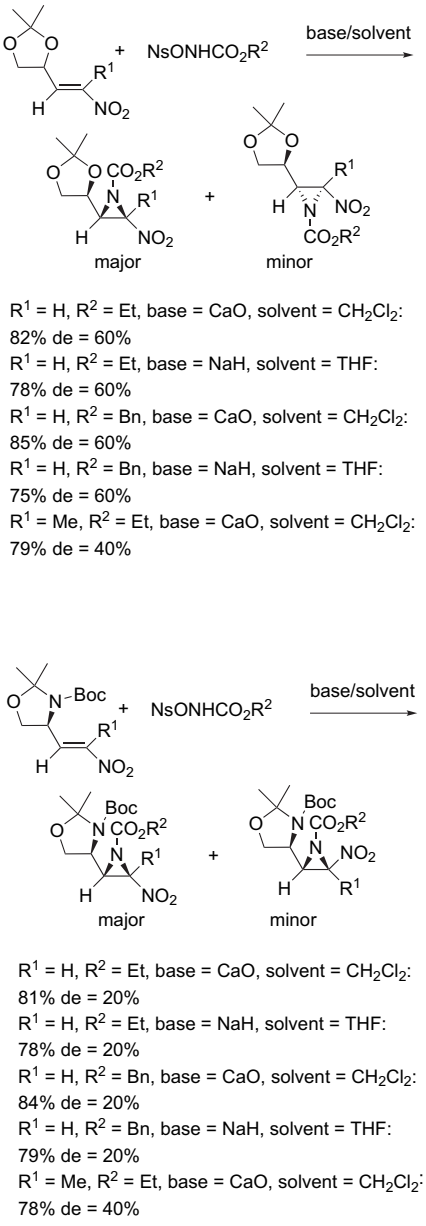
Scheme 20. Aziridination of 8-phenylmenthol-derived α,β-unsaturated esters with 3-acetoxyamino-2-ethylquinazolinone.

For many years, Pellacani et al. have developed an efficient direct aziridination methodology based on the aza-Michael-initiated ring closure (aza-MIRC) reaction promoted by inorganic bases on alkyl nosyloxycarbamates, starting from electron-poor alkenes.[36] An asymmetric version of this methodology was proposed by these authors by using chiral alkyl nosyloxycarbamates as the chiral auxiliaries.[37] Thus, the chiral nosyloxycarbamate derived from Helmchen's auxiliary was reacted via an aza-MIRC pathway with several α,β-unsaturated olefins in the presence of calcium oxide as a base, providing the corresponding highly functionalised aziridines in good yields and moderate diastereoselectivities (≤46% de), as shown in Scheme 21. Similarly, the chiral nosyloxycarbamate derived from menthol was condensed onto ethyl 2-acetylcrotonate to give the corresponding aza-MIRC product in high yield, albeit with moderate diastereoselectivity (Scheme 21).

More recently, these workers reported another asymmetric version of the aza-MIRC reaction based, in this case, on the involvement of chiral (*E*)-nitro alkenes as the chiral auxiliaries, which reacted with various alkyl nosyloxycarbamates, allowing the corresponding chiral aziridines to be synthesised in high yields and better diastereoselectivities of up to 60% de (Scheme 22).[38] Using this method, optically active (*E*)-nitro alkenes carrying a 1,3-dioxolane or 1,3-oxazolidine residue underwent stereoselective aziridinations in the presence of alkyl nosyloxycarbamates. Interestingly, it was demonstrated that the stereochemical outcome of the process was strongly influenced by the chiral residue considered, giving stereomers, regardless of the reaction conditions



Scheme 21. Aziridinations of α,β-unsaturated olefins by chiral alkyl nosyloxycarbamates.



Scheme 22. Aziridinations of chiral (*E*)-nitro alkenes with alkyl nosyloxycarbamates.

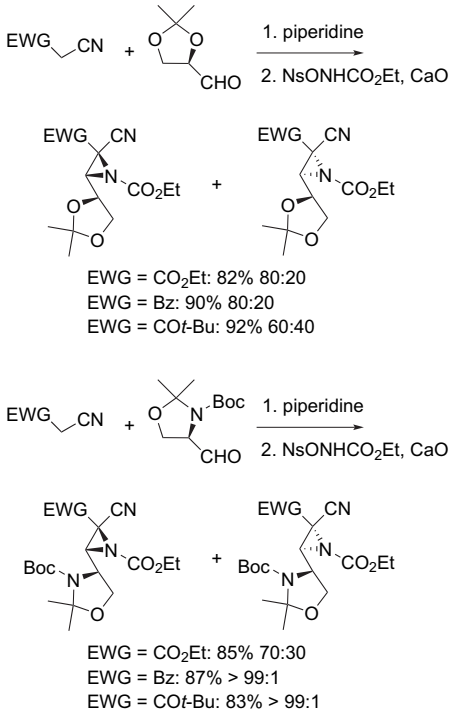
(nature of the base, solvent or aminating agent). Interestingly, different stereochemical outcomes were observed according to the nature of the resident chiral residue, chiral 1,3-dioxolane or chiral 1,3-oxazolidine. Indeed, the aziridination reaction of the 1,3-dioxolane derivative occurred with complete retention of stereochemistry of the substrates, while the aziridination of the 1,3-oxazolidine led to the formation of only one of the possible diastereomers of aziridines, which gave in fact a mixture of two diastereomers due to the expected free rotation around the single bond of the reaction intermediates.

In 2009, the same authors employed this methodology to develop a novel asymmetric Knoevenagel–aza-MIRC domino reaction.[39] Thus, a two-step, one-pot synthesis of highly functionalised chiral aziridines, starting from cyanomethylene compounds and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboaldehyde or Garner's aldehyde, was successfully developed. Indeed, the first step of the process was the reaction between cyanomethylene compounds and optically active aldehydes mediated by catalytic piperidine, generating the corresponding chiral alkenes, which were added in the second step of the sequence by ethyl nosyloxycarbamate, yielding the corresponding expected aziridines in high yields and moderate-to-high diastereoselectivities of up to 98% de (Scheme 23).

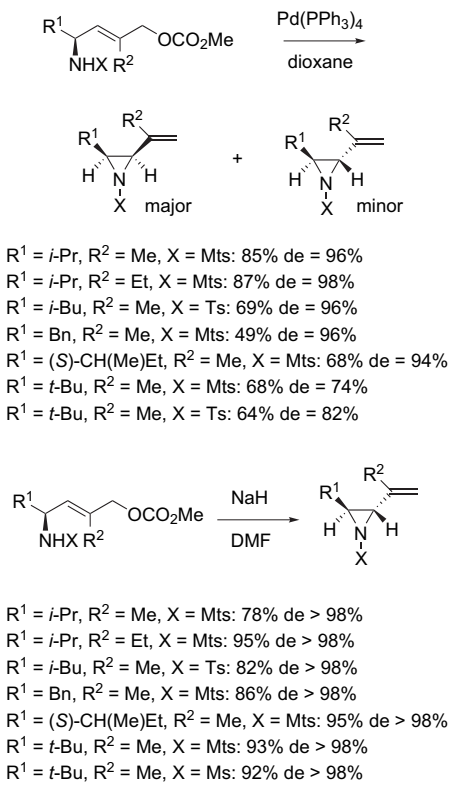
2.1.3. Miscellaneous reactions. In 2004, Tanaka et al. reported the stereodivergent synthesis of chiral 2-alkenylaziridines on the basis of intramolecular palladium(0)-catalysed 2,3-*cis*-selective aziridinations and base-mediated 2,3-*trans*-selective aziridinations.[40] Indeed, whereas the treatment of the chiral allylic mesylates of *N*-protected 2-alkyl-4-amino-(*E*)-2-alken-1-ols with sodium hydride in DMF yielded exclusively the corresponding thermodynamically less stable 2,3-*trans*-2-alkenyl-3-alkylaziridines, the exposure of the chiral methyl carbonates of *N*-protected 2-alkyl-4-amino-(*E*)-2-alken-1-ols to a catalytic amount of $Pd(PPh_3)_4$ in 1,4-dioxane or THF afforded predominantly the corresponding thermodynamically more stable 2,3-*cis*-2-alkenyl-3-alkylaziridines (Scheme 24). The exclusive formation of 2,3-*trans*-aziridines from the mesylates could be rationalized by assuming a 1,3-allylic strain in the aza-anionic intermediates. Interestingly, these authors have demonstrated that the introduction of an alkyl group on the double bond of the vinylaziridines improved the thermodynamic preference for the 2,3-*cis*-2-vinylaziridines over the 2,3-*trans*-isomers to up to 98% de, although the alkyl group apparently made the *cis*-isomers more congested as well as the corresponding trans-isomers. This novel asymmetric aziridination process provided a powerful methodology for the synthesis of either of the two diastereomers of 2-alkenylaziridines from single intermediates.

2.2. Addition to imines

Amongst the different methods for achieving asymmetric aziridinations based on the use of chiral auxiliaries, a large area belongs to imine aziridinations, which can be subdivided into three major conceptual categories involving the reactions of imines with



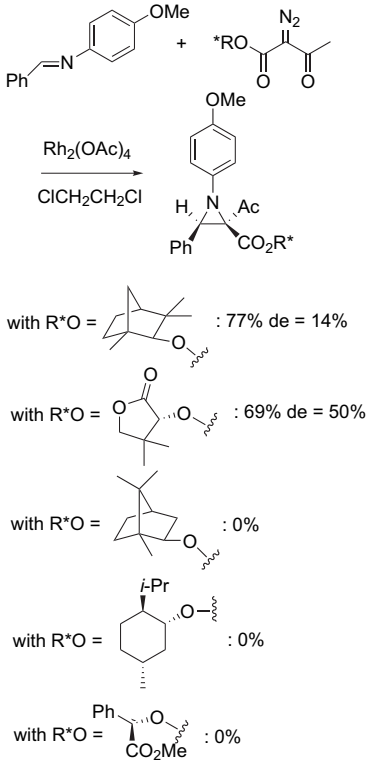
Scheme 23. Direct syntheses of chiral functionalised cyanoaziridines by Knoevenagel–aza-MIRC domino reactions.



Scheme 24. Palladium-catalysed intramolecular aziridinations.

carbenes, α-haloenolates (aza-Darzens) or ylides. Enantiocontrol can be achieved by using either chiral imines or chiral nucleophiles.

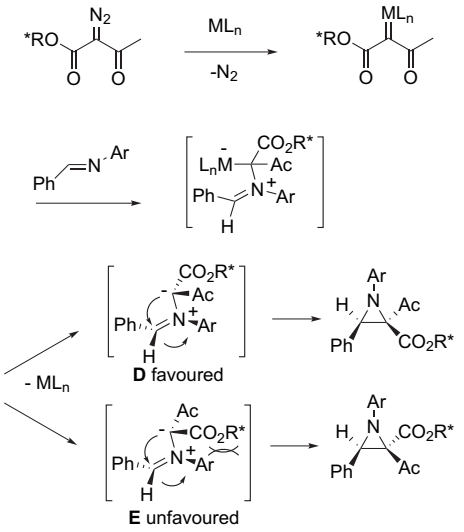
2.2.1. Carbene methodology. The reaction of carbenes with Schiff bases to afford aziridines is well known.[41] In particular, the addition of carbenes generated from diazo compounds to imines is highly attractive, considering the generally good yield, high product stereoselectivity and ease of procedure. Transition-metal complexes, Lewis acids, Brønsted acids, lithium perchlorate and ionic liquids have been found to promote efficiently the addition of diazoacetates to imines. The corresponding aziridine carboxylates are prepared generally in good yields. In addition to diazoacetates, other diazo compounds such as diazoacetoacetates have also been successfully added to imines, providing highly functionalised aziridines. In 2009, Huang et al. examined the rhodium-catalysed addition of diazoacetoacetates derived from various chiral alcohols to imines.[42] It was shown that the involvement of chiral diazoacetoacetates derived from menthol or borneol did not provide the reaction conditions the expected aziridines, but complex mixtures of products, from which no substantial amount of aziridines could be isolated. On the other hand, the reaction of (1*R*)-*endo*-(+)-fenchol-derived diazoacetoacetate depicted in Scheme 25 with *N*-benzylidene-4-methoxyaniline in the presence of $Rh_2(OAc)_4$ afforded the corresponding *cis*-aziridine in good yield, albeit with low diastereoselectivity (14% de). A better diastereoselectivity of 50% de was obtained by using (*R*)-pantolactone-derived diazoacetoacetate, which led to the corresponding *cis*-aziridine in good yield (Scheme 25). According to these results, it seems that the structure of the chiral alcohols has a large effect on the reactivity of the corresponding diazoacetoacetates. For example, the diazoacetoacetates having available C–H bonds gave, preferentially, competitive C–H insertion products instead of aziridination products.



Scheme 25. Rh-catalysed addition of chiral diazoacetoacetates to imine.

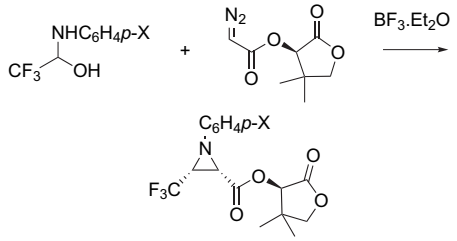
In order to explain the cis stereoselectivity of this process, these authors have proposed the mechanism depicted in Scheme 26. Methyl diazoacetoacetate is decomposed by rhodium acetate to generate a metal carbene, which reacts with the imine to provide the azomethine ylide. The consequent intramolecular ring-closing step occurs via conformation **D** to provide the *cis*-aziridine stereoselectively.

Conformation **E** is unfavoured, due to large steric interactions between the ester group and the *N*-aryl moiety of the imine.



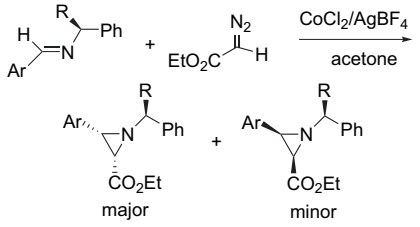
Scheme 26. Proposed mechanism for Rh-catalysed addition of diazoacetoacetates to imines.

Organofluorine compounds have attracted the attention of synthetic organic chemists, due to their potential activity both in the fields of material sciences and biological sciences.[43] In this context, Akiyama et al. have developed the synthesis of chiral CF_3-substituted aziridines by asymmetric Lewis acid-mediated aziridination of aldimines with chiral diazoacetates.[44] While the chiral diazoacetates derived from either menthol or binaphthol monomethyl ether were not effective for the $BF_3{\cdot}Et_2O$-catalysed aziridination of imine equivalents, such as *N*,*O*-acetals, the aziridination of the latter substrates performed with a chiral diazo ester derived from (*R*)-pantolactone provided the expected CF_3-substituted aziridines with both high *cis* selectivity (>95:5) and excellent diastereoselectivity (>92% de), as shown in Scheme 27.



Scheme 27. Aziridination of aldimines with chiral (*R*)-pantolactone-derived diazoacetate.

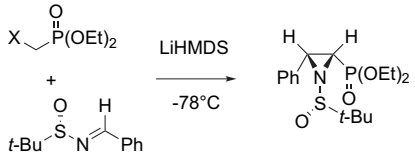
In 2005, Lee and Song reported the asymmetric synthesis of *cis*-aziridines from chiral *N*-benzylimines and ethyl diazoacetate using cobalt(II) as Lewis acid catalyst.[45] A wide range of chiral imines were investigated for this novel process, providing the corresponding chiral *cis*-aziridines in moderate-to-high yields and ratios of the two *cis*-aziridines of up to 2.7, as shown in Scheme 28. The best results were observed with imines bearing an electron-withdrawing substituent at the carbon atom, while *p*-methoxybenzaldimine bearing an electron-releasing substituent at carbon gave no reaction. Finally, the ratios of the two *cis*-aziridines produced in these reactions were found to vary from 1.3 to 2.7. These aziridines were further converted into the corresponding arylalanine derivatives by regioselective hydrogenolytic ring opening.



R = H, Ar = Ph: 45%
R = Me, Ar = Ph: 64% major/minor = 2.1
R = Me, Ar = *p*-FC_6H_4: 66% major/minor = 2.2
R = Me, Ar = *o*-ClC_6H_4: 65% major/minor = 2.2
R = Me, Ar = *m*-ClC_6H_4: 71% major/minor = 2.4
R = Me, Ar = *p*-ClC_6H_4: 69% major/minor = 2.1
R = Me, Ar = *p*-BrC_6H_4: 70% major/minor = 2.0
R = Me, Ar = *p*-$NO_2C_6H_4$: 89% major/minor = 2.7
R = Me, Ar = *p*-CNC_6H_4: 85% major/minor = 2.3
R = Me, Ar = *p*-Tol: 43% major/minor = 2.4
R = Me, Ar = *p*-$MeOC_6H_4$: 0%
R = Me, Ar = 2-Naph: 58% major/minor = 1.3
R = Me, Ar = 2-Py: 34% major/minor = 1.8

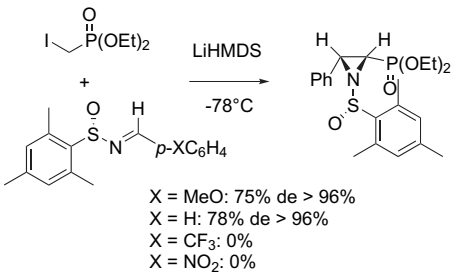
Scheme 28. Co-catalysed aziridination of *N*-benzylimines and ethyl diazoacetate.

2.2.2. Aza-Darzens and analogous reactions. The aza-Darzens reaction is analogous to the Darzens synthesis of epoxides, but employs imines instead of ketones or aldehydes. The asymmetric version of the aza-Darzens reaction includes the use of either a chiral imine or a chiral α-halo enolate as the chiral auxiliary. As an example, Davis et al. have developed asymmetric aza-Darzens reactions involving the addition of halomethylphosphonate anions to enantiopure sulfinimines, providing directly the corresponding chiral *cis*-*N*-sulfinylaziridine-2-phosphonates.[46] Indeed, the reaction between the diethyl iodo- or tosylphosphonates, depicted in Scheme 29, and the chiral sulfinimine, derived from (*S*)-(+)-*tert*-butanesulfinamide and benzaldehyde, provided in the presence of LiHMDS the corresponding aziridines in moderate-to-high yields and as a single diastereomer.



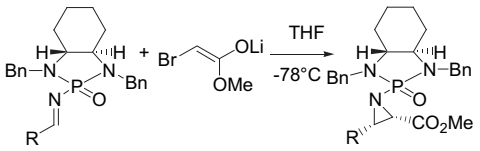
Scheme 29. Aza-Darzens reaction of chiral sulfinimine with diethyl iodo- or tosylphosphonates.

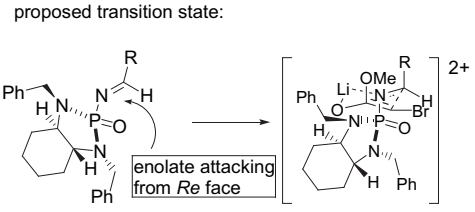
The scope of the preceding methodology could be extended to the use of chiral *N*-(2,4,6-trimethylphenylsulfinyl)imines, which reacted with diethyl iodomethylphosphonate to give the corresponding chiral *cis*-*N*-sulfinylaziridine-2-phosphonates in high yields and almost complete diastereoselectivity (>96% de), as shown in Scheme 30.[47] It must be noted, however, that aryl sulfinimines containing electron-attracting groups gave complex mixtures by using this methodology.



Scheme 30. Aza-Darzens reaction of chiral sulfinimines with diethyl iodophosphonate.

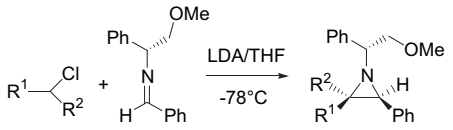
More recently, Li and Kattuboina have successfully developed asymmetric aza-Darzens reactions employing novel chiral *N*-phosphonyl imines as the electrophiles and the preformed lithium enolate of methyl 2-bromoacetate.[48] This novel methodology allowed the corresponding chiral aziridines to be formed in modest-to-good yields and good-to-excellent diastereoselectivities, as shown in Scheme 31. The electrophilicity of these novel stable chiral *N*-phosphonyl imines could be controlled by introducing a variety of electron-donating or -withdrawing groups onto the nitrogen to replace the benzyl group. Interestingly, no *trans*-aziridines were detected for all of the examples studied. In order to explain the stereoselectivity of the reaction, these authors have proposed a cyclic six-membered transition state depicted in Scheme 31. The attack of the *E*-configured lithium enolate of methyl 2-bromoacetate onto the *N*-phosphonyl imine should be directed onto the *Re*-face. The bulky moiety of the chiral auxiliary is pushed away by the sterically hindered side of the six-membered transition state. There are two smaller steric moieties, hydrogen and a lone pair of electrons existing along the enolate attacking pathway within a widely open space of the *N*-phosphonyl imine template. This asymmetric environment ensures the resulting *S*-chirality on the carbonyl addition centre as well as the chirality of the α-position of the *N*-phosphonyl aziridine-2-carboxylic esters.

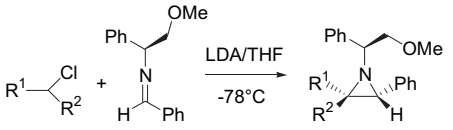


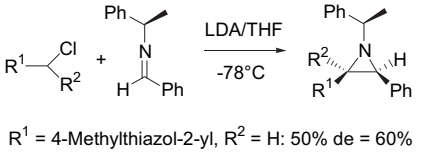


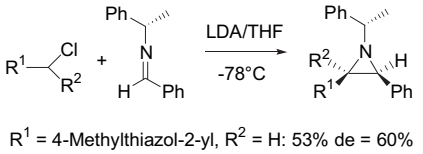
Scheme 31. Aza-Darzens reaction of chiral *N*-phosphonyl imines with lithium enolate of methyl 2-bromoacetate.

In 2004, Troisi et al. demonstrated that lithiated (α-chloroalkyl)heterocycles, generated by deprotonation with LDA in THF, added to various enantiopure imines, affording the corresponding chiral hetero-substituted aziridines in a diastereoselective manner and with satisfactory yields, as shown in Scheme 32.[49] The different steric hindrance and coordinating power of the alkyl group, linked to the imine nitrogen atom, could influence the aziridine ring-closure process and, consequently, the diastereoselectivity of the process. Indeed, aziridines synthesised from chiral imines bearing a methoxymethyl group were isolated with a higher diastereoselectivity than those prepared from chiral imines bearing a methyl group.





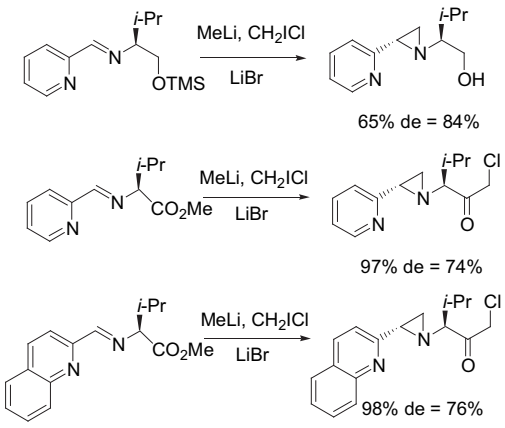




Scheme 32. Aza-Darzens reactions of chiral imines with lithiated (α-chloroalkyl)-heterocycles.

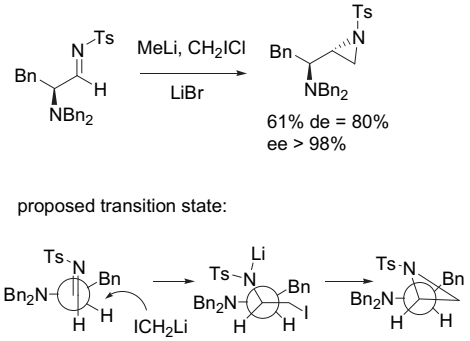
In 2006, Savoia et al. reported a novel asymmetric protocol for the preparation of chiral 2-(2-pyridyl)aziridines from chiral 2-pyridineimines.[50] Using this procedure, the addition of chloromethyllithium, generated in situ from methyllithium and chloroiodomethane in the presence of lithium bromide, onto the chiral imine, derived from 2-pyridinecarboxaldehyde and (*S*)-valinol protected as its *O*-trimethylsilyl ether, provided the corresponding 1,2-disubstituted aziridine in good yield and diastereoselectivity, as shown in Scheme 33. This protocol was extended to another 2-pyridineimine derived from (*S*)-valine methyl ester, which led to

the corresponding aziridine in good yield and with a diastereoselectivity of 74% de (Scheme 33). Similarly, the reaction of a chiral 2-quinolineimine depicted in Scheme 33 gave the corresponding aziridine-α-choroketone, in comparable yield and with a diastereoselectivity of 76% de.



Scheme 33. Aza-Darzens reactions of chiral 2-pyridineimines and 2-quinolineimine with chloromethyllithium.

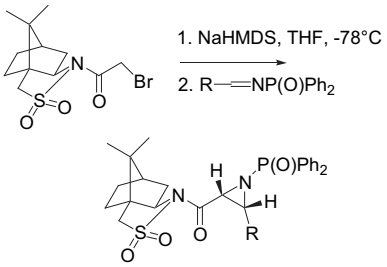
Moreover, in situ-generated iodomethyllithium was condensed by Concellon et al. onto imines derived from *p*-toluenesulfonamides, yielding the corresponding aziridines.[51] In particular, the reaction of the chiral aldimine derived from phenylalaninal allowed access to the corresponding enantiopure (2*R*,1′*S*)-2-(1′-aminoalkyl)aziridine with very high diastereoselectivity (Scheme 34). The stereoselectivity of this process was explained by the addition of iodomethyllithium to the chiral aminoimine taking place under nonchelation control, assuming that the energetically more favoured transition state has the larger substituent (*N*,*N*-dibenzylamino) *anti* to the attack of the iodomethyllithium (Scheme 34).



Scheme 34. Aza-Darzens reaction of chiral phenylalaninal-derived aldimine with chloromethyllithium.

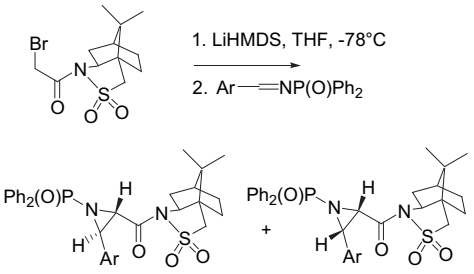
On the other hand, it is also possible to involve a chiral enolate as the chiral auxiliary for the aza-Darzens process. As an example, Sweeney et al. have studied the aza-Darzens reaction of a wide range of *N*-diphenylphosphinyl imines with chiral camphorsultam-derived α-bromoenolate.[52] In all cases of imines, the corresponding enantiopure *cis*-aziridines were isolated in good yields and with virtually complete diastereo- and enantiocontrol, as shown in Scheme 35.

These authors have demonstrated that the stereoselectivity of this process was dependent upon the structure of the imine substituent.[53] Indeed, the inherent cis selectivity of the reaction could be inverted to give exclusively the trans-configured products, depending on the substitution pattern of the arylimine (Scheme 36).



R = Ph: 71% *cis:trans* = 100:0 de > 90%
R = *p*-$NO_2C_6H_4$: 75% *cis:trans* = 100:0 de > 90%
R = *p*-$MeOC_6H_4$: 78% *cis:trans* = 100:0 de > 90%
R = *o*-$NO_2C_6H_4$: 70% *cis:trans* = 100:0 de > 90%
R = *p*-BrC_6H_4: 60% *cis:trans* = 100:0 de > 90%
R = 2-Naph: 72% *cis:trans* = 100:0 de > 90%
R = CH=CHF: 67% *cis:trans* = 100:0 de > 90%
R = 2-Fu: 68% *cis:trans* = 100:0 de > 90%
R = *t*-Bu: 40% *cis:trans* = 100:0 de > 90%
from (2*S*)-sultam:
R = Ph: 71% *cis:trans* = 100:0 de > 90%
R = *p*-FC_6H_4: 57% *cis:trans* = 100:0 de > 90%
R = 2,6-$Cl_2C_6H_3$: 60% *cis:trans* = 100:0 de > 90%
R = *m*-BrC_6H_4: 60% *cis:trans* = 100:0 de > 90%
R = *p*-$MeOC_6H_4$: 60% *cis:trans* = 100:0 de > 90%
R = 2-Py: 67% *cis:trans* = 100:0 de > 90%
R = $CH=CH_2$: 47% *cis:trans* = 100:0 de > 90%

Scheme 35. Aza-Darzens reaction of chiral camphorsultam-derived α-bromoenolate with *N*-diphenylphosphinyl imines.

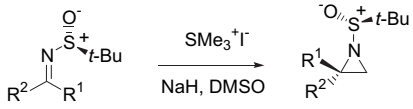


Ar = *o*-BrC_6H_4: 67% *trans:cis* = 100:0 de = 100%
Ar = *o*-IC_6H_4: 73% *trans:cis* = 100:0 de = 100%
Ar = *o*-$MeOC_6H_4$: 65% *trans:cis* = 100:0 de = 100%
Ar = *o*-$CF_3C_6H_4$: 69% *trans:cis* = 100:0 de = 100%
Ar = *o*-ClC_6H_4: 68% *trans:cis* = 80:20 de = 100%
Ar = *o*-FC_6H_4: 84% *trans:cis* = 50:50 de = 100%
Ar = *o*-Tol: 87% *trans:cis* = 50:50 de = 100%
Ar = *o*-EtC_6H_4: 93% *trans:cis* = 37:63 de = 100%
Ar = *o*-$NO_2C_6H_4$: 72% *trans:cis* = 0:100 de = 100%
Ar = Ph: 71% *trans:cis* = 0:100 de = 100%

Scheme 36. Aza-Darzens reaction of chiral camphorsultam-derived α-bromoenolate with *ortho*-substituted *N*-diphenylphosphinyl arylimines.

2.2.3. Ylide-mediated aziridination. In addition to carbenes, carbenoids and α-haloenolates, ylides have also been widely used to achieve asymmetric aziridinations of imines. Indeed, an efficient strategy for the synthesis of chiral aziridines is the reaction of ylides with imines. The reaction between an ylide and an imine forms a betaine, which ringcloses to form an aziridine through elimination of the heteroatom-containing leaving group originating from the ylide. The main class of ylides used in asymmetric aziridination reactions is constituted by sulfur ylides. This asymmetric process can be accomplished using either chiral imines as the chiral auxiliaries, such as chiral sulfinylimines in the reaction with sulfonium ylides,[54] or chiral sulfur ylides as the chiral auxiliaries.[55] Concerning the first approach involving chiral sulfinylimines,[56]

Stockman et al. have developed asymmetric reactions of dimethylsulfonium methylide derived from trimethylsulfonium iodide with a wide range of aromatic, heterocyclic and aliphatic *tert*-butylsulfinylaldimines, providing the corresponding chiral aziridines in good yields and diastereoselectivities of up to 95% de[57] As shown in Scheme 37, electron-rich, electron-poor, sterically hindered and primary alkyl imines were all successful substrates. Moreover, the scope of this convenient methodology could be extended to some chiral *tert*-butylsulfinylketimines, providing the corresponding chiral highly substituted aziridines in high diastereoselectivity (Scheme 37).[58] In contrast to aldimines, however, it must be noted that ketimines were, in general, found not to be suitable substrates for the reaction with dimethylsulfonium methylide. Indeed, only three of the nine ketimines exposed to these reaction conditions furnished significant amounts of the desired aziridines.

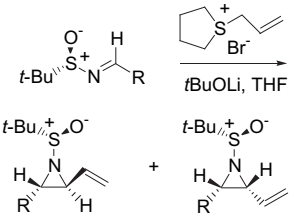


R^1 = H, R^2 = *p*-$MeOC_6H_4$: 65% de = 87%
R^1 = H, R^2 = 2-Py: 77% de = 90%
R^1 = H, R^2 = 3-Py: 74% de = 77%
R^1 = H, R^2 = 2-Fu: 72% de = 91%
R^1 = H, R^2 = Cy: 63% de > 95%
R^1 = H, R^2 = *n*-Pent: 65% de = 80%
R^1 = R^2 = Ph: 73% de > 95%
R^1 = Et, R^2 = Cy: 47% de > 95%
R^1 = Me, R^2 = *n*-Hex: 36% de > 95%

Scheme 37. Reaction of dimethylsulfonium methylide with chiral *tert*-butylsulfinylimines.

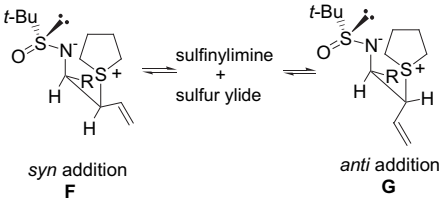
In 2004, the scope of this methodology was extended to another sulfonium ylide, such as that derived from *S*-allyl tetrahydrothiophenium bromide, which was condensed onto a wide variety of chiral *tert*-butylsulfinylaldimines.[59] The expected corresponding chiral vinylaziridines were formed in good yields and trans stereoselectivity combined with excellent diastereoselectivity of up to 95% de. In this case, the use of LiO*t*-Bu as the base in THF exhibited the best results (Scheme 38). In order to explain the trans stereoselectivity of the reaction, the authors have proposed a process in two stages. The initial addition step is reversible and is thought to proceed via a quasi [2+2] addition driven by electrostatic attraction, to form the intermediates **F** and **G** (Scheme 38). The *anti* addition intermediate **G** is significantly more stable than the *syn* addition product **F**, due to decreased *gauche* interactions. For ring closure to occur, rotation to an antiperiplanar configuration of the *N* and *S* substituents is required. The transition from a high-energy intermediate **F** to a significantly lower-energy rotamer drives the equilibrium to the antiperiplanar configuration, while the rotation of the low-energy intermediate **G** to a sterically more hindered rotamer is disfavoured. This is believed to be the rate-determining step. Thus, ring closure gives a predominance of the *trans*-aziridine.

In 2006, these authors applied this methodology to a range of variously substituted chiral *tert*-butylsulfinylketimines, which allowed a convenient access to a diverse range of highly substituted chiral aziridines to be achieved in up to 78% yield and>90% de (Scheme 39).[58] The best results were found when the reaction was performed in DMSO as the solvent.

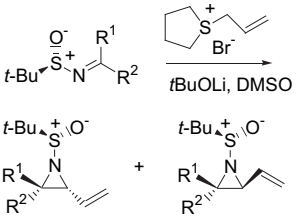


R = Ph: 68% *trans/cis* = 71:29 de (*trans*) = 90%
R = *p*-$MeOC_6H_4$: 76% *trans/cis* = 82:18 de (*trans*) = 92%
R = *p*-$NO_2C_6H_4$: 74% *trans/cis* = 59:41 de (*trans*) = 84%
R = 2-Naph: 64% *trans/cis* = 80:20 de (*trans*) > 95%
R = Et: 44% *trans/cis* = 80:20 de (*trans*) = 90%
R = *n*-Pent: 67% *trans/cis* = 82:18 de (*trans*) > 95%
R = *n*-Non: 58% *trans/cis* = 81:19 de (*trans*) > 95%
R = *i*-Bu: 62% *trans/cis* = 83:17 de (*trans*) > 95%
R = *c*-Pr: 61% *trans/cis* = 72:28 de (*trans*) = 86%
R = Cy: 78% *trans/cis* = 83:17 de (*trans*) > 95%
R = 2-py: 54% *trans/cis* = 88:12 de (*trans*) = 88%
R = 2-Fu: 55% *trans/cis* = 67:33 de (*trans*) > 95%
R = (*E*)-CH=CHPh: 82% *trans/cis* = 83:17 de (*trans*) > 95%

proposed transition states:



Scheme 38. Reaction of *S*-allyl tetrahydrothiophenium bromide with chiral *tert*-butylsulfinylaldimines.

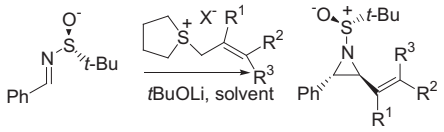


R^1 = R^2 = Ph: 85% de > 95%
R^1 = Me, R^2 = Ph: 78% *trans/cis* = 75:25
de (*trans*) > 95%
R^1,R^2 = $(CH_2)_4$: 55% de > 95%
R^1 = Et, R^2 = CH_2-CH(Me)Et: 55% *trans/cis* = 72:28
de (*trans*) > 95%
R^1 = Et, R^2 = 2-thiophene: 72% *trans/cis* = 60:40
de (*trans*) > 95%
R^1 = Et, R^2 = 2-thiazole: 56% *trans/cis* = 55:45
de (*trans*) = 90%
R^1 = Me, R^2 = *n*-Hex: 55% *trans/cis* = 69:31
de (*trans*) > 95%

Scheme 39. Reaction of *S*-allyl tetrahydrothiophenium bromide with chiral *tert*-butylsulfinylketimines.

In addition, more varying substitutions on the alkene of the chiral vinylaziridines could be achieved by these workers by involving a range of other ylides derived from various substituted allyltetrahydrothiophenium salts.[60] In this way, the reaction of substituted sulfur allyl ylides to *tert*-butylphenylsulfinylimine gave a range of substituted chiral vinylaziridines in good yields and moderate-to-excellent diastereoselectivities of up to 99% de, albeit with variable

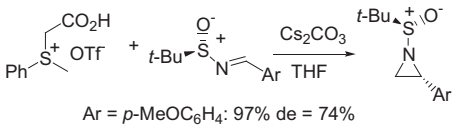
trans:*cis* ratios ranging from 50:50 to 100:0 (Scheme 40). In this study, it was found that the use of THF as the solvent tended to give the best compromise between stereoselectivity and conversion, with DMSO giving the best conversion at the expense of *trans*:*cis* selectivity.



$R^1 = R^2 = R^3 = H$, X = Br, solvent = THF:
68% *trans:cis* = 70:30 de (*trans*) = 90%
$R^1 = R^2 = R^3 = H$, X = Br, solvent = DMSO:
75% *trans:cis* = 50:50 de (*trans*) = 20%
$R^1 = R^3 = H$, R^2 = Me, X = Br, solvent = THF: 0%
$R^1 = R^3 = H$, R^2 = Me, X = Br, solvent = DMSO:
85% *trans:cis* = 67:23 de (*trans*) = 20%
$R^1 = R^3 = H$, R^2 = Ph, X = BF_4, solvent = THF: 0%
$R^1 = R^3 = H$, R^2 = Ph, X = BF_4, solvent = DMSO:
75% *trans:cis* = 60:40 de (*trans*) = 2%
$R^1 = H$, $R^2 = R^3$ = Me, X = Br, solvent = THF: 0%
$R^1 = H$, $R^2 = R^3$ = Me, X = Br, solvent = DMSO:
66% *trans:cis* = 70:30 de (*trans*) = 36%
$R^1 = R^3 = H$, R^2 = TMS, X = OTs, solvent = THF:
90% *trans:cis* = 92:8 de (*trans*) = 100%
$R^1 = R^3 = H$, R^2 = TMS, X = OTs, solvent = DMSO:
70% *trans:cis* = 55:45 de (*trans*) = 0%
R^1 = Me, $R^2 = R^3 = H$, X = Br, solvent = THF:
56% *trans:cis* = 70:30 de (*trans*) = 100%
R^1 = Me, $R^2 = R^3 = H$, X = Br, solvent = DMSO:
63% *trans:cis* = 60:40 de (*trans*) = 100%

Scheme 40. Reaction of substituted sulfur allyl ylides with chiral *tert*-butylphenylsulfinylimine.

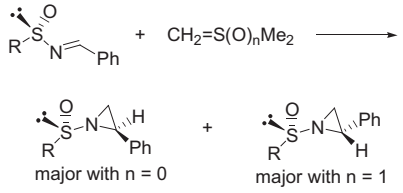
Very recently, Forbes et al. have reported the employment of another sulfonium salt depicted in Scheme 41, which was successfully condensed onto aryl-substituted *tert*-butylsulfinylaldimines in the presence of Cs_2CO_3 as the base in THF.[61] In this context, a series of chiral aziridines were isolated in excellent yields and low-to-good diastereoselectivities of up to 74% de, as shown in Scheme 41. Indeed, although moderate levels of diastereocontrol were observed, the fact that extremely high levels of conversion were obtained in a process, which did not rely on DMSO as solvent and strong bases was encouraging.



Ar = *p*-$MeOC_6H_4$: 97% de = 74%
Ar = *p*-ClC_6H_4: 96% de = 56%
Ar = 2,6-$Cl_2C_6H_3$: 94% de = 54%
Ar = Ph: 95% de = 48%
Ar = 3-Ac-4-OHC_6H_3: 93% de = 60%
Ar = *p*-AcC_6H_4: 89% de = 32%

Scheme 41. Reaction of sulfonium ylide with chiral aryl-substituted *tert*-butylsulfinylaldimines.

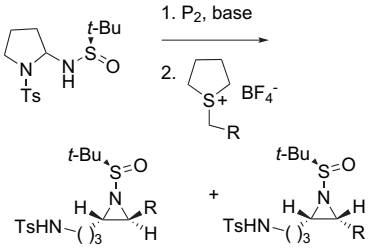
In 2005, Khiar et al. developed other chiral sulfinylaldimines bearing a less sterically demanding substituent, such as an isopropyl group, presenting, in comparison with a *tert*-butyl group, the advantages of lower molecular weight and higher reactivity, which could be a good alternative to the more popular *tert*-butylsulfinyl group.[62] These authors elaborated a comparative study demonstrating that the isopropylsulfinyl group behaved better than the *tert*-butylsulfinyl and *p*-tolylsulfinyl groups, both in terms of reactivity (time for the reaction to be complete) and stereoselectivity in the reaction of chiral sulfinylaldimines with dimethylsulfonium or dimethyloxosulfonium ylide (Scheme 42). As an example, a diastereoselectivity of 70% de was obtained in 48 h in the case of the *tert*-butylsulfinylaldimine, whereas the same diastereoselectivity was achieved with the corresponding isopropylsulfinylaldimine in only 1 h.



R= *p*-Tol, n = 0: time = 2 h, de = 20%
R= *p*-Tol, n = 1: time = 48 h, de = 46%
R= *t*-Bu, n = 0: time = 48 h, de = 70%
R= *t*-Bu, n = 1: time = 168 h, de = 90%
R= *i*-Pr, n = 0: time = 1 h, de = 70%
R= *i*-Pr, n = 1: time = 48 h, de = 46%

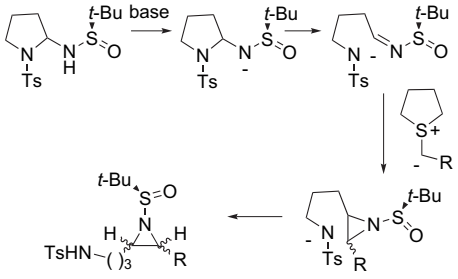
Scheme 42. Reactions of dimethylsulfonium or dimethyloxosulfonium ylide with chiral *N*-sulfinyl aldimines.

In 2007, Aggarwal and Kokotos reported the asymmetric reaction of chiral *tert*-butylsulfinyl aminals as precursors of imines with aryl-, allyl-, and amide-stabilised sulfur ylides, which led to the corresponding aziridines in high yields and with good stereoselectivities of up to 92:8 *trans*/*cis* and >90% de (Scheme 43).[63]



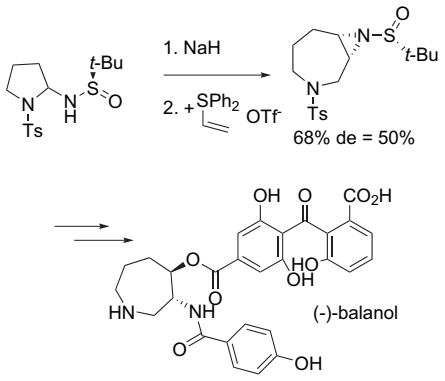
R = *p*-$MeOC_6H_4$: 43% *trans/cis* = 82:18
de (*trans*) = 30% de (*cis*) > 90%
R = *p*-ClC_6H_4: 66% *trans/cis* = 92:8
de (*trans*) = 70% de (*cis*) > 90%
R = $CH{=}CH_2$: 73% *trans/cis* = 57:43
de (*trans*) > 90% de (*cis*) > 90%
R = CONHPh: 63% *trans/cis* = 52:48
de (*trans*) > 90% de (*cis*) > 90%

proposed mechanism:



Scheme 43. Reaction of sulfur ylides with chiral *tert*-butylsulfinyl aminals.

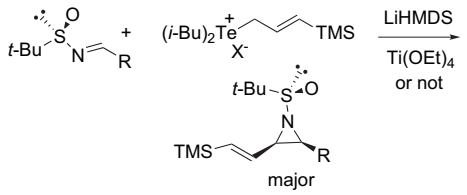
This methodology was applied by Aggarwal et al. to the total synthesis of the protein kinase C inhibitor, (−)-balanol.[64] The key step of this synthesis was constituted by the reaction of diphenyl vinyl sulfonium triflate salt with the chiral aminal described above in the presence of NaH as the base, providing the corresponding aziridine in good yield and moderate diastereoselectivity (Scheme 44).



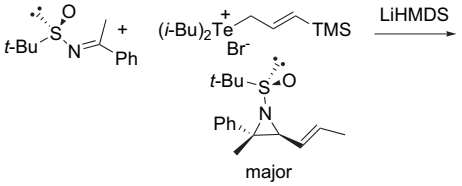
Scheme 44. Synthesis of (−)-balanol.

On the other hand, asymmetric aziridinations have also been achieved by Tang et al. by using telluronium allyl ylides instead of sulfur ylides.[65] They showed that the reaction of various allylic telluronium ylides with enantiopure *N*-*tert*-butylsulfinyl imines provided the corresponding optically active *cis*-2-substituted vinylaziridines with excellent diastereoselectivities and in good-to-excellent yields. The best results were obtained in the presence of LiHMDS as the base combined with $Ti(OEt)_4$ as an additive. The procedure was applied to a wide range of imines such as aryl and heteroaryl aldimines as well as alkyl and α,β-unsaturated aldimines, as shown in Scheme 45. Furthermore, the reaction was operative with ketimines, giving the corresponding *cis*-aziridines in high yields and excellent diastereoselectivities. In order to explain the diastereoselectivity of the reaction, these authors have proposed the mechanism depicted in Scheme 45, in which the telluronium ylide attacks the imine to form the intermediates **H** and **I**. Transformation of these intermediates into the corresponding intermediates **J** and **K** by rotation was followed by an intramolecular anti-elimination to afford the vinylaziridine. Obviously, intermediate **H** was favoured over intermediate **I**, due to steric hindrance, and thus, the *cis*-aziridine formed preferentially.

The second methodology to prepare chiral aziridines by condensation of ylides onto imines consists of using chiral sulfur ylides as the chiral auxiliaries. Several groups have demonstrated ingenious catalytic asymmetric approaches to chiral aziridines based on the generation of chiral *S*-ylides. For example, Aggarwal et al., via the reaction of chiral sulfides with rhodium metallocarbenes, have reported on a range of substituted heterocycles, which could be generated in high yields and with excellent control of both absolute and relative stereochemistry. In particular, these workers have developed a reliable method, which generated diazo compounds in situ.[66] This approach was based on the Bamford–Stevens reaction, which uses tosylhydrazone salts as diazo precursors. In the presence of phase-transfer catalysts,[67] the tosylhydrazone salts are cleanly converted into the diazo compounds, which are trapped by a transition-metal catalyst, resulting in the formation of a metal–carbene complex. This complex subsequently reacts with a chiral sulfide to form the corresponding chiral sulfur ylide, which finally reacts with an imine to furnish the expected aziridine. This methodology was employed as the key step in a synthesis of the taxol side chain.[68] As summarized in Scheme 46, the reaction between an

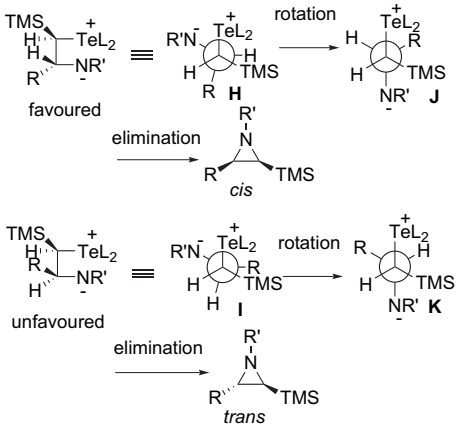


with X = Br and with $Ti(OEt)_4$:
R = Ph: 98% *cis*/*trans* = 95/5 de (*cis*) > 98%
R = 1-Naph: 98% *cis*/*trans* = 96/4 de (*cis*) > 98%
R = 2-Fu: 93% *cis*/*trans* = 95/5 de (*cis*) = 94%
R = *p*-ClC_6H_4: 96% *cis*/*trans* = 95/5 de (*cis*) > 98%
R = *p*-$CF_3C_6H_4$: 98% *cis*/*trans* = 95/5 de (*cis*) > 98%
R = *p*-Tol: 98% *cis*/*trans* = 95/5 de (*cis*) = 97%
R = (*E*)-CH=CHPh: 88% *cis*/*trans* = 91/9 de (*cis*) = 88%
R = (*E*)-CH(Me)=CHPh: 98% *cis*/*trans* = 96/4 de (*cis*) = 87%
R = (*E*)-CH(Et)=CH(*i*-Pr): 91% *cis*/*trans* = 92/8 de (*cis*) = 86%
with X = BPh_4 and without $Ti(OEt)_4$:
R = Cy: 83% *cis*/*trans* = 90/10 de (*cis*) > 98%
R = *t*-Bu: 53% *cis*/*trans*> 97/3 de (*cis*) > 98%



76% *trans*/*cis* = 97/3 de (*trans*) > 98%

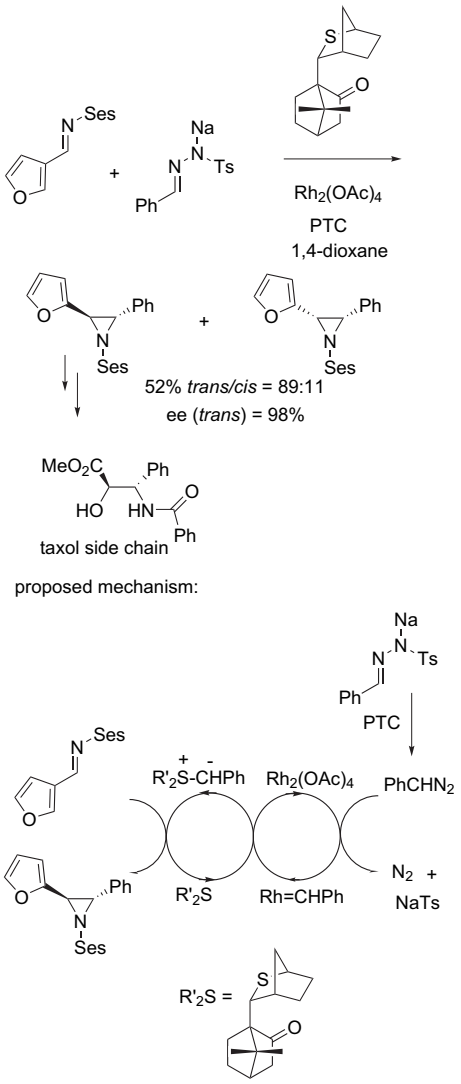
proposed mechanism:



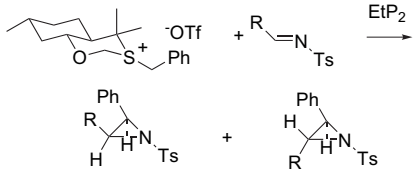
Scheme 45. Reactions of allylic telluronium ylides with chiral *N*-*tert*-butylsulfinyl imines.

N-trimethylsilylethylsulfonyl imine and benzaldehyde tosylhydrazone salt in the presence of a phase-transfer catalyst, $Rh_2(OAc)_4$, and a catalytic quantity of a chiral sulfide, which was recycled during the process, afforded the desired aziridine in good yield as a 89:11 *trans*/*cis* diastereomeric mixture, in which the major trans-diastereomer was obtained with an enantiomeric excess of 98%.

On the other hand, Eliel's oxathiane has been used by Solladié-Cavallo et al. as the precursor of a diastereo- and enantiopure sulfur ylide, employed as the chiral auxiliary for the asymmetric synthesis of *N*-tosyl aziridines.[69] Thus, the aziridines were formed as *trans*/*cis* diastereomeric mixtures by reaction of the sulfonium salt derived from Eliel's oxathiane with various tosylimines in the presence of a phosphazene base (EtP_2) to generate the ylide. Both corresponding *cis*- and *trans*-aziridines were obtained with exceptionally high enantiomeric purities of >99% ee, as shown in Scheme 47. In this case, the chiral auxiliary was used in a stoichiometric amount, but was recovered in high yield and re-used.



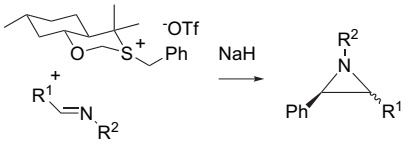
Scheme 46. Synthesis of taxol side chain by aziridination of imine with chiral in situ generated sulfur ylide.



R = 9-Anth: 88% *cis/trans* = 55/45
ee (*cis*) = 100% ee (*trans*) = 99%
R = 9-Phen: 75% *cis/trans* = 53/47
ee (*cis*) = 100% ee (*trans*) = 100%
R = 1-Naph: 70% *cis/trans* = 30/70
ee (*cis*) = 100% ee (*trans*) = 99%
R = *t*-Bu: 80% *cis/trans* = 100/0
ee (*cis*) = 99%
R = Cy: 60% *cis/trans* = 96/4
ee (*cis*) = 100% ee (*trans*) = 100%
R = Ph: *cis/trans* = 60/40
ee (*trans*) = 99%
R = *p*-$NO_2C_6H_4$: *cis/trans* = 50/50
ee (*cis*) = 100% ee (*trans*) = 99%
R = *p*-$MeOC_6H_4$: *cis/trans* = 70/30
ee (*cis*) = 100%

Scheme 47. Reaction of chiral Eliel's oxathiane-derived ylide with tosylimines by using EtP_2 as base.

Even though this method was amenable to gram-quantity synthesis, and the chiral auxiliary could easily be recovered and re-used, the practicality of this procedure was limited by the use of the sensitive and expensive phosphazene base. In this context, Hamersak et al. have recently developed an application of this method for the asymmetric synthesis of *N*-Ses, *N*-Boc, and *N*-Ts disubstituted aziridines by using sodium hydride as the base.[70] As shown in Scheme 48, NaH was successfully used as a substitute for the expensive and sensitive base EtP_2, without any major influence on the yield, enantioselectivity or diastereoselectivity.

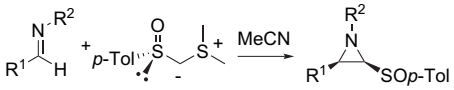


R^1 = Ph, R^2 = Ts: 60% *cis/trans* = 60/40 ee (*trans*) = 98%
R^1 = PMP, R^2 = Ts: 57% *cis/trans* = 58/42
ee (*cis*) = 98%
R^1 = *t*-Bu, R^2 = Ts: 68% *cis/trans* = 100/0
ee (*cis*) = 97%
R^1 = 1-Naph, R^2 = Ts: 60% *cis/trans* = 31/69
ee (*cis*) = 96% ee (*trans*) = 96%
R^1 = 2-Phen, R^2 = Ts: 76% *cis/trans* = 45/55
ee (*cis*) = 95% ee (*trans*) = 96%
R^1 = Ph, R^2 = Ses: 68% *cis/trans* = 44/56 ee (*trans*) > 99%
R^1 = PMP, R^2 = Ses: 47% *cis/trans* = 63/37
ee (*cis*) > 99% ee (*trans*) = 98%
R^1 = 1-Naph, R^2 = Ses: 63% *cis/trans* = 24/76
ee (*cis*) = 97% ee (*trans*) = 98%
R^1 = Ph, R^2 = Boc: 60% *cis/trans* = 10/90
ee (*trans*) = 97%
R^1 = PMP, R^2 = Boc: 31% *cis/trans* = 9/91
ee (*trans*) = 96%
R^1 = 1-Naph, R^2 = Boc: 75% *cis/trans* = 2/98
ee (*trans*) = 96%

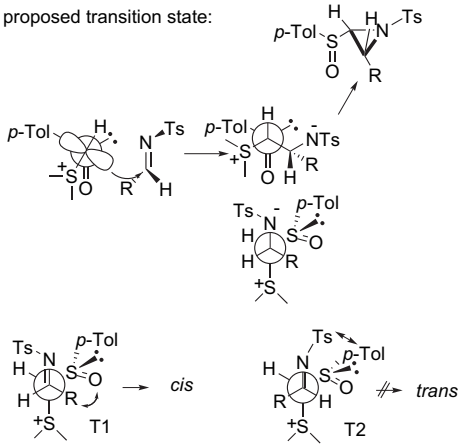
Scheme 48. Reaction of chiral Eliel's oxathiane-derived ylide with *N*-protected imines by using NaH as base.

In 2007, Midura designed a new type of chiral sulfur ylide, containing an enantiopure sulfinyl group bonded to the ylidic carbon atom.[71] Thus, (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide reacted with *N*-tosylimines to give the corresponding *cis*-sulfinyl aziridines with full enantio- and diastereoselectivity and high yields, as shown in Scheme 49. The high facial selectivity observed in the aziridination reactions could be explained by the reasonable assumption that the ylide adopted the conformation depicted in Scheme 49, which determined the stereochemical course of the process. The exclusive formation of *cis*-isomers was probably caused by the difference in the ease of betaine formation. Transition state T2 leading to an *anti* betaine is disfavoured due to repulsive interactions between the sulfinyl moiety of the ylide and the tosyl substituent on the nitrogen. This interaction in T2 must be much stronger than the interaction between the sulfinyl group and the R group of the imine in the transition state T1 leading to a *syn* betaine (Scheme 49).

In 2007, Gais et al. reported the generation of conjugated cyclic and acyclic allyl aminosulfoxonium ylides and their application to the asymmetric aziridination of *N*-*tert*-butylsulfonyl imino esters, which gave enantio-enriched alkenyl- and cycloalkenyl-aziridine carboxylates for which only a few asymmetric syntheses had been described.[72] When the ylides were generated from aminosulfoxonium-substituted β,γ-unsaturated α-amino acids by treatment with DBU, they provided, by reaction with the in situ-generated *N*-*tert*-butylsulfonyl imino ester, the corresponding *cis*-alkenylaziridinecarboxylates as major diastereomers in excellent yields, good diastereoselectivities and



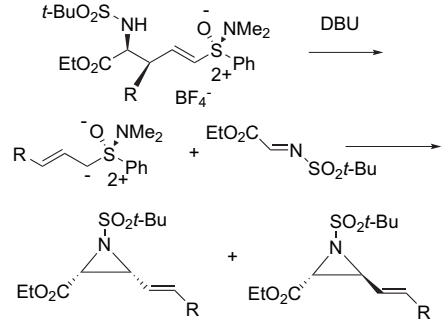
R^1 = Ph, R^2 = Ts: 88% *cis*/*trans* = 100:0 de = 100%
R^1 = *p*-BrC_6H_4, R^2 = Ts: 92% *cis*/*trans* = 100:0 de = 100%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Ts: 93% *cis*/*trans* = 100:0 de = 100%
R^1 = *n*-Bu, R^2 = Ts: 72% *cis*/*trans* = 100:0 de = 100%
R^1 = *i*-Pr, R^2 = Ts: 81% *cis*/*trans* = 100:0 de = 100%
R^1 = Ph, R^2 = *p*-TolS(O): 76% *cis*/*trans* = 90:10 de = 100%
R^1 = R^2 = Ph: 0%



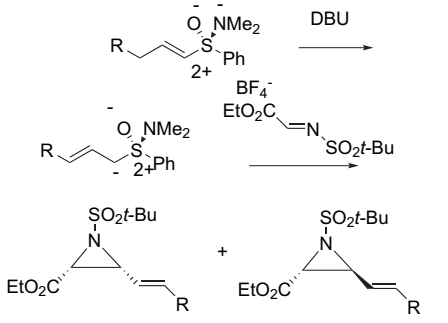
Scheme 49. Reaction of (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide with *N*-tosylimines.

moderate-to-high enantioselectivities (Scheme 50). The formation of these aziridines was also possible starting from 1-alkenyl aminosulfoxonium salts, which gave, upon treatment with DBU, the corresponding 1-alkenyl aminosulfoxonium ylides, which reacted with the externally added *N*-*tert*-butylsulfonyl imino ester. The diastereo- and enantioselectivities for the formation of the aziridines from the 1-alkenyl salts differed significantly, however, from those starting from the amino acid derivatives. Indeed, as shown in Scheme 50, the aziridines were obtained in good yields, albeit with low *cis*/*trans* diastereoselectivities and moderate enantioselectivities. In addition, this methodology could be applied to the synthesis of cycloalkenylaziridinecarboxylates by the reaction of cyclic allyl aminosulfoxonium ylides with imino ester in good yields, low diastereoselectivities and medium-to-high enantioselectivities (Scheme 50).

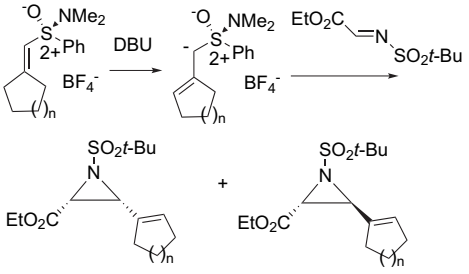
In addition, Sunoj and Janardanan have recently reported a density functional theory investigation on the factors controlling enantio- and diastereoselection in asymmetric aziridination reactions by the addition of chiral bicyclic sulfur ylides to substituted aldimines.[73] High levels of enantioselection were predicted towards the formation of (2*S*,3*S*)-*cis*- and (2*R*,3*S*)-*trans*-aziridines by the addition of stabilised ylide (Ac), respectively, to SO_2Me and CO_2Me protected aldimines. Similarly, high enantioselectivity was predicted for the formation of (2*S*,3*R*)-*cis*-aziridines from semi-stabilized (Ph) ylide. This study highlighted that a correct prediction of the extent of enantioselection requires a knowledge of the activation barriers for the elementary steps beyond the initial addition step. In the case of stabilized ylides, the ring closure was found to be crucial in controlling enantio- and diastereoselection. A cumulative effect of electronic as well as other weak interactions was identified as factors contributing to the relative energies of transition states, leading to enantio- and diastereomeric products for the stabilized ylide addition to aldimines. On the contrary, steric control appeared to be quite dominant with semistabilized ylide addition.



R = Ph: 94% *trans*/*cis* = 93:7 ee (*cis*) > 98% ee (*trans*) = 30%
R = *i*-Pr: 91% *trans*/*cis* = 91:9 ee (*cis*) = 92% ee (*trans*) = 26%
R = Cy: 93% *trans*/*cis* = 90:10 ee (*cis*) = 71% ee (*trans*) = 48%
R = *t*-Bu: 94% *trans*/*cis* = 91:9 ee (*cis*) = 50% ee (*trans*) = 5%



R = *i*-Pr: 70% *cis*/*trans* = 64:36 ee (*cis*) = 76% ee (*trans*) = 49%
R = Cy: 68% *cis*/*trans* = 70:30 ee (*cis*) = 47% ee (*trans*) = 45%
R = Me: 65% *cis*/*trans* = 60:40 ee (*cis*) = 65%

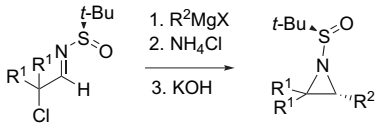


n = 1: 70% *cis*/*trans* = 60:40 ee (*cis*) = 79% ee (*trans*) = 90%
n = 2: 73% *cis*/*trans* = 60:40 ee (*cis*) = 76% ee (*trans*) = 56%
n = 3: 71% *cis*/*trans* = 60:40 ee (*cis*) = 78% ee (*trans*) = 57%
n = 4: 66% *cis*/*trans* = 50:50 ee (*cis*) = 70% ee (*trans*) = 25%

Scheme 50. Reactions of chiral allyl aminosulfoxonium ylides with imino ester.

2.2.4. Miscellaneous reactions. Several groups have proposed other various methods to prepare chiral aziridines starting from imines. As an example, De Kimpe et al. have reported a novel stereoselective synthesis of chiral 2-arylated and 2-alkylated aziridines on the basis of the reaction of α-chloro *N*-(*tert*-butanesulfinyl)-aldimines with Grignard reagents, affording β-chloro *N*-sulfinamides in good yields as non-isolated intermediates.[74] The latter compounds were ring closed towards the corresponding *N*-sulfinyl aziridines in a high-yielding, one-pot reaction, or after a separate treatment with a base in some cases. As shown in Scheme 51, high levels of diastereoselectivities of up to 92% de were observed. This diastereoselectivity was explained via the coordinating ability of the α-chloro atom with magnesium, resulting in an opposite stereochemical outcome to that generally observed for non-functionalised *N*-sulfinyl imines.

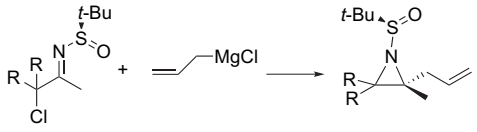
Moreover, these workers have attempted to extend this methodology to α-chloro *N*-(*tert*-butanesulfinyl)ketimines, but, in this case, treatment of the latter imines with a Grignard reagent led to



$R^1 = R^2$ = Et, X = Br: 82% de = 84%
R^1 = Et, R^2 = Ph, X = Cl: 77% de = 92%
R^1 = Et, R^2 = CH=CH_2, X = Cl: 83% de = 86%
R^1 = Et, R^2 = CH_2-CH=CH_2, X = Cl: 90% de = 24%
R^1,R^1 = $(CH_2)_5$, R^2 = Et, X = Br: 82% de = 84%
R^1 = Et, R^2 = CH_2-CH=CH_2, X = Cl: 90% de = 24%
R^1,R^1 = $(CH_2)_5$, R^2 = Ph, X = Cl: 43% de = 40%
R^1 = Et, R^2 = CH_2-CH=CH_2, X = Cl: 90% de = 24%
R^1,R^1 = $(CH_2)_5$, R^2 = CH=CH_2, X = Br: 85% de = 72%
R^1 = Et, R^2 = CH_2-CH=CH_2, X = Cl: 90% de = 24%
R^1,R^1 = $(CH_2)_5$, R^2 = CH_2-CH=CH_2, X = Cl: 84% de = 40%

Scheme 51. Reaction of chiral α-chloro *N*-sulfinyl aldimines with Grignard reagents.

the synthesis of the corresponding chiral *N*-(1-substituted cyclopropyl)-*tert*-butanesulfinamides in good yields and diastereoselectivities via 1,3-dehydrohalogenation and subsequent addition of the Grignard reagent to the intermediate cyclopropylideneamine.[75] Only in the case of allylmagnesium chloride did the reaction lead to the corresponding aziridines in high yields and diastereoselectivities of up to 90% de, as shown in Scheme 52.



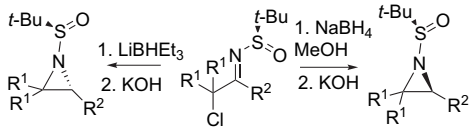
R = Me: 95% de > 90%
R = Et: 91% de = 90%
R,R = $(CH_2)_5$: 83% de = 86%

Scheme 52. Reaction of chiral α-chloro *N*-sulfinyl ketimines with allylmagnesium chloride.

In a complementary context, these authors have shown that the reduction of α-chloro *N*-(*tert*-butylsulfinyl)imines led to the corresponding chiral aziridines in good-to-excellent yields.[76] Therefore, upon reduction of (R_S)-*N*-(*tert*-butylsulfinyl)imines with $NaBH_4$ in THF, in the presence of MeOH, the intermediate (R_S,*S*)-β-chloro sulfinamides were formed in excellent yields and diastereoselectivities (>96% de). A simple treatment of the latter sulfinamides with KOH afforded the corresponding (R_S,*S*)-*N*-(*tert*-butylsulfinyl)aziridines as almost single diastereomers in quantitative yields, as shown in Scheme 53. On the contrary, the epimers, (R_S,*R*)-*N*-(*tert*-butylsulfinyl)aziridines, were synthesised by changing the reducing agent from $NaBH_4$ to $LiBHEt_3$. Thus, (R_S,*R*)-*N*-(*tert*-butylsulfinyl)aziridines were achieved in good yields and diastereoselectivities of up to 84% de by reduction of (R_S)-*N*-*tert*-butylsulfinyl α-halo imines performed with $LiBHEt_3$ and subsequent treatment with KOH.

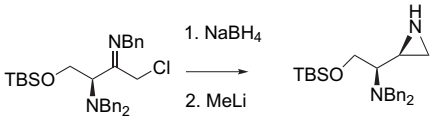
Similarly, Concellon et al. have recently reported the synthesis of a chiral amino aziridine by reduction of its corresponding serine-derived chiral α-amino ketimine with $NaBH_4$ and further treatment with MeLi.[77] This reduction process was performed with total diastereoselectivity, as depicted in Scheme 54.

In 2008, Hodgson et al. developed the reaction of *N*-(2-chloroethylidene)-*tert*-butylsulfinamide with various organocerium reagents, which provided an efficient and highly diastereoselective access to terminal *N*-*tert*-butylsulfinyl aziridines.[78] Alkyl- and allylcerium reagents added with essentially complete diastereocontrol, whereas the reaction was less diastereoselective for aryl-, heteroaryl- and alkynyl-cerium reagents. In order to demonstrate the applicability of this reaction in asymmetric synthesis, *n*-$DecCeCl_2$ was added to a chiral imine to give the corresponding chiral aziridine in good yield and high diastereoselectivity of 94% de (Scheme 55).



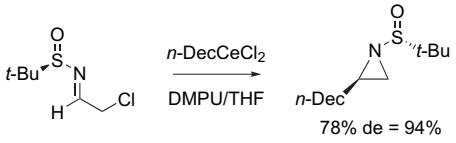
with $NaBH_4$:
R^1 = Me, R^2 = H: 95% ee = 100%
R^1 = Me, R^2 = Ph: 95% ee = 100%
R^1 = R^2 = Me: 88% de = 96%
R^1 = Et, R^2 = Me: 92% de = 98%
R^1 = H, R^2 = Ph: 90% de > 96%
R^1 = H, R^2 = *p*-ClC_6H_4: 89% de > 96%
R^1 = H, R^2 = *p*-BrC_6H_4: 91% de > 96%
with $LiBHEt_3$:
R^1 = R^2 = Me: 61% de = 56%
R^1 = Et, R^2 = Me: 57% de = 60%
R^1 = H, R^2 = Ph: 62% de = 74%
R^1 = H, R^2 = *p*-ClC_6H_4: 66% de = 78%
R^1 = H, R^2 = *p*-BrC_6H_4: 71% de = 84%

Scheme 53. Reductions of chiral α-chloro *N*-sulfinyl imines.



77% de > 95%

Scheme 54. Reduction of chiral α-amino ketimine.

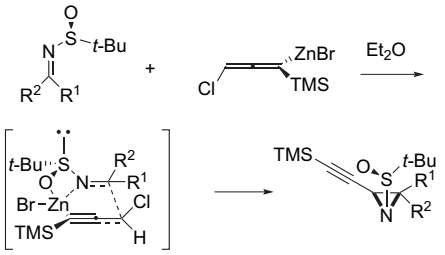


78% de = 94%

Scheme 55. Reaction of organocerium reagent with chiral *N*-(2-chloroethylidene)-*tert*-butylsulfinamide.

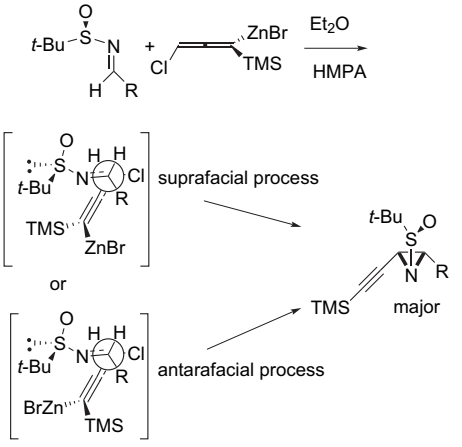
Despite their great potential, relatively little investigation has been undertaken so far on the synthesis of chiral alkynylaziridines. In this context, Ferreira and Chemla have developed a concise and efficient synthesis of enantiopure *trans*-ethynyl *N*-*tert*-butylsulfinyl aziridines based on the condensation of the allenylzinc species[79] derived from 3-chloro-1-trimethylsilylpropyne onto *N*-*tert*-butylsulfinyl aldimines and ketimines (Scheme 56).[80] The general excellent stereoselectivity of >96% de was shown to result from a high kinetic resolution in the reaction of the racemic allenylzinc reagent with enantiopure *N*-*tert*-butylsulfinyl imines. This kinetic resolution was shown to be the consequence of the zinc being coordinated by both the oxygen and the nitrogen atoms of the sulfinyl imine in a chelate-type, four-membered transition state (Scheme 56).

It was demonstrated that HMPA had a dramatic influence on the stereochemical outcome of the condensation of the allenylzinc reagent onto chiral *N*-*tert*-butylsulfinyl aldimines.[81] Indeed, performing the reaction in the presence of 60 equiv of HMPA in Et_2O allowed the corresponding *cis*-ethynylaziridines to be formed as the major products with good-to-high selectivities (Scheme 57). The cis selectivity was postulated to result from a high kinetic resolution through a synclinal transition state in a supra- or antarafacial S_E2' process, which has been supported by semiempirical AM1 and MM2 calculations. Furthermore, after chromatographic separation over silica gel, the major *cis*-aziridines were obtained as diastereo- and enantiomerically pure products (>96% de and >99% ee).



R^1 = H, R^2 = *n*-Pr: 70% *trans/cis* = 90:10 de > 96%
R^1 = H, R^2 = (*E*)-CH=CHMe: 67% *trans/cis* = 94:6 de > 96%
R^1 = H, R^2 = *i*-Pr: 64% *trans/cis* = 96:4 de > 96%
R^1 = H, R^2 = Cy: 56% *trans/cis* = 90:10 de > 96%
R^1 = H, R^2 = Ph: 58% *trans/cis* = 91:9 de > 96%
R^1 = Me, R^2 = Ph: 54% *trans/cis* = 91:9 de > 96%

Scheme 56. Reaction of allenylzinc reagent with chiral *N*-*tert*-butylsulfinyl imines.

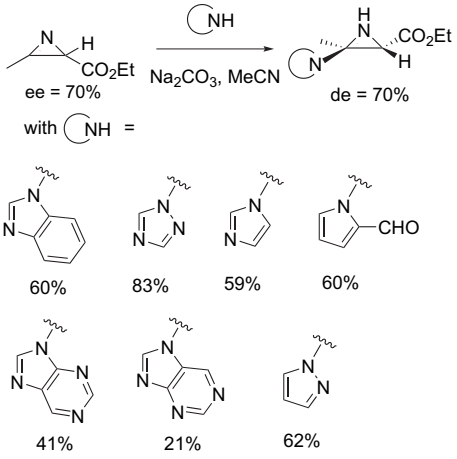


R = Me: 64% *cis/trans* = 89:11 de > 96%
R = *n*-Pr: 54% *cis/trans* = 84:16 de > 96%
R = *n*-Hept: 56% *cis/trans* = 78:22 de > 96%
R = (*E*)-CH=CHMe: 55% *cis/trans* = 84:16 de > 96%
R = (*E*)-CH=CH(*n*Pent): 62% *cis/trans* = 71:29 de > 96%
R = (*E*)-CH=CHPh: 56% *cis/trans* = 87:13 de > 96%
R = $(CH_2)_2$Ph: 50% *cis/trans* = 71:29 de > 96%
R = C≡C(*n*Pent): 60% *cis/trans* = 73:27 de > 96%

Scheme 57. Reaction of allenylzinc reagent with chiral *N*-*tert*-butylsulfinyl aldimines in the presence of HMPA.

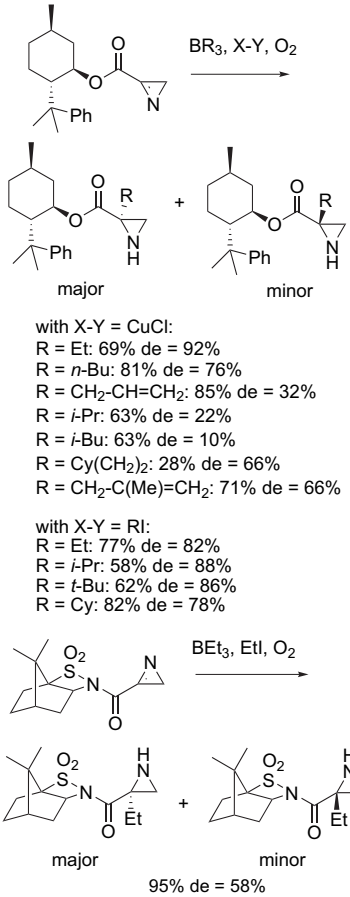
2.3. Addition to azirines

Azirines (three-membered cyclic imines) correspond to the smallest nitrogen-unsaturated heterocyclic system, with two carbon atoms and one double bond in a three-membered ring. Substituted azirines are versatile compounds,[82] and have been used for the preparation of various substituted aziridines. The chemistry of these compounds is dominated by processes in which the strain of the three-ring system is relieved. Indeed, the pronounced reactivity of these compounds is due to their ring strain, the electron-rich nature of the C=N bond and the nitrogen lone pair. Asymmetric nucleophilic addition to azirines is a potentially attractive entry to enantio-enriched aziridines. As an example, Alves et al. have developed nucleophilic additions of nitrogen heterocycles to a chiral 2*H*-azirine-2-carboxylic ester, giving access to optically active aziridine esters.[83] Thus, the relatively non-activated chiral 2*H*-azirine-2-carboxylic ester depicted in Scheme 58 was used as an electrophile in addition reactions to five-membered ring and five-fused aromatic nitrogen heterocycles, providing the corresponding aziridine esters in moderate-to-good yields and with excellent diastereoselectivity.



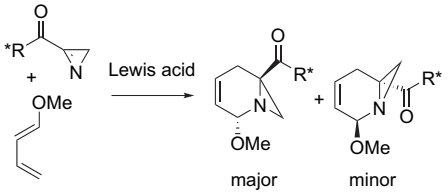
Scheme 58. Reaction of nitrogen heterocycles with chiral 2*H*-azirine-2-carboxylic ester.

A new entry to enantio-enriched aziridines has been reported by Somfai et al. on the basis of an asymmetric radical addition of trialkylboranes to various chiral 2*H*-azirine-3-carboxylates.[84] In particular, high diastereoselectivities of up to 82% de were obtained by using 8-phenylmenthol-derived azirine as the chiral auxiliary, which was reacted with various trialkylboranes (Scheme 59). In comparison, another chiral auxiliary, such as Oppolzer's sultam-derived azirine, gave a better yield, albeit with a lower diastereoselectivity (Scheme 59). It was shown that performing the reaction in the presence of CuCl as a Lewis acid could further increase the diastereoselectivity of the reaction.

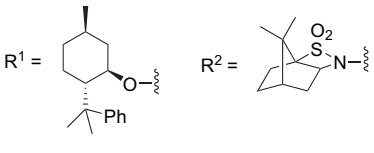


Scheme 59. Radical additions of trialkylboranes to chiral 2*H*-azirine-3-carboxylates.

The hetero Diels–Alder reaction is an exceptionally powerful synthetic method for the construction of six-membered heterocycles.[85] In one single transformation, up to four new stereocentres with defined stereochemistry can be formed. By applying azirines as dienophiles, it is possible to form highly functionalised products with a fused [4.1.0] ring system as well as polycyclic structures incorporating the same fused subunit. The aza-Diels–Alder reactions between azirines and many dienes are known to give products with complete regio- and *endo*-selectivities.[86] The azirines are, despite their ring strain, generally poor dienophiles in normal electron-demand Diels–Alder reactions unless substituted by an activating group, such as an ester, amide, or phosphonate group. In order to achieve control of the absolute stereochemistry of the formed stereocentres, various chiral azirines have been employed as chiral auxiliaries. As an example, Somfai et al. have developed the asymmetric aza-Diels–Alder reactions of 8-phenylmenthol-derived azirine and Oppolzer's sultam-derived azirine with 1-methoxy-1,3-butadiene in the presence of a Lewis acid, providing the corresponding highly functionalised tetrahydropyridines.[87] According to the nature of the Lewis acid involved in mediating the cycloaddition, i.e., magnesium and zinc halides as well as lanthanide complexes, dramatic variations in the level of diastereoselectivity were observed, as summarized in Scheme 60. The best results for 8-phenylmenthol-derived azirine were obtained by using $MgBr_2 \cdot OEt_2$ or $ZnCl_2 \cdot OEt_2$ as the Lewis acid, while no selectivity was observed without a Lewis acid. On the other hand, the effect of the Lewis acid on the reaction was not as clear in the case of the sultam azirine, which gave only a moderate diastereoselectivity of up to 40% de when employing $MgBr_2 \cdot OEt_2$ as the Lewis acid.

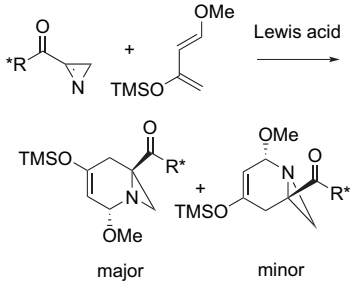


with R* = R^1:
without Lewis acid: 100% de = 0%
with Lewis acid = $MgBr_2.OEt_2$: 82% de = 87%
with Lewis acid = $ZnCl_2.OEt_2$: 62% de = 80%
with Lewis acid = $YbCl_3$: 43% de = 27%
with R* = R^2:
without Lewis acid: 95% de = 21%
with Lewis acid = $MgBr_2.OEt_2$: 38% de = 40%
with Lewis acid = $ZnCl_2.OEt_2$: 69% de = 27%
with Lewis acid = $YbCl_3$: 100% de = 25%

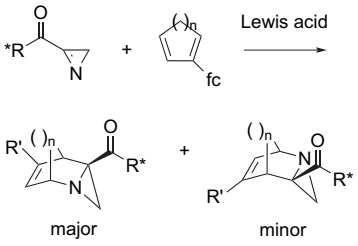


Scheme 60. Lewis acid-mediated aza-Diels–Alder reaction of chiral azirines with 1-methoxy-1,3-butadiene.

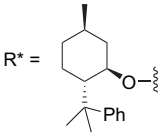
This comparative study between these two chiral auxiliaries clearly demonstrated the 8-phenylmenthol-derived azirine to be the most promising substrate for these reactions. To confirm the usefulness of this process, an additional set of dienes were reacted with this chiral azirine.[87] The dienes chosen were Danishefsky's diene, cyclopentadiene, cyclohexadiene and 2-(trimethylsilyloxy)-1,3-cyclohexadiene, which provided the corresponding aziridines in the presence of $MgBr_2 \cdot OEt_2$ or $ZnCl_2 \cdot OEt_2$ as the Lewis acid with good-to-excellent diastereoselectivities of up to 97% de and useful yields (Scheme 61).



without Lewis acid: 90% de = 30%
with Lewis acid = $MgBr_2.OEt_2$: 56% de = 96%
with Lewis acid = $ZnCl_2.OEt_2$: 31% de = 87%



R' = H, n = 1:
without Lewis acid: 99% de = 8%
with Lewis acid = $MgBr_2.OEt_2$: 88% de = 85%
with Lewis acid = $ZnCl_2.OEt_2$: 99% de = 58%
R' = H, n = 2:
without Lewis acid: 100% de = 20%
with Lewis acid = $MgBr_2.OEt_2$: 0%
with Lewis acid = $ZnCl_2.OEt_2$: 99% de = 80%
R' = OTMS, n = 2:
without Lewis acid: 80% de = 30%
with Lewis acid = $MgBr_2.OEt_2$: 99% de = 97%
with Lewis acid = $ZnCl_2.OEt_2$: 99% de = 34%

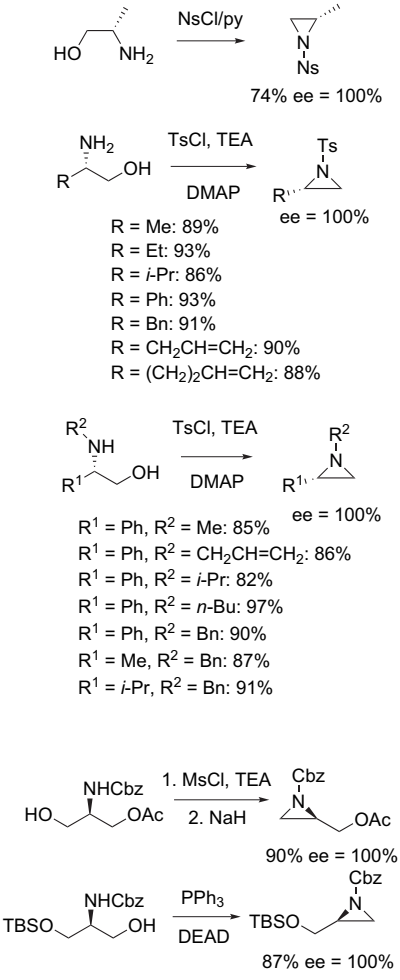


Scheme 61. Lewis acid-mediated aza-Diels–Alder reactions of 8-phenylmenthol-derived azirine with various dienes.

2.4. Aziridination via intramolecular substitution

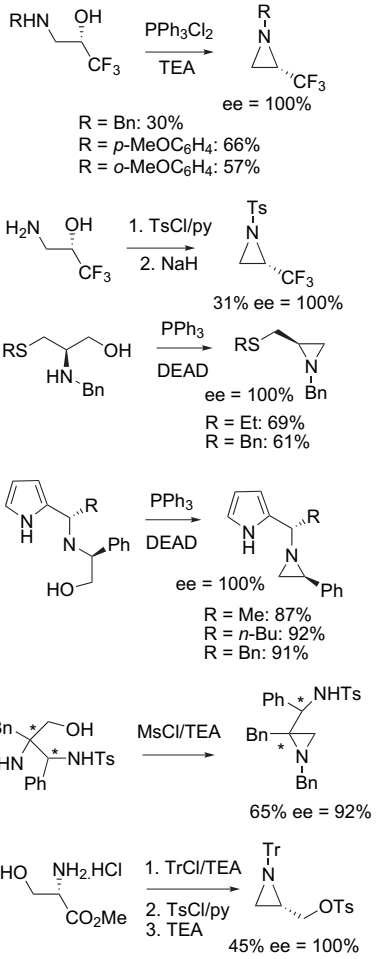
Chiral aziridines can be readily formed by ring closure of chiral appropriately substituted amines. Indeed, the S_N2-type cyclisation of enantiopure 1,2-amino alcohols, 1,2-amino halides, 1,2-azido alcohols, 1,2-amino sulfides, 1,2-amino selenides or epoxides constitutes one of the most versatile and efficient routes to chiral aziridines. Thus, the reaction can be readily achieved when the hydroxyl functional group is converted into a nucleofuge. The intramolecular nucleophilic displacement reaction by either an amide anion or an amine lone pair yields the aziridine ring. This class of aziridine-forming reaction includes the first reaction reported to afford aziridines. Thus, in 1888, Gabriel reported that aziridines could be prepared in a two-step process, by chlorination of ethanolamines with thionyl chloride, followed by alkali-induced cyclisation.[3]

2.4.1. From 1,2-amino alcohols. In recent years, several groups have described the synthesis of relatively simple chiral aziridines starting from 1,2-amino alcohols. As an example, Jabin et al. have performed the reaction of (*S*)-aminopropan-1-ol with NsCl in pyridine, leading to the corresponding enantiopure aziridine in 74% yield, which was further converted into an enantiopure calyx[6]azacryptand (Scheme 62).[88] In the same context, Badia et al. have set up a very efficient and simple procedure for the preparation of chiral *N*-tosyl 2-alkyl aziridines in a single step starting from the corresponding chiral 1,2-amino alcohols.[89] The designed protocol involved a sequential one-pot N-tosylation–O-tosylation and a final intramolecular nucleophilic substitution step, which delivered the target heterocycles in excellent yields, as shown in Scheme 62. The same procedure could also be successfully applied for the preparation of other *N*-alkyl substituted aziridines, although, in this case, an N-alkylation procedure was performed prior to the cyclisation step (Scheme 62). In addition, Borch and Choi have reported a highly efficient and novel synthesis of enantiopure 2-hydroxymethylaziridines using lipase-catalysed desymmetrisation followed by aziridine ring-formation reactions.[90] The results concerning the aziridine ring formation, starting from either the monoacetate of *N*-protected serinol or TBS-protected *N*-protected serinol, are collected in Scheme 62.



Scheme 62. Syntheses of aziridines from simple 1,2-amino alcohols.

Uneyama et al. have developed the synthesis of chiral α-trifluoromethyl aziridines, starting from the corresponding enantiopure α-trifluoromethyl amino alcohols (Scheme 63).[91] Similarly, Braga et al. have reported the synthesis of chiral aziridine sulfides to be used as ligands for palladium-catalysed asymmetric allylic alkylations.[92] Thus, the treatment of α-thioethers of amino alcohols derived from (*R*)-cysteine with triphenylphosphine combined with DEAD led to the expected enantiopure aziridine sulfides in good yields, as shown in Scheme 63. These conditions were also applied by Savoia et al. to enantiopure β-hydroxyamines derived from (*S*)-phenylglycinol bearing a pyrrole moiety, providing the corresponding chiral pyrrole-aziridines in excellent yields (Scheme 63).[93] In 2009, Ghorai et al. reported the asymmetric synthesis of highly substituted aziridines bearing contiguous quaternary and tertiary stereocentres in good yields and high enantioselectivities by treating the corresponding amino alcohols with mesyl chloride and triethylamine (Scheme 63).[94] In addition, Harrity et al. have developed an efficient and practical route to an enantiomerically pure aziridinylmethyl tosylate starting from (*S*)-serine methyl ester hydrochloride.[95] This substrate was successively treated with trityl chloride, tosyl chloride and then triethylamine to give the expected enantiopure aziridine in 45% overall yield, as shown in Scheme 63. This aziridine was a key intermediate to prepare chiral triazolylalanine derivatives.

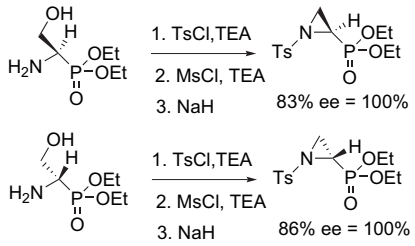


Scheme 63. Syntheses of functionalised aziridines from 1,2-amino alcohols.

The intramolecular S_N2 substitution methodology has been applied to the synthesis of various functionalised chiral aziridines. As an example, in the course of studying the condensation of enantiopure α-trifluoromethylated aziridinyl anions with various electrophiles,

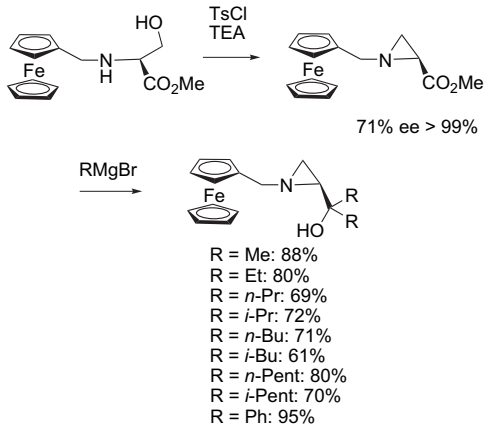
With the aim of preparing chiral β-substituted α-amino phosphonates, Dolence and Roylance have developed a versatile approach for the synthesis of chiral aziridine 2-phosphonates from either (*R*)- or (*S*)-phosphonoserine amino alcohols, which were subsequently

submitted to N-tosylation, O-mesylation and then cyclisation with sodium hydride.[96] As shown in Scheme 64, the expected chiral aziridine 2-phosphonates were isolated in good yields.



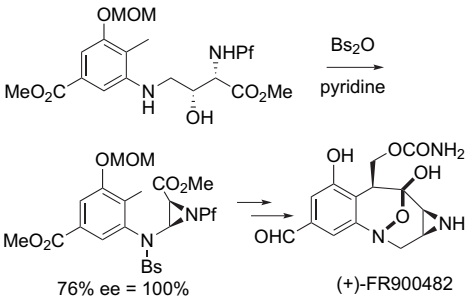
Scheme 64. Synthesis of aziridine 2-phosphonates.

In 2004, Wang et al. reported the synthesis of chiral ferrocenyl aziridino alcohols from L-serine and ferrocenecarboxaldehyde in order to employ them as chiral catalysts for the asymmetric addition of diethylzinc to aldehydes.[97] The *N*-alkyl-L-serine ester depicted in Scheme 65 was converted upon treatment with triethylamine combined with *p*-toluenesulfonyl chloride into its corresponding *N*-alkylaziridine, which was subsequently converted into a series of *N*-ferrocenylmethylaziridin-2-ylmethanols by using RMgBr in good yields.



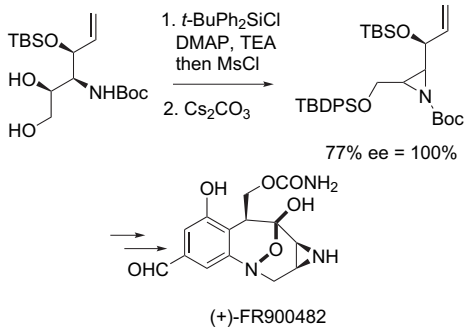
Scheme 65. Synthesis of *N*-ferrocenyl aziridino alcohols.

The asymmetric aziridination based on the use of 1,2-amino alcohols has been applied by several groups for developing total syntheses of various biologically active products. As an example, the key step of a formal enantiospecific synthesis of the antitumour antibiotic, (+)-FR900482, developed by Paleo et al., was constituted by the aziridination of a chiral 1,2-amino alcohol derived from L-vinylglycine mediated by benzenesulfonic anhydride in pyridine (Scheme 66).[98]



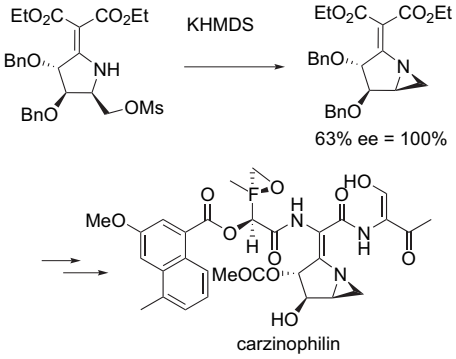
Scheme 66. Synthesis of (+)-FR900482.

In 2008, Trost and O'Boyle reported another total synthesis of (+)-FR900482, involving the asymmetric aziridination of a chiral amino diol depicted in Scheme 67, which was selectively silylated and mesylated.[99] The mesylate was then exposed to caesium carbonate, affording the expected enantiopure aziridine in good yield, which was further transformed into the final (+)-FR900482.



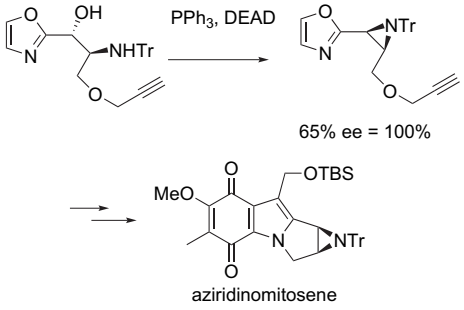
Scheme 67. Synthesis of (+)-FR900482.

In 2003, Terashima et al. developed the total synthesis of carzinophilin, an antitumour antibiotic, which involved as a key step the asymmetric aziridination of a chiral pyrrolidin-2-ylidenemalonate derived from β-D-arabinofuranose.[100] Thus, the treatment of this pyrrolidin-2-ylidenemalonate with KHMDS led to the expected aziridine in good yield, as shown in Scheme 68.



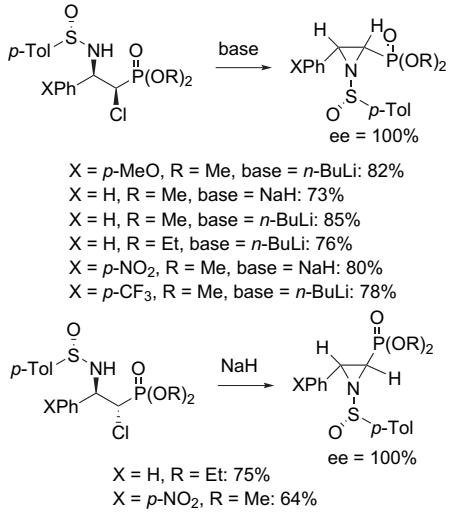
Scheme 68. Synthesis of carzinophilin.

In 2007, Vedejs et al. reported the synthesis of enantiopure aziridinomitosene, which was based on the asymmetric aziridination of a chiral oxazole 1,2-amino alcohol derived from L-serine (Scheme 69).[101]



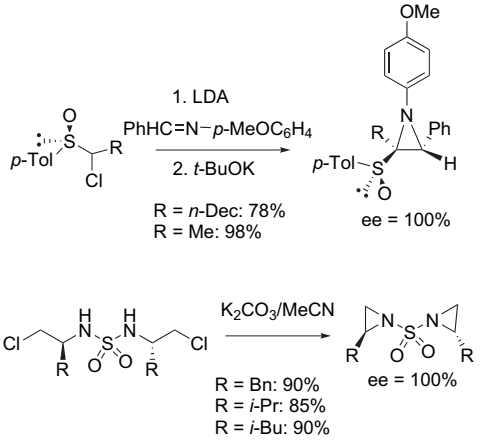
Scheme 69. Synthesis of aziridinomitosene.

2.4.2. From 1,2-amino halides. Davis et al. have reported the synthesis of chiral *N*-sulfinylaziridine 2-phosphonates by cyclisation of the corresponding β-amino α-chlorophosphonates by treatment with NaH or *n*-BuLi as a base.[46] As shown in Scheme 70, high yields and enantioselectivities were obtained in all cases of aziridines.



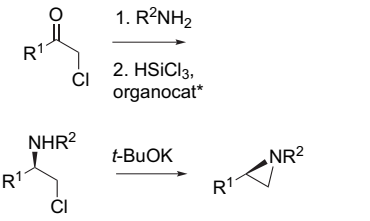
Scheme 70. Syntheses of *N*-sulfinylaziridine 2-phosphonates.

In 2003, Satoh and Fukuda described the synthesis of optically active sulfinylaziridines having a 4-methoxyphenyl group on their nitrogen atom from optically active 1-chloroalkyl *p*-tolyl sulfoxides and an imine derived from benzaldehyde and *p*-anisidine stereoselectively and in good overall yields (Scheme 71).[102] These aziridines were further converted into various α- and β-amino acid derivatives. In the same context, chiral substituted 1,1′-sulfonylbisaziridines were obtained by treatment of the corresponding chiral *N*,*N*′-bis(1-alkyl-2-chloroethyl)sulfamides with K_2CO_3 in high yields (Scheme 71).[103]



Scheme 71. Syntheses of *N*-sulfinyl aziridines and 1,1′-sulfonylbisaziridines.

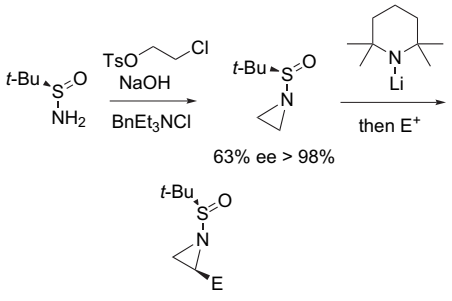
More recently, Kocovsky et al. developed an organocatalytic reductive amination of α-chloroketones, yielding chiral α-chloroamines, which were subsequently treated with *t*BuOK to furnish a wide range of 1,2-diaryl aziridines in excellent yields and enantioselectivities, as shown in Scheme 72.[104]



R^1 = Ph, R^2 = *p*-$MeOC_6H_4$: 98% ee = 95%
R^1 = *p*-FC_6H_4, R^2 = *p*-$MeOC_6H_4$: 98% ee = 94%
R^1 = *p*-ClC_6H_4, R^2 = *p*-$MeOC_6H_4$: 94% ee = 100%
R^1 = R^2 = Ph: 92% ee = 90%
R^1 = *p*-FC_6H_4, R^2 = Ph: 94% ee = 86%
R^1 = *p*-ClC_6H_4, R^2 = Ph: 98% ee = 100%
R^1 = 2-Naph, R^2 = Ph: 92% ee = 90%
R^1 = *p*-Tol, R^2 = *p*-$MeOC_6H_4$: 96% ee = 92%
R^1 = R^2 = *p*-$MeOC_6H_4$: 76% ee = 100%
R^1 = *p*-$CF_3C_6H_4$, R^2 = *p*-$MeOC_6H_4$: 73% ee = 100%
R^1 = 2-Naph, R^2 = *p*-$MeOC_6H_4$: 91% ee = 100%
R^1 = *m*-Tol, R^2 = *p*-$MeOC_6H_4$: 97% ee = 92%
R^1 = *m*-$MeOC_6H_4$, R^2 = *p*-$MeOC_6H_4$: 94% ee = 92%
R^1 = *o*-ClC_6H_4, R^2 = *p*-$MeOC_6H_4$: 96% ee = 96%
R^1 = *o*-ClC_6H_4, R^2 = *p*-ClC_6H_4: 97% ee = 100%
R^1 = *o*-ClC_6H_4, R^2 = *p*-FC_6H_4: 91% ee = 100%

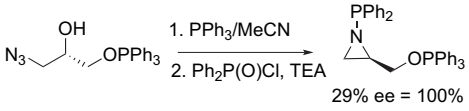
Scheme 72. Synthesis of 1,2-diaryl aziridines.

In addition, a new entry to chiral terminal aziridines was reported by Hodgson et al., in 2008, on the basis of ring lithiation of *N*-*tert*-butylsulfinyl aziridine in good yield and excellent enantioselectivity of up to 98% ee (Scheme 73).[105] The latter chiral aziridine was further submitted to an α-lithiation–electrophile trapping sequence, providing the expected terminal aziridines.



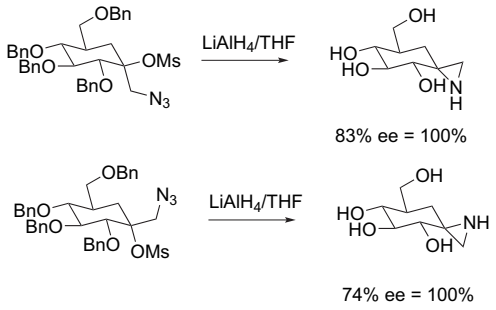
Scheme 73. Synthesis of *N*-*tert*-butylsulfinyl aziridine.

2.4.3. From 1,2-azido alcohols. Chiral aziridines can also be prepared by cyclisation of enantiopure 1,2-azido alcohols. As an example, Sweeney and Cantrill have developed an efficient synthesis of (2*R*)-*N*,*O*-bis(diphenylphosphinyl)-2-(hydroxymethyl)aziridine, starting from the corresponding 1,2-azido alcohol derived from (*R*)-glycidol.[106] This reaction consisted of a two-step process, summarized in Scheme 74. The azide was reacted firstly with triphenylphosphine in refluxing acetonitrile, giving a crude product, which was obtained simply by removal of the solvent. This crude oil was then dissolved in dichloromethane and treated sequentially with triethylamine and diphenylphosphinic chloride, providing the expected aziridine in moderate yield.



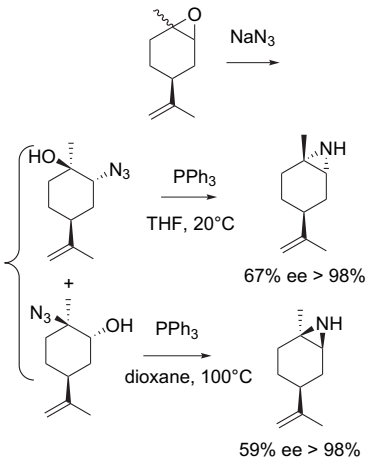
Scheme 74. Synthesis of (2*R*)-*N*,*O*-bis(diphenylphosphinyl)-2-(hydroxymethyl)aziridine.

Glycosidase inhibitors of carbasugar-derived spiroaziridines have been synthesised by Vasella et al. by treatment with $LiAlH_4$ in THF of the corresponding chiral azido methanesulfonates prepared from validoxylamine A-derived cyclohexanone.[107] As shown in Scheme 75, the expected enantiopure spiroaziridines were obtained in high yields.



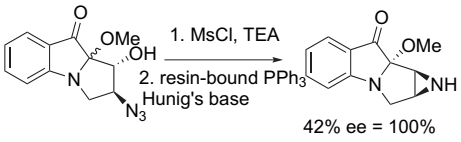
Scheme 75. Syntheses of spiroaziridines.

In 2003, Schirmeister[108] and Kostyanovsky[109] independently studied the synthesis of enantiopure *trans*-aziridine-2,3-dicarboxylates from the corresponding *anti*-3-azido-2-hydroxysuccinates. The desired dimethyl, diethyl, dibenzyl and diallyl *trans*-aziridines were obtained in good yields (70–75%) by treatment of these 1,2-azido alcohols with PPh_3 in DMF. On the other hand, Voronkov et al. have reported a short, efficient and scaleable route to both enantiopure isomers of limonene aziridines, starting from the commercially available mixture of limonene oxides.[110] This methodology was extremely efficient, avoiding the separation of the limonene oxides (and subsequent separate processing of each diastereomer) by either physical or chemical methods. The key to the efficiency of the separation was the exploitation of the differences in rate between the two azido alcohol diastereomers in the ring closure. Indeed, the Staudinger reaction of the secondary azide was much faster, and so it was converted completely into the corresponding *trans*-aziridine at room temperature over a period of 48 h. This resulting *trans*-aziridine was easily separated from the unreacted tertiary azido alcohol by a simple acid–base extraction. Next, the conversion of the tertiary azido alcohol to the corresponding *cis*-aziridine required elevated temperatures and proceeded smoothly in refluxing dioxane over a period of 16 h. Both of the aziridine isomers were obtained in good yields and with enantioselectivities of >98% ee (Scheme 76).



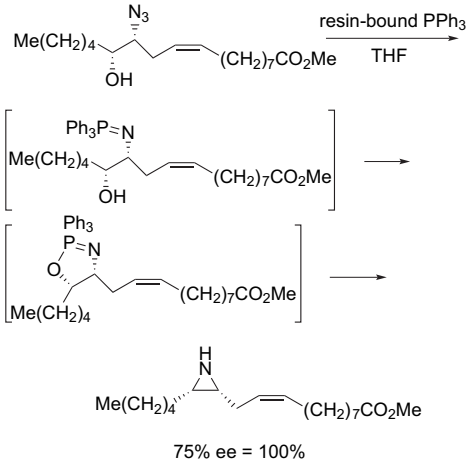
Scheme 76. Synthesis of limonene aziridines.

The last step of the enantioselective synthesis of an aziridinomitosane, accomplished by Miller et al., was constituted by the cyclisation of an enantiopure tricyclic 1,2-azido alcohol depicted in Scheme 77.[111] This reaction was achieved in two steps with resin-bound PPh_3, affording the expected aziridinomitosane with the trans configuration in good yield (Scheme 77).



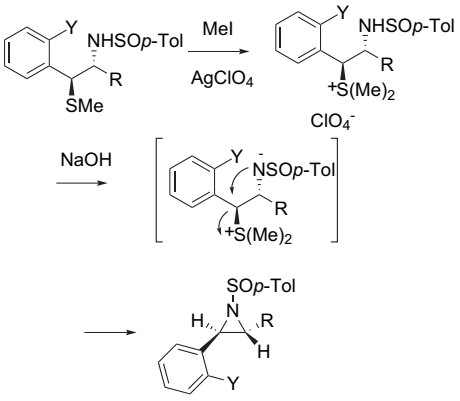
Scheme 77. Synthesis of aziridinomitosane.

In addition, Metzger and Fürmeier have developed the first preparation of chiral fat-derived aziridines, with the twin goals of increasing the variety of interesting fatty compounds with aziridine functions and gaining a deeper insight into their biological properties.[112] The same methodology as described above, based on the use of resin-bound PPh_3, was applied, for example, to the enantiopure azido alcohol derived from chiral methyl vernolate, depicted in Scheme 78. Thus, upon treatment with resin-bound PPh_3, the corresponding unsaturated *cis*-aziridine was isolated in good yield as a single enantiomer, according to the mechanism summarised in Scheme 78. This represented the first enantiomerically pure aziridine based on fats and oils.



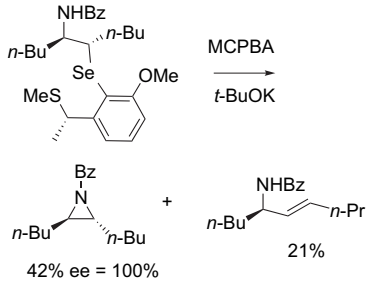
Scheme 78. Synthesis of fat-derived aziridine.

2.4.4. From 1,2-amino sulfides and 1,2-amino selenides. In 2006, Arroyo et al. reported a new entry to optically pure *trans*-2,3-disubstituted *N*-sulfinyl aziridines, starting from 1,2-amino sulfides, involving the formation of a sulfonium salt intermediate followed by intramolecular nucleophilic attack by the sulfinamide nitrogen atom.[113] In this context, a series of chiral aziridines were obtained in high yields and diastereoselectivities of up to 98% de, as shown in Scheme 79.



Scheme 79. Synthesis of *trans*-2,3-disubstituted *N*-sulfinyl aziridines from 1,2-amino sulfides.

Similarly, Tiecco et al. have shown that enantiopure benzoylamino selenides could lead to the formation of the corresponding aziridines upon treatment with *meta*-chloroperbenzoic acid.[114] As shown in Scheme 80, the chiral aziridine was submitted to a spontaneous deselenenylation and isolated in moderate yield, along with the corresponding α,β-unsaturated amide resulting from an elimination process.

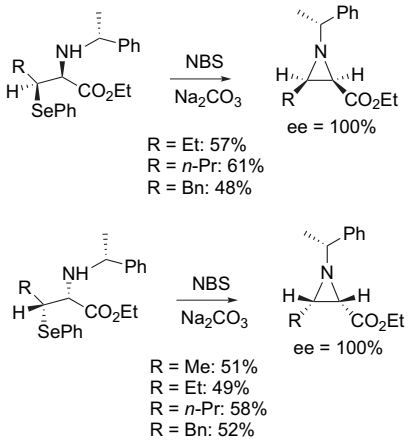


Scheme 80. Synthesis of aziridine from 1,2-amino selenide.

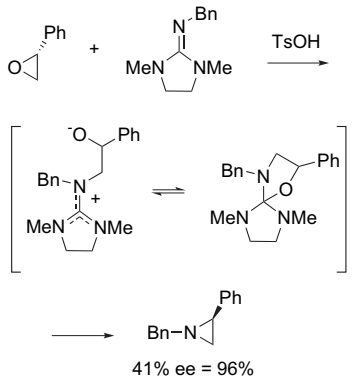
Moreover, the synthesis of a series of enantiopure *cis*-aziridine esters has been developed by Pannecoucke et al. on the basis of the cyclisation of chiral amino selanyl esters induced by the selanyl group activation with either Meerwein's salt or NBS.[115] The best results, collected in Scheme 81, were generally obtained by using NBS.

2.4.5. From epoxides. In 2004, Ishikawa et al. demonstrated that it was possible to directly convert chiral epoxides into chiral aziridines by using guanidines as a nitrene source.[116] The reaction of guanidine with the epoxide was supposed to afford a betaine species, depicted in Scheme 82, which produced the corresponding aziridine via a spiro intermediate. This process proceeded via inversion of configuration at the asymmetric carbon on (*R*)-styrene oxide with high chirality control (96% ee).

In another context, Bartoli et al. have reported the asymmetric aminolytic kinetic resolution of racemic terminal

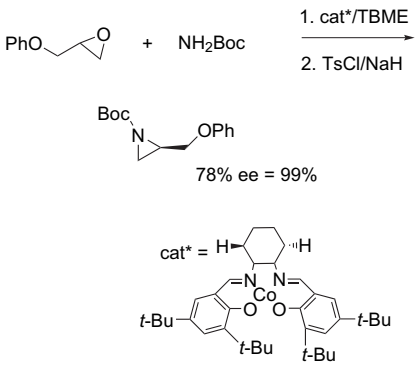


Scheme 81. Syntheses of aziridine esters from 1,2-amino selanyl esters.



Scheme 82. Synthesis of aziridine from chiral epoxide by using guanidine.

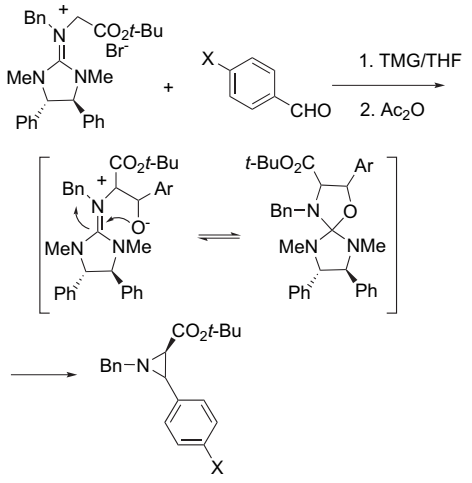
epoxides using carbamates as the nucleophiles catalysed by a chiral (salen)Co(III) complex, which provided a straightforward method for the synthesis of chiral 1,2-amino alcohols.[117] The viability of this novel strategy was proved by the synthesis of a highly enantio-enriched *N*-Boc protected aziridine, starting from racemic glycidyl phenyl ether using a practical one-pot procedure shown in Scheme 83. The aminolytic kinetic resolution of this epoxide was performed in the presence of *tert*-butyl carbamate and a chiral cobalt catalyst, affording with complete regioselectivity the corresponding enantiopure *N*-Boc protected aziridine in high yield.



Scheme 83. Synthesis of aziridine via aminolytic kinetic resolution of epoxide.

2.5. Miscellaneous reactions

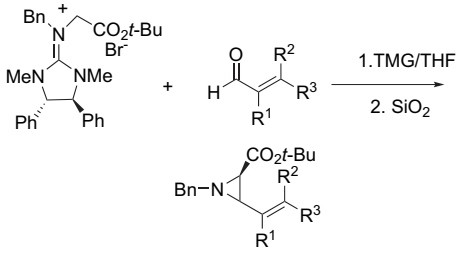
In 2001, a novel guanidinium ylide-mediated procedure was reported by Ishikawa et al.,[118] in which guanidinium ylides reacted with aldehydes to form aziridines. The first step was the formation of a C–C bond between a guanidinium salt and an arylaldehyde under basic conditions, in which an initially formed zwitterionic species was in equilibrium with a non-ionic spiro compound. The second step of the process was the fragmentation of this intermediate, triggered by Ac_2O or SiO_2, to afford the expected aziridine and urea. As shown in Scheme 84, the reaction of various *p*-substituted benzaldehydes with a chiral guanidinium salt in the presence of TMG as a base led, after subsequent treatment with Ac_2O, to the corresponding aziridines in good yields and variable diastereo- and enantioselectivities according to the nature of the aldehyde substrate.[119] For example, benzaldehydes bearing a strong electron-donating group allowed the corresponding *trans*-aziridines to be obtained in both excellent diastereo- and enantioselectivities.



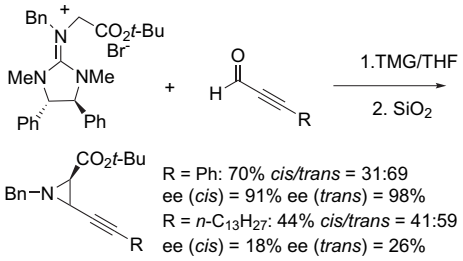
X = O*t*-Bu: 67% *trans/cis* = 95:5 ee (*trans*) = 92%
X = OMe: 81% *trans/cis* = 95:5 ee (*trans*) = 91%
X = Me: 76% *trans/cis* = 41:59
ee (*trans*) = 93% ee (*cis*) = 90%
X = H: 80% *trans/cis* = 27:73
ee (*trans*) = 88% ee (*cis*) = 86%
X = Cl: 92% *trans/cis* = 36:64
ee (*trans*) = 84% ee (*cis*) = 86%
X = CO_2Me: 80% *trans/cis* = 35:65
ee (*trans*) = 72% ee (*cis*) = 79%
X = CN: 53% *trans/cis* = 66:34
ee (*trans*) = 32% ee (*cis*) = 16%
X = NO_2: 70% *trans/cis* = 59:41
ee (*trans*) = 11% ee (*cis*) = 10%

Scheme 84. Synthesis of aziridines by reaction of aldehydes with chiral guanidinium salt.

The scope of this methodology could be extended by these authors to α,β-unsaturated aldehydes, which successfully led, in similar conditions, to a variety of chiral α,β-unsaturated aziridine-2-carboxylates in good-to-moderate yields and with the chirality of the guanidinium ylide effectively transferred to the 2- and 3-positions of the azirine products with diastereo- and enantioselectivities of up to 93% de and 98% ee, respectively (Scheme 85).[120]



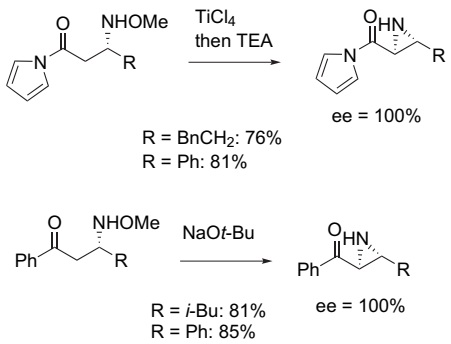
R^1 = Me, R^2 = R^3 = H: 92% *cis/trans* = 87:13
ee (*cis*) = 89% ee (*trans*) = 82%
R^1 = R^2 = R^3 = H: 62% *cis/trans* = 50:50
ee (*cis*) = 58%
R^1 = R^2 = H, R^3 = *n*-$C_{13}H_{27}$: 87% *cis/trans* = 53:47
ee (*cis*) = 95% ee (*trans*) = 97%
R^1 = H, R^2 = R^3 = Me: 5% *cis/trans* = 80:20
R^1,R^3 = $(CH_2)_4$, R^2 = H: 51% *cis/trans* = 65:35
ee (*cis*) = 99%
R^1 = R^2 = H, R^3 = Ph: 82% *cis/trans* = 27:73
ee (*cis*) = 75% ee (*trans*) = 65%
R^1 = Me, R^2 = H, R^3 = Ph: 51% *cis/trans* = 18:82
ee (*cis*) = 93% ee (*trans*) = 92%
R^1 = Ph, R^2 = Me, R^3 = H: 30% *cis/trans* = 93:7
ee (*cis*) = 98%
R^1 = H, R^2 = R^3 = Ph: 42% *cis/trans* = 76:24
ee (*cis*) = 91% ee (*trans*) = 87%



R = Ph: 70% *cis/trans* = 31:69
ee (*cis*) = 91% ee (*trans*) = 98%
R = *n*-$C_{13}H_{27}$: 44% *cis/trans* = 41:59
ee (*cis*) = 18% ee (*trans*) = 26%

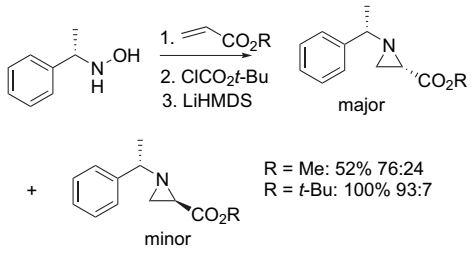
Scheme 85. Syntheses of aziridines by reactions of α,β-unsaturated aldehydes with chiral guanidinium salt.

Shibasaki et al. have prepared chiral α-acylpyrrole aziridines in excellent yields by treating the corresponding methoxylamines with $TiCl_4$ combined with Et_3N, as shown in Scheme 86.[121] In another study, these workers have achieved other chiral acylaziridines by cyclisation of the corresponding chiral methoxylamines performed in the presence of NaO*t*-Bu as base in high yields (Scheme 86).[122]



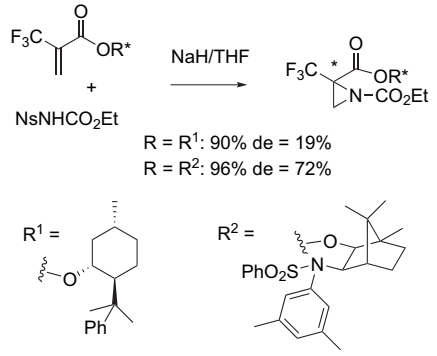
Scheme 86. Syntheses of aziridines from chiral methoxylamines.

In 2006, Bew et al. demonstrated that, after O-acylation, the conjugate addition products of (*S*)-*N*-(α-methylbenzyl)hydroxylamine underwent an efficient diastereoselective 3-*exo*-tet ring closure reaction, affording the corresponding substituted (*S*)-*N*-(α-methylbenzyl)aziridines in good-to-excellent yields and good diastereoselectivities of up to 86% de (Scheme 87).[123]



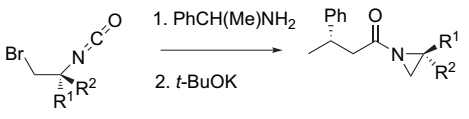
Scheme 87. Synthesis of aziridines from (*S*)-*N*-(α-methylbenzyl)hydroxylamine.

In 2004, Tardella et al. investigated the asymmetric aza-Michael addition of nosyloxycarbamates to 2-(trifluoromethyl)acrylates, demonstrating that it provided either the corresponding α-trifluoromethyl β-amino esters or the corresponding aziridines in high yields by changing the reaction conditions.[124] Indeed, when the amination was performed in the presence of CaO, an aza-Michael 1,4-addition occurred, giving the α-trifluoromethyl β-amino esters, whereas the use of NaH promoted an aza-Michael-initiated ring closure, yielding directly the aziridines. As shown in Scheme 88, the use of (−)-8-phenylmenthol as the chiral auxiliary induced a low diastereoselectivity, while more satisfactory results were obtained by using the bulkier Helmchen's auxiliary.



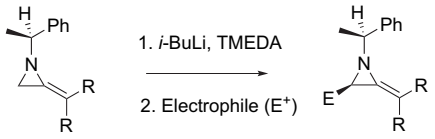
Scheme 88. Synthesis of aziridines from chiral 2-(trifluoromethyl)acrylates.

More recently, Gade et al. reported the synthesis of chiral aziridinecarboxamides by the reaction of enantiopure 2-bromo isocyanates with phenylethylamine in the presence of a base such as *t*-BuOK.[125] The first reaction intermediates in these reactions were β-bromourea derivatives, which were formed by the nucleophilic attack of the amine and could be detected at low temperature by NMR spectroscopy. Adding the base at low temperature led selectively to the aziridinecarboxamides in moderate-to-good yields (Scheme 89).



Scheme 89. Synthesis of aziridinecarboxamides from chiral 2-bromo isocyanates.

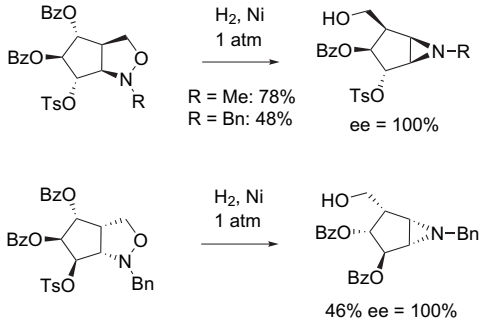
On the other hand, Shipman et al. have observed high levels of diastereocontrol for the lithiation and alkylation of a 2-isopropylidineaziridine bearing an (*S*)-α-methylbenzyl group on nitrogen.[126] As shown in Scheme 90, the chiral aziridinyl anion was alkylated by a series of electrophiles, yielding the corresponding alkylated isopropylidineaziridines in good yields and diastereoselectivities of up to 90% de.



R = H, Electrophile = BnBr: 70% de = 14%
R = Me, Electrophile = BnBr: 68% de = 88%
R = Me, Electrophile = MeI: 47% de = 80%
R = Me, Electrophile = TMSCl: 80% de = 90%
R = Me, Electrophile = CH_2=CH-CH_2Br: 63% de = 84%
R = Me, Electrophile = Ph_2CO: 43% de = 88%

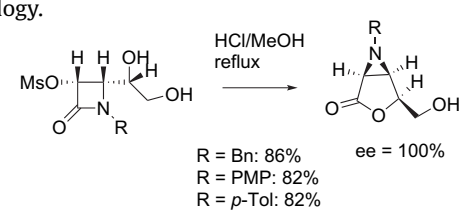
Scheme 90. Synthesis of alkylated isopropylidineaziridines.

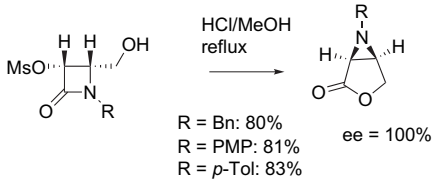
In another context, Bols et al. have developed the synthesis of various chiral bicyclic aziridines through the reductive cleavage of the N–O bond of chiral 1,2-oxazines carried out with Raney nickel at 1 atm of hydrogen pressure.[127] As shown in Scheme 91, the reaction of 1,2-oxazines derived from D-glucose and D-mannose provided the corresponding enantiopure aziridines in moderate-to-good yields.



Scheme 91. Syntheses of bicyclic aziridines from chiral 1,2-oxazines.

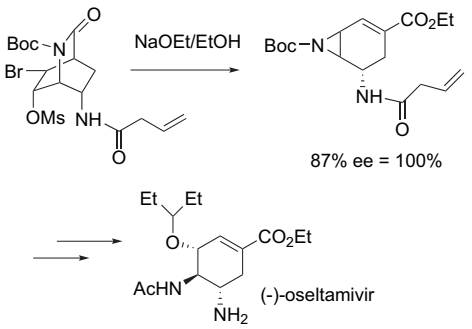
2,3-Aziridino-γ-lactones represent important precursors for biologically important glutamic acid derivatives. In this context, Deshmukh and Kale have developed an efficient entry to chiral 2,3-aziridino-γ-lactones from azetidin-2-ones.[128] This methodology was based on an acid-catalysed tandem intramolecular azetidinone ring opening, followed by aziridine ring formation via elimination of a mesylate group. As shown in Scheme 92, a series of enantiopure aziridino-γ-lactones could be prepared in good yields using this methodology.





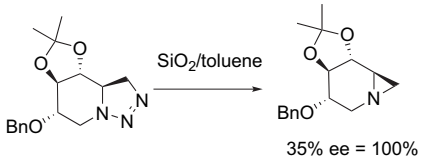
Scheme 92. Syntheses of aziridino-γ-lactones.

The total synthesis of the potent inhibitor of neuraminidase, (−)-oseltamivir, elaborated by Fukuyama et al. in 2007, incorporated the formation of a bicyclic aziridine by rearrangement of a chiral allyl carbamate.[129] Therefore, treatment of this carbamate with NaOEt resulted in ethanolysis of *N*-Boc lactam, dehydrobromination and aziridine formation, which provided the desired aziridine in excellent yield (Scheme 93). This aziridine was further converted into the final (−)-oseltamivir in four steps.



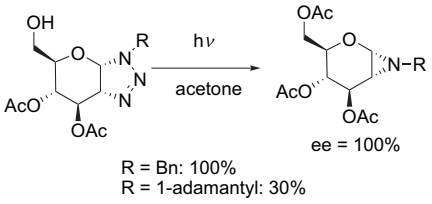
Scheme 93. Synthesis of (−)-oseltamivir.

In the course of preraring 1-deoxynojirimycin derivatives, Murphy and Zhou have found that the treatment of a chiral 1,2,3-triazoline, derived from D-glucono-*δ*-lactone, provided the corresponding aziridine through decomposition, suggesting that the acidic nature of the gel promoted the loss of nitrogen.[130] As shown in Scheme 94, the tricyclic aziridine was obtained in moderate yield.



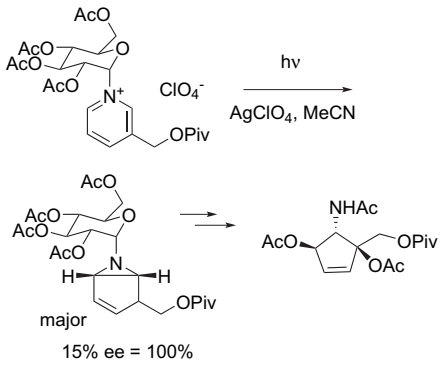
Scheme 94. Synthesis of tricyclic aziridine by thermal decomposition of chiral 1,2,3-triazoline.

On the other hand, the photochemical decomposition of triazolines derived from D-glucose has been studied by Finney and Dahl.[131] The photolysis of chiral triazolines, as depicted in Scheme 95, provided the corresponding aziridines in moderate-to-quantitative yields.



Scheme 95. Synthesis of aziridines by photochemical decomposition of D-glucose-derived triazolines.

Another photocyclization reaction providing chiral aziridines has been developed by Mariano et al., starting from a chiral pyridinium perchlorate derived from D-glucose.[132] Irradiation of this substrate in aqueous $NaHCO_3$ generated a mixture of isomeric *N*-glycosyl-bicyclic-aziridines, which could be partially separated by silica gel chromatography to yield the major enantiopure aziridine, depicted in Scheme 96, in 15% yield. This aziridine was subsequently converted into the aminocyclitol core (trehazolamine) of the potent trehalase inhibitor, trehazolin.



Scheme 96. Synthesis of aziridine by photocyclization of chiral pyridinium perchlorate.

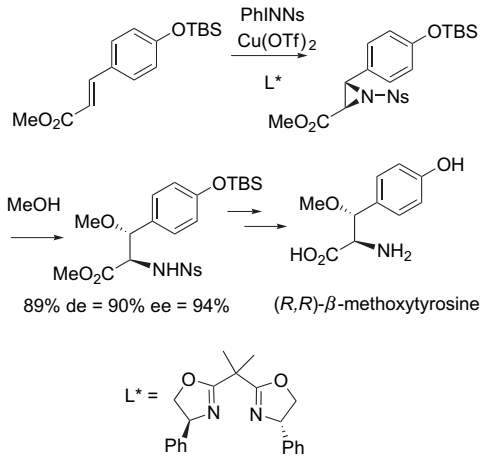
3. Aziridination based on use of chiral catalysts

3.1. Aziridination via nitrene transfer to alkenes

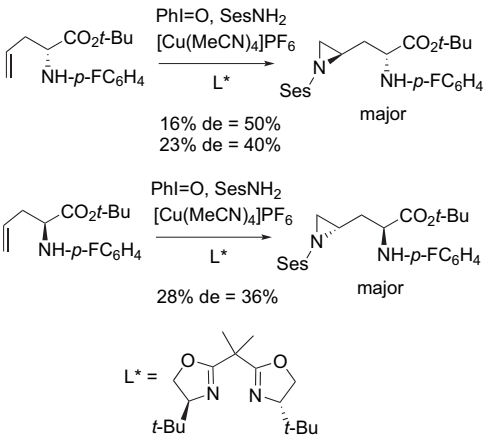
3.1.1. Cu-catalysed aziridination. Although a wide variety of chiral catalysts including copper, rhodium, ruthenium and other metal complexes have been developed in the past two decades, the field of asymmetric aziridination catalysis has remained for a long time relatively undeveloped. The most commonly employed chiral catalyst systems that have been developed to date for the enantioselective aziridination via nitrene transfer to alkenes are based on copper complexes. The main mechanistic issues of the Cu-catalysed aziridination of olefins are the transformation of a copper–nitrene intermediate, the oxidation state of the metal and the nature of the nitrene transfer. It must be noted that experimental evidence for the existence of a metallonitrene has been provided by Jacobsen et al.[133] The type of chiral ligands, which have been most successfully applied to the Cu-catalysed asymmetric aziridination is constituted by the class of bisoxazolines. More generally, the C_2-symmetric chiral bisoxazolines have emerged as a class of important and efficient ligands in an increasing number of aymmetric transformations over the last decade.[134] The aziridination of alkenes using Cu–bisoxazoline complexes was pioneered by Evans et al., in 1991.[135] In 2007, Cranfill and Lipton reported the use of Evans' bisoxazoline ligand for the asymmetric aziridination of *p*-coumarate TBS ether in the presence of $Cu(OTf)_2$ and PhINNs (*N*-(*p*-nitrophenylsulfonyl)iminophenyliodinane) as the nitrene source in dichloromethane.[136] This process allowed the corresponding chiral *trans*-aziridine to be obtained in high yield, and with diastereo- and enantioselectivity of 90% de and 94% ee, respectively (Scheme 97). In fact, the crude aziridine was directly dissolved in methanol, providing the corresponding methoxy amine by aziridine ring opening. This successful reaction constituted the key step of a total synthesis of (*R*,*R*)-*β*-methoxytyrosine, which is a constituent of several cyclic depsipeptide natural products.

In 2003, Dauban et al. studied the Cu-catalysed aziridination of allylglycine derivatives, which constituted the first example of the application of this metal-catalysed nitrene transfer to a nitrogen-containing substrate.[137] It was shown that the Cu-catalysed and iodosylbenzene-mediated aziridination of chiral *N*-(9-phenylfluorenyl)allylglycine *tert*-butyl ester led to the corresponding chiral aziridine in moderate yield and diastereoselectivity. As shown in Scheme 98, the reaction was carried out in the presence of a combination of *tert*-butyl Evans' bisoxazoline ligand with $[Cu(MeCN)_4]PF_6$. The modest yields observed appeared to be mainly related to the low reactivity of unsubstituted terminal

olefins in general. It was not clear, however, whether or not the nitrogen atom of the substrate had an influence on the course of the reaction.



Scheme 97. Synthesis of (*R*,*R*)-β-methoxytyrosine by aziridination mediated by Evans's bisoxazoline ligand.

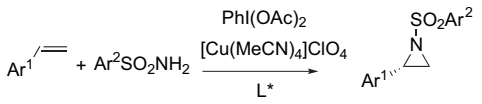


Scheme 98. Aziridinations of allylglycine derivatives mediated by Evans' bisoxazoline ligand.

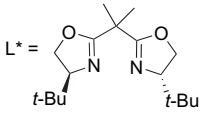
This ligand has also been employed by Che et al. to develop asymmetric alkene Cu-catalysed aziridinations mediated by $PhI(OAc)_2$ in the presence of sulfonamides to generate the nitrene precursors (PhI=NR).[138] This one-pot procedure, employing $[Cu(MeCN)_4]PF_6$ as the copper complex, had been optimised using *p*-nitrobenzenesulfonamide as the nitrene source, allowing the corresponding chiral aziridines to be formed in good-to-excellent yields and enantioselectivities of up to 75% ee. The results obtained from a range of olefins are collected in Scheme 99.

Moreover, this ligand has been used by Dauban et al. to promote the intramolecular Cu-catalysed aziridination of a wide range of sulfamates.[139] This reaction was performed in the presence of PhI=O and $[Cu(MeCN)_4]PF_6$, affording the corresponding chiral aziridines in yields of up to 86% and enantiomeric excesses of up to 84%, as shown in Scheme 100. In particular, it is interesting to note that this nitrene transfer occurred with equal success for simple aliphatic olefins and electron-poor alkenes, substrates for which no enantioselective aziridination has been reported to date.

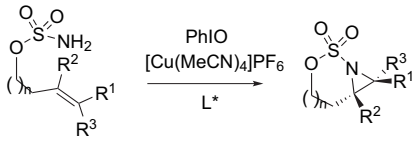
The size of the chelate in the reactive metal complex of bisoxazolines is an important feature of the catalyst, since it will control the orientation of the substituents on the two oxazolines around the metal ion and the distance between the substituents and the



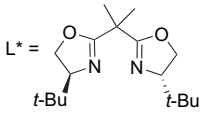
Ar^1 = Ph, Ar^2 = *p*-$NO_2C_6H_4$: 94% ee = 75%
Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4: 90% ee = 52%
Ar^1 = *p*-FC_6H_4, Ar^2 = *p*-$NO_2C_6H_4$: 95% ee = 72%
Ar^1 = *p*-FC_6H_4, Ar^2 = *p*-ClC_6H_4: 95% ee = 51%
Ar^1 = *p*-FC_6H_4, Ar^2 = *p*-Tol: 84% ee = 40%
Ar^1 = *p*-$CF_3C_6H_4$, Ar^2 = *p*-$NO_2C_6H_4$: 64% ee = 51%
Ar^1 = *p*-$CF_3C_6H_4$, Ar^2 = *p*-ClC_6H_4: 68% ee = 43%
Ar^1 = *p*-$CF_3C_6H_4$, Ar^2 = *p*-Tol: 43% ee = 38%
Ar^1 = *p*-Tol, Ar^2 = *p*-$NO_2C_6H_4$: 78% ee = 45%
Ar^1 = *p*-Tol, Ar^2 = *p*-ClC_6H_4: 80% ee = 43%
Ar^1 = Ar^2 = *p*-Tol: 61% ee = 32%
Ar^1 = *m*-$NO_2C_6H_4$, Ar^2 = *p*-$NO_2C_6H_4$: 82% ee = 52%
Ar^1 = *m*-$NO_2C_6H_4$, Ar^2 = *p*-ClC_6H_4: 89% ee = 48%
Ar^1 = *m*-$NO_2C_6H_4$, Ar^2 = *p*-Tol: 77% ee = 45%
Ar^1 = *m*-Tol, Ar^2 = *p*-$NO_2C_6H_4$: 68% ee = 57%
Ar^1 = *m*-Tol, Ar^2 = *p*-ClC_6H_4: 78% ee = 42%
Ar^1 = *m*-Tol, Ar^2 = *p*-Tol: 76% ee = 37%



Scheme 99. Aziridination of alkenes mediated by Evans' bisoxazoline ligand.

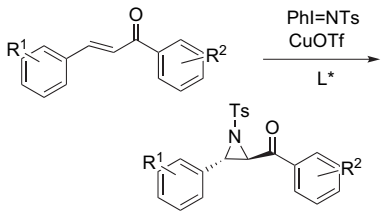


R^1 = Ph, R^2 = R^3 = H, n = 1: 86% ee = 84%
R^1 = R^2 = R^3 = H, n = 1: 81% ee = 52%
R^1 = R^3 = H, R^2 = Me, n = 1: 24% ee = 36%
R^1 = Me, R^2 = R^3 = H, n = 1: 80% ee = 80%
R^1 = Et, R^2 = R^3 = H, n = 1: 83% ee = 80%
R^1 = CO_2Me, R^2 = R^3 = H, n = 1: 79% ee = 62%
R^1 = R^2 = H, R^3 = Et, n = 1: 86% ee = 72%
R^1 = R^2 = R^3 = H, n = 2: 72% ee = 47%

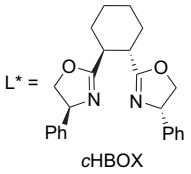


Scheme 100. Intramolecular aziridination of sulfamates mediated by Evans' bisoxazoline ligand.

metal ions. This implies that the chelate size of bisoxazolines can tune the chiral environment at the catalytic centre and then affect the enantioselectivity of asymmetric catalytic reactions. In order to keep the designed chiral environment at the catalytic centre, a series of rigid backbone-linked bisoxazolines were designed and synthesised by Xu et al. As an example, these workers have prepared a series of cyclohexane-linked bisoxazolines (*c*HBoxes), which have been investigated as chiral ligands for the asymmetric Cu-catalysed aziridination of chalcones performed in the presence of PhI=NTs as the nitrene source.[140] As summarized in Scheme 101, the involvement of (*S*,*S*)-1,2-bis-[(*S*)-(4-phenyl)oxazolin-2-yl]cyclohexane as the chiral ligand in combination with CuOTf allowed the aziridination of a wide range of chalcones to be achieved in good-to-high yields and enantioselectivities of up to 99% ee. It was found that the enantioselectivity was not substituent dependent with respect to chalcones.



$R^1 = R^2$ = H: 56% ee = 91%
R^1 = *p*-Me, R^2 = H: 62% ee = 94%
R^1 = *p*-F, R^2 = H: 62% ee = 90%
R^1 = *p*-Cl, R^2 = H: 80% ee = 95%
$R^1 = R^2$ = *p*-Me: 50% ee > 99%
R^1 = H, R^2 = *p*-Me: 71% ee > 99%
R^1 = H, R^2 = *p*-OMe: 73% ee = 97%
$R^1 = R^2$ = *p*-Cl: 80% ee = 95%
R^1 = *p*-Cl, R^2 = *p*-Me: 72% ee = 85%
R^1 = H, R^2 = *p*-Br: 63% ee = 86%
R^1 = *m*-F, R^2 = H: 64% ee = 92%
R^1 = *p*-CF_3, R^2 = H: 51% ee = 80%

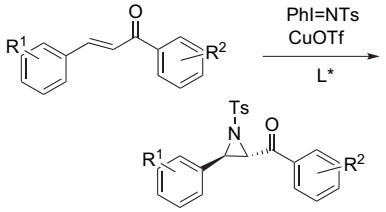


*c*HBOX

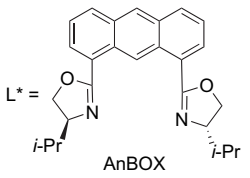
Scheme 101. Aziridination of chalcones mediated by *c*HBOX ligand.

With the aim of finding other efficient bisoxazoline ligands, these authors have developed another novel rigid backbone-containing bisoxazoline ligand (AnBox), in which the two oxazoline rings were attached via the 1,8-positions of a rigid anthracene ring.[141] The use of this ligand for similar reactions to those just described has led to the corresponding *trans*-aziridines with comparably high enantioselectivities of up to 99% ee, but with the opposite enantioselectivity, compared with both the *c*HBOX ligand and Evans' bisoxazoline ligand (Scheme 102). In addition, the results indicated that the enantioselectivity was substituent dependent with respect to the chalcones, in contrast with the results obtained by using *c*HBOX as the ligand. In general, chalcones bearing electron-donating substituents showed higher enantioselectivities than those bearing electron-withdrawing groups. Moreover, it was demonstrated that the coordination of the oxygen atom of the carbonyl group in the chalcones with the copper in the catalyst and the π–π stacking interaction between the aryl group of the nitrene and the aryl substituent attached to the C=C double bond in the chalcones were indispensable for obtaining a high enantioselectivity in the asymmetric aziridination. In 2007, these authors demonstrated that the substituent-dependent enantioselectivity in the asymmetric aziridination of chalcones catalysed by the AnBOX ligand was rationalised by the π–stacking interaction between the ligand backbone and the substrates, primarily confirmed by the use of bulky substrates and of catalysts without aromatic backbones, such as *c*HBOX and Evans' bisoxazoline ligand.[142]

In a complementary study, these authors have investigated the efficiency of the three bisoxazolines, Evans' ligand, *c*HBOX ligand and AnBOX ligand, to induce chirality in the aziridination of 1,3-dienes.[143] When the reaction was performed in the presence of PhI=NTs combined with CuOTf and the bisoxazoline ligand, the corresponding aziridines were obtained in moderate yields and with enantioselectivities of up to 80% ee, diastereoselectivities of up to 99% de, and regioselectivities of up to 99:1, as shown in Scheme 103. It was shown that α,β,γ,δ-unsaturated ketones usually produced *cis*-γ,δ-aziridinated products, while 1,4-diphenyl-1,3-butadiene afforded both the *cis*- and *trans*-aziridine derivatives as major products by the use of the different bisoxazoline ligands.



$R^1 = R^2$ = H: 80% ee = 96%
R^1 = *p*-Me, R^2 = H: 86% ee = 98%
R^1 = *p*-Cl, R^2 = H: 70% ee = 76%
R^1 = *m*-Cl, R^2 = H: 76% ee = 84%
R^1 = *o*-Cl, R^2 = H: 91% ee = 79%
R^1 = *m*-F, R^2 = H: 85% ee = 71%
R^1 = H, R^2 = *p*-Me: 92% ee > 99%
$R^1 = R^2$ = *p*-Me: 59% ee > 99%
R^1 = *p*-Me, R^2 = *p*-Cl: 51% ee = 68%
R^1 = *p*-Ph, R^2 = H: 35% ee = 87%
R^1 = *p*-F, R^2 = H: 72% ee = 62%
R^1 = *p*-Br, R^2 = H: 58% ee = 52%
R^1 = *p*-OMe, R^2 = H: 61% ee = 37%
R^1 = H, R^2 = *p*-OMe: 74% ee = 62%
R^1 = *m*-F, R^2 = H: 85% ee = 71%
R^1 = *p*-CF_3, R^2 = H: 69% ee = 67%

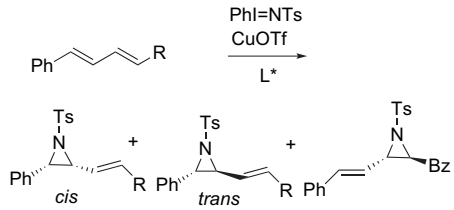


AnBOX

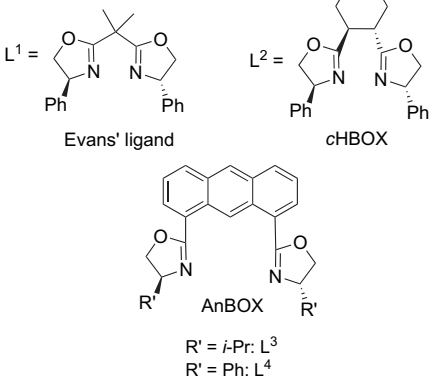
Scheme 102. Aziridination of chalcones mediated by AnBox ligand.

In 2004, Mayoral et al. demonstrated that Evans' bisoxazoline ligands could be immobilised by electrostatic interactions with anionic supports, furnishing recyclable catalysts for the aziridination of styrene by PhI=NTs as the nitrene precursor.[144] Three different anionic supports were used, namely laponite, a synthetic clay, SAC-13, a nafionsilica nanocomposite with 13% nafion content, and SiO_2–CF_2SO_3H, prepared by grafting a partially fluorinated chain with a sulfonic acid group on silica gel. Although the yields of aziridines were good in all of the cases studied, the enantioselectivity was found to depend on the nature of the chiral ligand (Scheme 104). With a bisoxazoline ligand bearing phenyl substituents, the enantioselectivity was always around 25% ee, as in solution. On the other hand, when the chiral ligand had *tert*-butyl groups attached, the enantioselectivity was noticeably lower than that observed in the homogeneous phase as a consequence of the presence of free copper on the solid.

In the same context, Hutchings et al. have studied the heterogeneous aziridination of styrene using copper-exchanged zeolite HY in the presence of Evans' ligands.[145] Two nitrene donors, PhI=NTs and PhI=NNs, were investigated for each ligand. Excellent enantioselectivities of up to 85% ee were obtained by using PhI=NNs, as shown in Scheme 105. It is interesting to note that, in all cases, the heterogeneously catalysed reaction gave a much higher enantioselection than the comparable homogeneously

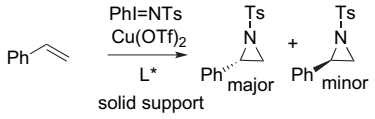


R = Bz, L* = L^3: 64% 26:3:71 ee (*cis*) = 36% (2*S*,3*R*)
R = Bz, L* = L^4: 59% 87:13:0 ee (*cis*) = 13% (2*S*,3*R*)
R = Bz, L* = L^2: 73% 99:0:1 ee (*cis*) = 36% (2*R*,3*S*)
R = Bz, L* = L^1: 28% 100:0:0 ee (*cis*) = 80% (2*R*,3*S*)
R = Ac, L* = L^3: 51% 100:0:0 ee (*cis*) = 6% (2*R*,3*S*)
R = Ac, L* = L^2: 25% 100:0:0 ee (*cis*) = 19% (2*R*,3*S*)
R = Ph, L* = L^3: 68% 26:74 ee (*cis*) = 12% (2*S*,3*R*)
ee (*trans*) = 14% (*S*,*S*)
R = Ph, L* = L^4: 32% 61:39 ee (*cis*) = 22% (2*S*,3*R*)
ee (*trans*) = 24% (*S*,*S*)
R = Ph, L* = L^2: 21% 68:32 ee (*cis*) = 60% (2*R*,3*S*)
ee (*trans*) = 48% (*R*,*R*)
R = Ph, L* = L^1: 22% 18:82 ee (*cis*) = 21% (2*R*,3*S*)
ee (*trans*) = 34% (*R*,*R*)

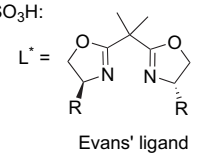


R' = *i*-Pr: L^3
R' = Ph: L^4

Scheme 103. Aziridination of 1,3-dienes mediated by bisoxazoline ligands.



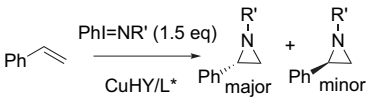
with support = laponite:
R = Ph: 75% ee = 25%
R = *t*-Bu: 60% ee = 2%
with support = SiO_2-CF_2SO_3H:
R = Ph: 58% ee = 26%
R = *t*-Bu: 57% ee = 0%
with support = SAC-13:
R = Ph: 73% ee = 21%



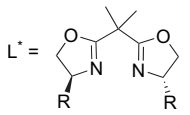
Scheme 104. Heterogeneous aziridination of styrene mediated by Evans' ligand immobilised by electrostatic interactions.

catalysed reaction performed with $Cu(OTf)_2$. It was possible to even increase the enantioselectivity of the reaction to up to 92% ee by using a 1:3 PhI=NNs:styrene ratio.

This highly efficient methodology could be extended to the heterogeneous aziridination of a series of styrene derivatives, providing the corresponding aziridines in high yields and enantioselectivities of up to 95% ee, as shown in Scheme 106.[146] In all cases of substrates, higher enantioselection could be achieved with

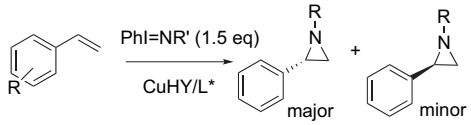


R = Ph, R' = Ns: 78% ee = 85%
R = *t*-Bu, R' = Ns: 68% ee = 83%
R = Ph, R' = Ts: 78% ee = 76%
R = *t*-Bu, R' = Ts: 58% ee = 24%

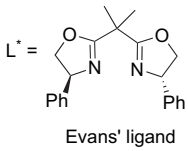


Scheme 105. Heterogeneous aziridination of styrene mediated by Evans' ligand immobilised on zeolite HY.

the heterogeneously catalysed reaction, when compared with the homogeneously catalysed reaction. The effect was considered to be due mainly to the enhanced confinement of the substrate within the pores of the zeolite.



R = 2-Cl: 78% ee = 88%
R = 3-Cl: 82% ee = 95%
R = 4-Cl: 85% ee = 94%
R = 2-F: 82% ee = 72%
R = 2-Br: 60% ee = 85%
R = 4-Br: 90% ee = 74%
R = 2-Me: 60% ee = 79%
R = 4-OMe: 71% ee = 64%
R = 3-NO_2: 63% ee = 65%



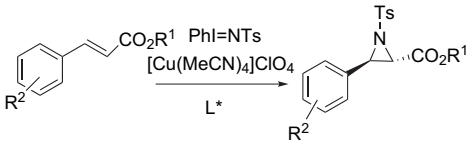
Scheme 106. Heterogeneous aziridination of styrene derivatives mediated by Evans' ligand immobilised on zeolite HY.

On the other hand, several chiral ligands other than bisoxazolines have also been investigated in recent years for the Cu-catalysed asymmetric aziridination of olefins. As an example, Ding and Wang have developed a novel chiral C_2-symmetric diimine ligand derived from D-mannitol, which was found to be highly efficient for the enantioselective control of the Cu-catalysed asymmetric aziridination of olefins with PhI=NTs as the nitrene source.[147] Indeed, the corresponding *trans*-aziridines were isolated in good-to-excellent yields with enantioselectivities of up to 99% ee, as shown in Scheme 107. The catalyst system was also extended to a one-pot enantioselective aziridination of olefins by using $TsNH_2/PhI(OAc)_2$ as the nitrene source. In this case, most reactions proceeded smoothly to give the corresponding products in moderate yields and with good-to-excellent enantioselectivities of up to 96% ee (Scheme 107).

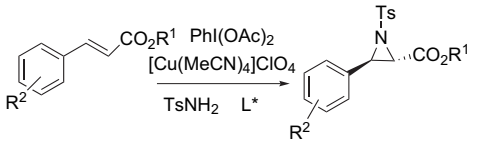
In 2003, a chiral binaphthyldiimine ligand, BINIM-DC, was found by Suga et al. to be a highly efficient ligand for the Cu-catalysed asymmetric aziridination of olefins with PhI=NTs as the nitrene precursor.[148] In particular, high levels of enantioselectivity of up to 98% ee were obtained in the aziridination reactions of 3-arylpropenoate and 1,3-disubstituted 2-propen-1-one derivatives, as shown in Scheme 108.

A moderate enantioselectivity was obtained by Dauban et al. by using a chiral diiminocyclohexane ligand in the intramolecular Cu-catalysed aziridination of a sulfamate. This reaction was performed in the presence of PhI=O and $[Cu(MeCN)_4]PF_6$, affording the corresponding aziridine in good yield, as shown in Scheme 109.[139]

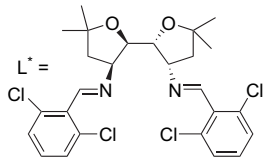
While C_2-symmetric ligands have been extensively used for various metal-mediated enantioselective organic transformations, the analogous C_3-symmetric systems have received much less



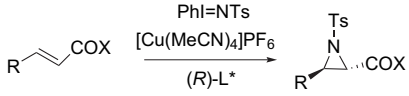
R^1 = Me, R^2 = H: 97% ee = 88%
R^1 = Ph, R^2 = H: 96% ee = 87%
R^1 = *t*-Bu, R^2 = H: 99% ee > 99%
R^1 = *t*-Bu, R^2 = 4-F: 99% ee = 98%
R^1 = *t*-Bu, R^2 = 4-Cl: 97% ee = 98%
R^1 = *t*-Bu, R^2 = 4-Br: 97% ee = 98%
R^1 = *t*-Bu, R^2 = 4-Me: 86% ee = 94%
R^1 = *t*-Bu, R^2 = 4-MeO: 95% ee = 80%
R^1 = *t*-Bu, R^2 = 2-NO_2: 63% ee = 99%
R^1 = *t*-Bu, R^2 = 2,3-MeO: 67% ee = 97%



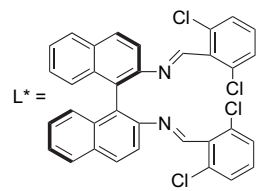
R^1 = *t*-Bu, R^2 = H: 49% ee = 96%
R^1 = *t*-Bu, R^2 = 4-F: 55% ee = 95%
R^1 = *t*-Bu, R^2 = 4-Cl: 45% ee = 95%
R^1 = *t*-Bu, R^2 = 4-Me: 39% ee = 88%
R^1 = *t*-Bu, R^2 = 4-MeO: 41% ee = 74%
R^1 = *t*-Bu, R^2 = 2-NO_2: 19% ee = 97%



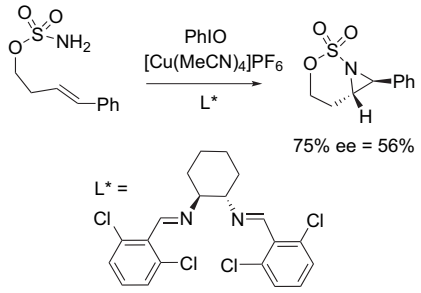
Scheme 107. Aziridinations of olefins mediated by diimine ligand.



from (*R*)-BINIM-DC:
R = *p*-ClC_6H_4, X = OMe: 82% ee = 81% (2*S*,3*R*)
R = 1-Naph, X = OMe: 74% ee = 77% (2*S*,3*R*)
R = 2-Naph, X = OMe: 74% ee = 68% (2*S*,3*R*)
R = Ph, X = OPh: 48% ee = 89% (2*S*,3*R*)
R = Ph, X = O*t*-Bu: 57% ee = 98% (2*S*,3*R*)
R = X = Ph: 87% ee = 84% (2*S*,3*R*)
from (*S*)-BINIM-DC:
R = *p*-CNC_6H_4, X = OMe: 69% ee = 90% (2*R*,3*S*)
R = *p*-Tol, X = OMe: 41% ee = 83% (2*R*,3*S*)
R = Me, X = OMe: 13% ee = 36% (2*R*,3*S*)
R = H, X = OMe: 30% ee = 43% (2*R*,3*S*)
R = *p*-ClC_6H_4, X = O*t*-Bu: 64% ee = 97% (2*R*,3*S*)
R = *p*-CNC_6H_4, X = O*t*-Bu: 73% ee = 95% (2*R*,3*S*)
R = X = Ph: 79% ee = 86% (2*R*,3*S*)
R = Ph, X = Me: 73% ee = 67% (2*R*,3*S*)

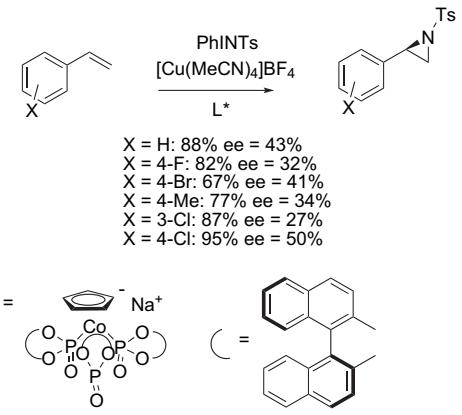


Scheme 108. Aziridination of olefins mediated by BINIM-DC ligand.



Scheme 109. Intramolecular aziridination of sulfamate mediated by diiminocyclohexane ligand.

attention.[149] In this context, Leung et al. have reported the synthesis of a chiral C_3-symmetric oxygen tripodal ligand derived from (*S*)-BINOL.[150] The potential of this anionic tris(phosphinite) ligand was evaluated for the Cu-catalysed aziridination of styrene. Therefore, the use of the corresponding Cu(I) complex prepared in situ from $[Cu(MeCN)_4]BF_4$ combined with PhI=NTs as the nitrene source allowed the styrene aziridine to be afforded in 67% yield and moderate enantioselectivity of 43% ee (Scheme 110). When this catalytic system was applied to various substituted styrenes, better enantioselectivities could be obtained of up to 61% ee for the corresponding aziridines, as shown in Scheme 110.



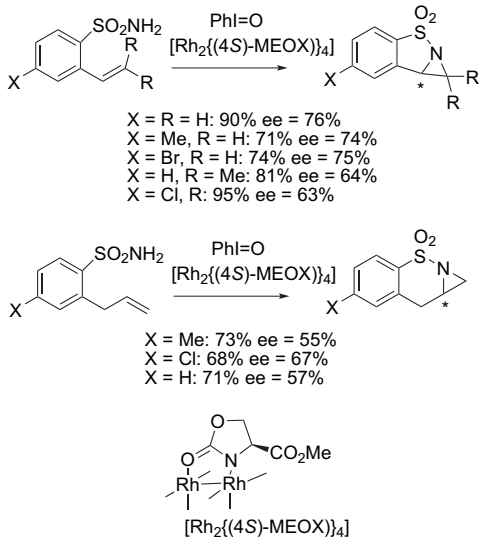
X = H: 88% ee = 43%
X = 4-F: 82% ee = 32%
X = 4-Br: 67% ee = 41%
X = 4-Me: 77% ee = 34%
X = 3-Cl: 87% ee = 27%
X = 4-Cl: 95% ee = 50%

Scheme 110. Aziridination of styrenes mediated by BINOL-derived C_3-symmetric oxygen tripodal ligand.

In 2008, Gibson et al. investigated the efficiency of a copper(II) complex of a chiral cyclohexyl-fused azamacrocycle, such as (7a*R*,11a*R*)-1,4,7-trimethyldodecahydro-1*H*-1,4,7-benzotriazonine, to induce chirality in the aziridination of styrene with PhI=NTs as the nitrene source.[151] Disappointingly, the use of this chiral complex led to the corresponding racemic aziridine. In addition, Chanda et al. have reported the asymmetric synthesis of aziridines using bromamine-T as the nitrene source.[152] Therefore, the Cu-catalysed aziridination of styrene with bromamine-T was performed in the presence of various chiral cinchona alkaloids such as sparteine and *N*-benzyl ephedrine as the ligands. The best result was obtained by using the cinchona alkaloid, dihydroquinine, affording in the presence of $CuCl_2$ and bromamine-T in acetonitrile the expected aziridine in 39% yield and moderate enantioselectivity of 43% ee.

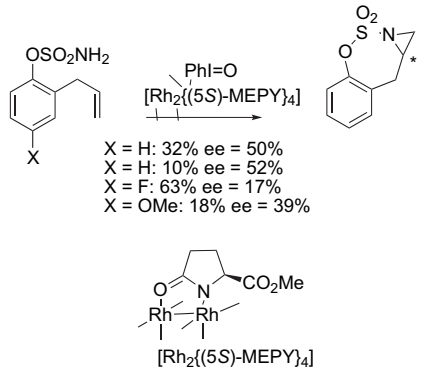
3.1.2. Rh-catalysed aziridination. Chiral rhodium(II) catalysts are complementary in scope to copper(I) catalysts in asymmetric carbene-transfer reactions. As an example, Che et al. have successfully applied $[Rh_2\{(4S)\text{-MEOX}\}_4]$ as the catalyst of choice for the intramolecular aziridination of a series of unsaturated sulfonamides.[153] In the presence of PhI=O as the oxidant, the corresponding

aziridines were obtained in good yields and enantioselectivities of up to 76% ee, as shown in Scheme 111.



Scheme 111. Intramolecular aziridinations of unsaturated sulfonamides mediated by $[Rh_2\{(4S)\text{-MEOX}\}_4]$.

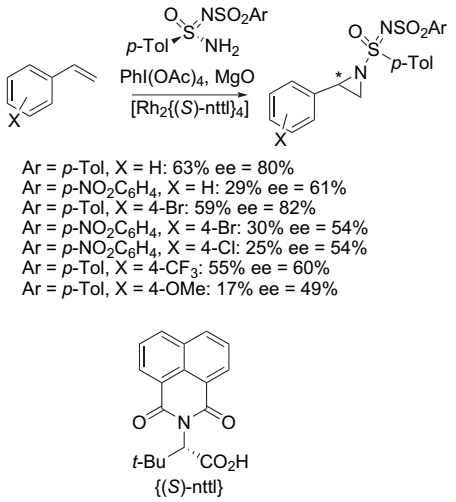
This rhodium catalyst was also used by Hayes et al. for the asymmetric aziridination of a range of homoallyl-carbamates performed in the presence of PhI=O, in 2006.[154] In these conditions, the expected aziridines were obtained as the major products, but in low enantioselectivities ranging from 1 to 23% ee. Another rhodium catalyst, $[Rh_2\{(5S)\text{-MEPY}\}_4]$, has been succeefully employed by Fruit and Müller to induce chirality in the intramolecular aziridination of 2-allyl substituted aromatic sulfamates.[155] The use of this catalyst in the presence of $PhI(OAc)_2$ combined with MgO allowed the corresponding tricyclic aziridines to be obtained in moderate-to-good yields and enantioselectivities of up to 52% ee (Scheme 112).



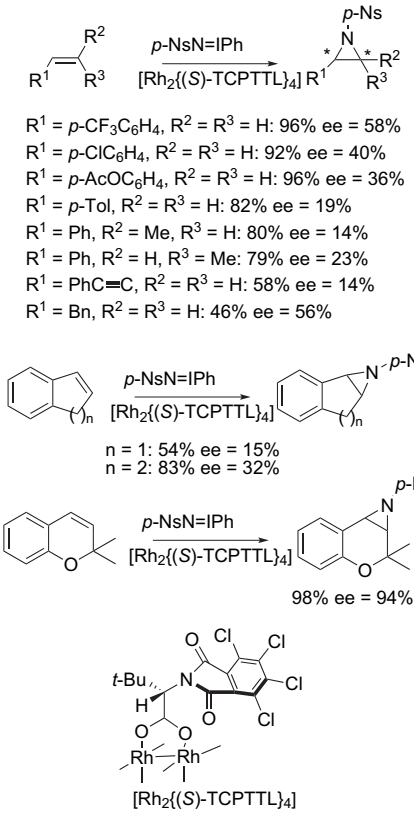
Scheme 112. Intramolecular aziridination of 2-allyl substituted aromatic sulfamates mediated by $[Rh_2\{(5S)\text{-MEPY}\}_4]$.

Another rhodium catalyst, $[Rh_2\{(S)\text{-nttl}\}_4]$, using the 1,8-naphthalimide of L-*tert*-leucine as a bridging ligand, has been successfully employed by Dauban et al. for the asymmetric aziridination of styrene derivatives with chiral sulfonimidamides as iminoiodane precursors.[156] In these conditions, the expected aziridines were obtained in modest-to-good yields with diastereoselectivities of up to 82% de, as shown in Scheme 113.

In addition, Hashimoto et al. have developed enantioselective aziridinations of a range of alkenes with [*N*-(4-nitrophenylsulfonyl)imino]phenyliodinane catalysed by $[Rh_2\{(S)\text{-TCPTTL}\}_4]$, which provided the corresponding aziridines in high yields and moderate enantioselectivities, except in the case of 2,2-dimethylchromene, which allowed a high level of enantioselectivity of 94% ee to be achieved (Scheme 114).[157]



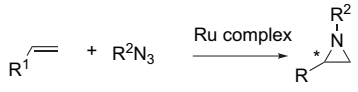
Scheme 113. Aziridination of styrenes with sulfonimidamides mediated by $[Rh_2\{(S)\text{-nttl}\}_4]$.



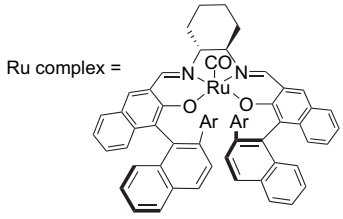
Scheme 114. Aziridinations of olefins with *p*-NsN=IPh mediated by $[Rh_2\{(S)\text{-TCPTTL}\}_4]$.

3.1.3. Ru-catalysed aziridination. Excellent enantioselectivities have been reported by Katsuki et al. for the asymmetric aziridination of a wide range of alkenes by using chiral ruthenium(salen)(CO) complexes in the presence of azide compounds as the nitrene precursors.[158] Various azide compounds were involved in these reactions, providing the corresponding aziridines in both high yields and enantioselectivities of up to 99% ee (Scheme 115). The best results were observed by using a robust fluorinated ruthenium complex or another rhodium complex, which possessed a phenyl substituent bearing chloro and trimethylsilyl groups at its

meta- and *para*-positions, respectively. Notably, the aziridination of less-reactive α,β-unsaturated esters and amides performed with 2-(trimethylsilyl)ethanesulfonyl azide ($SesN_3$) also proceeded with excellent enantioselectivities and good yields (Scheme 115).



R^1 = Ph, R^2 = *p*-Ns, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
90% ee = 87%
R^1 = *p*-BrC_6H_4, R^2 = *p*-Ns, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
93% ee = 83%
R^1 = PhC≡C, R^2 = *p*-Ns, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
98% ee = 98%
R^1 = PhC≡C, R^2 = *o*-Ns, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
58% ee = 87%
R^1 = Ph, R^2 = *o*-Ns, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
60% ee = 81%
R^1 = Ph, R^2 = *p*-Ts, Ar = Ph: 71% ee = 87%
R^1 = *p*-$NO_2C_6H_4$, R^2 = *p*-Ts, Ar = Ph: 98% ee = 92%
R^1 = *p*-BrC_6H_4, R^2 = Ses, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
76% ee = 92%
R^1 = Ph, R^2 = Ses, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
99% ee = 92%
R^1 = *p*-BrC_6H_4, R^2 = Ts, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
90% ee = 93%
R^1 = PhC≡C, R^2 = Ses, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
50% ee > 99%
R^1 = 2-$C_{10}H_7$, R^2 = Ts, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
69% ee = 91%
R^1 = *n*-Hex, R^2 = Ts, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
64% ee = 84%
R^1 = CO_2Bn, R^2 = Ses, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
81% ee > 99%
R^1 = CON(OMe)Bn, R^2 = Ses, Ar = 3,5-Cl_2-4-$(Me)_2SiC_6H_2$:
85% ee > 99%

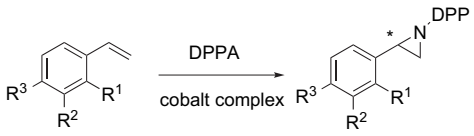


Scheme 115. Aziridination of olefins with azides mediated by ruthenium(salen)(CO) complexes.

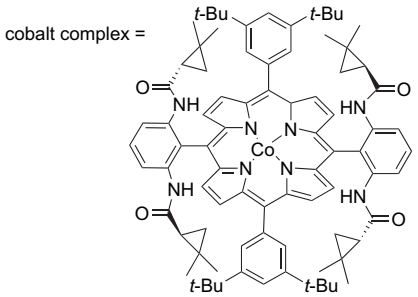
In addition, Che et al. have developed asymmetric intramolecular aziridinations of sulfonamides in the presence of $PhI(OAc)_2$ and a chiral ruthenium porphyrin [Ru(Por*)(CO)].[159] As an example, the reaction of 2-vinylbenzenesulfonamide afforded in these conditions the corresponding tricyclic aziridine in 65% yield, albeit with a low enantioselectivity of 9% ee.

3.1.4. Catalysis by other metals. In 2008, Zhang et al. developed the first co-catalysed asymmetric aziridination of olefins using diphenylphosphoryl azide (DPPA) as the nitrene source, affording the corresponding *N*-phosphorylated aziridines.[160] The reaction was carried out in the presence of D_2-symmetric chiral porphyrins, such as that depicted in Scheme 116. This novel catalyst system could be applied to a wide variety of aromatic olefins, giving the corresponding aziridines in good yields combined with moderate enantioselectivities of up to 53% ee.

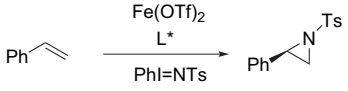
In 2008, Bolm et al. demonstrated that low-cost and non-toxic iron could be applied as catalyst to the asymmetric aziridination of styrene by using PhI=NTs as the nitrene source.[161] Indeed, the combination of iron(II) triflate with chiral ligands was found to induce chirality in the formation of styrene aziridine. Among various tridentate ligands, the (*S*,*S*)-*i*-Pr-py-BOX ligand was shown to be the most efficient, leading to the product with enantioselectivity of 40% ee and 72% yield (Scheme 117). Interestingly, 2,6-bis(*N*-pyrazolyl)pyridine ligands were also found to be applied as chiral ligands, giving albeit lower enantioselectivities (≤20% ee).



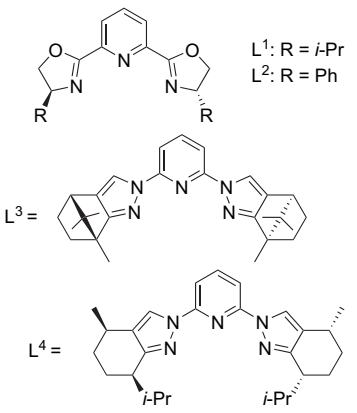
R^1 = R^2 = R^3 = H: 88% ee = 37%
R^1 = Me, R^2 = R^3 = H: 35% ee = 46%
R^1 = R^3 = H, R^2 = Me: 52% ee = 44%
R^1 = R^2 = H, R^3 = Me: 58% ee = 37%
R^1 = R^2 = H, R^3 = *t*-Bu: 77% ee = 53%
R^1 = R^2 = H, R^3 = Br: 65% ee = 28%
R^1 = Br, R^2 = R^3 = H: 68% ee = 7%
R^1 = R^3 = H, R^2 = Br: 58% ee = 45%
R^1 = R^2 = H, R^3 = Cl: 64% ee = 6%
R^1 = R^2 = H, R^3 = F: 72% ee = 17%
R^1 = R^2 = H, R^3 = CF_3: 64% ee = 44%
R^1 = R^3 = H, R^2 = NO_2: 58% ee = 46%



Scheme 116. Co-catalysed aziridination of olefins with DPPA.



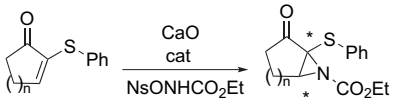
L* = L^1: 72% ee = 40%
L* = L^2: 51% ee = 25%
L* = L^3: 60% ee = 20%
L* = L^4: 40% ee = 6%



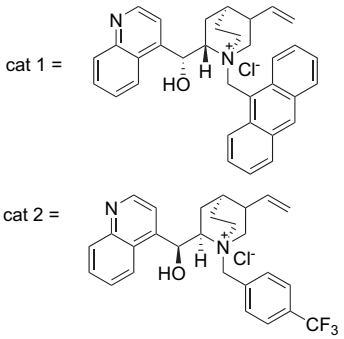
Scheme 117. Fe-catalysed aziridination of styrene.

In 2005, Zhou et al. reported the synthesis of a chiral mononuclear complex of Re(I)–NOBIN Schiff base via the reaction of $Re(CO)_5Cl$ and the corresponding tridentate ligand in methanol.[162] This ligand was derived from the reaction between NOBIN and 3,5-dichlorosalicylaldehyde. It was found that this novel rhenium catalyst showed some catalytic ability in the asymmetric aziridination of styrene and *p*-chlorostyrene, which gave the corresponding aziridines in yields of 36 and 30%, respectively, although without chiral induction.

3.1.5. Organocatalysed aziridination. For a long time, it was not known that organocatalysts could be used to catalyse the aziridination reactions.[163] In recent years, however, several examples of organocatalytic enantioselective aziridination of olefins have been successfully developed, and these have become a topic of interest in asymmetric organocatalysis. Among these reactions are those based on the use of quaternary salts of cinchona alkaloids as the catalysts to induce chirality in the aziridination of 2-(phenylsulfanyl)-2-cycloalkenones.[164] The reaction of these cycloalkenones with ethyl nosyloxycarbamate under phase-transfer conditions provided the corresponding aziridines in satisfactory yields and with enantioselectivities of up to 75% ee (Scheme 118).



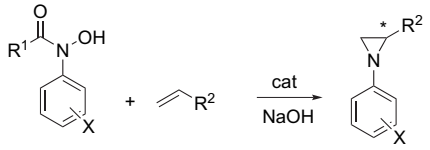
with cat 1:
n = 1: 25% ee = 48%
n = 2: 25% ee = 71%
n = 3: 43% ee = 48%
with cat 2:
n = 1: 18% ee = 25%
n = 2: 93% ee = 75%
n = 3: 29% ee = 60%



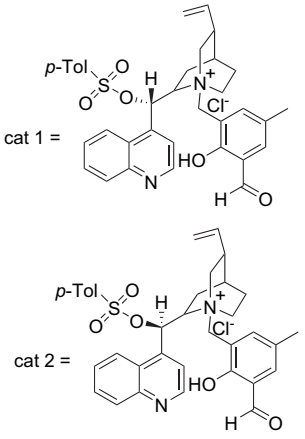
Scheme 118. Aziridination of 2-(phenylsulfanyl)-2-cycloalkenones mediated by cinchona alkaloids.

In the same context, Murugan and Siva have developed other cinchona alkaloids as chiral phase-transfer catalysts for the asymmetric aziridination of a wide range of electron-deficient olefins with *N*-acyl-*N*-aryl hydroxamic acids.[165] The corresponding chiral *N*-arylaziridines were isolated in good yields and with high enantioselectivities of up to 95% ee, as shown in Scheme 119. It was shown that the formation of the *R*- and *S*-aziridines was solely dependent on chiral transfer between the substrate and the catalyst.

More recently, Minakata et al. reported a new method for the aziridination of electron-deficient olefins based on the use of *N*-chloro-*N*-sodio carbamate.[166] These reactions were promoted by phase-transfer chiral ammonium salt catalysts derived from cinchona alkaloids, yielding the corresponding aziridines from α,β-unsaturated ketones, esters, sulfones and amides in good yields and with enantioselectivities of up to 86% ee, as shown in Scheme 120.



with cat 1:
R^1 = *t*-Bu, X = H, R^2 = CO_2*t*-Bu: 79% ee = 94% (*S*)
R^1 = *t*-Bu, X = 3-Br, R^2 = CO_2*t*-Bu: 87% ee = 76% (*S*)
R^1 = *t*-Bu, X = 4-Br, R^2 = CO_2*t*-Bu: 79% ee = 87% (*S*)
R^1 = Ph, X = 4-Me, R^2 = CO_2Me: 85% ee = 79% (*S*)
R^1 = Ph, X = 4-NO_2, R^2 = CO_2*t*-Bu: 41% ee = 43% (*S*)
with cat 2:
R^1 = *t*-Bu, X = 4-OMe, R^2 = CO_2*t*-Bu: 92% ee = 95% (*R*)
R^1 = *t*-Bu, X = 4-Cl, R^2 = CO_2*t*-Bu: 86% ee = 85% (*R*)
R^1 = *t*-Bu, X = 4-CO_2H, R^2 = Ph: 53% ee = 75% (*R*)
R^1 = *t*-Bu, X = 4-OH, R^2 = SOPh: 77% ee = 82% (*R*)
R^1 = *t*-Bu, X = H, R^2 = CO_2*t*-Bu: 56% ee = 88% (*R*)
R^1 = *t*-Bu, X = 4-Br, R^2 = CO_2Me: 49% ee = 76% (*R*)
R^1 = Ph, X = 4-Me, R^2 = CO_2*t*-Bu: 69% ee = 85% (*R*)
R^1 = *t*-Bu, X = 4-NO_2, R^2 = CO_2*t*-Bu: 92% ee = 89% (*R*)
R^1 = *t*-Bu, X = 4-Me, R^2 = CO_2*t*-Bu: 65% ee = 90% (*R*)

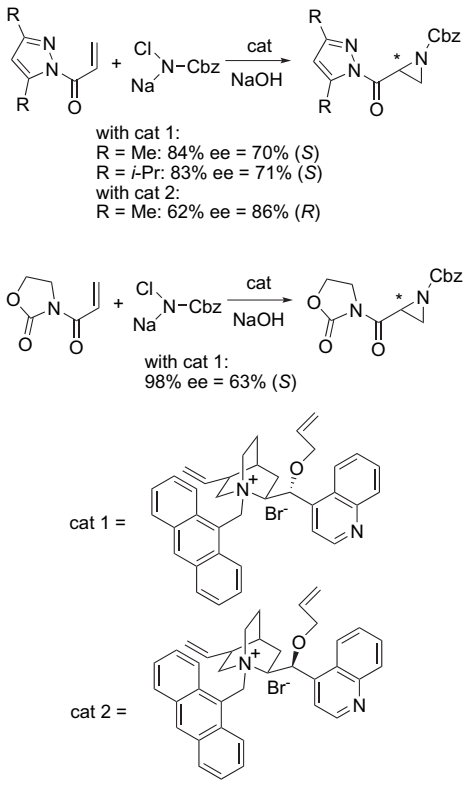


Scheme 119. Aziridination of olefins with *N*-acyl-*N*-aryl hydroxamic acids mediated by cinchona alkaloids.

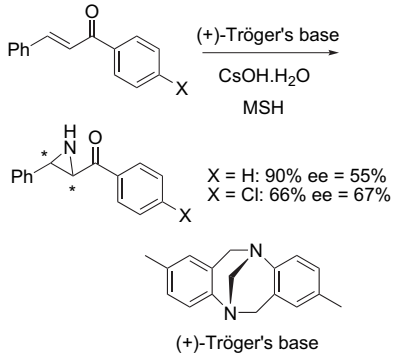
In 2006, Shi et al. reported a one-pot process, which involved the in situ generation of a hydrazinium salt, deprotonation of the hydrazinium to form an aminimide and subsequent aziridination by reaction with chalcones.[167] It was shown that *O*-mesitylenesulfonylhydroxylamine (MSH) could readily aminate various tertiary amines to give the corresponding hydrazinium salts in high yields. The asymmetric aziridination of chalcones was then examined by treating MSH and a chiral tertiary amine, such as (+)-Tröger's base, with a base, such as $CsOH·H_2O$. As shown in Scheme 121, a reasonable level of enantioselectivity of up to 67% ee could be obtained by applying these conditions to the aziridination of two chalcones.

In the same context, Armstrong et al. have developed the asymmetric aziridination of chalcone using an aminimide generated in situ from the treatment of a chiral tertiary amine, such as quinine, with *O*-(diphenylphosphinyl)hydroxylamine.[168] As shown in Scheme 122, a promising level of asymmetric induction of 56% ee was obtained for the aziridination of *E*-chalcone by using these conditions.

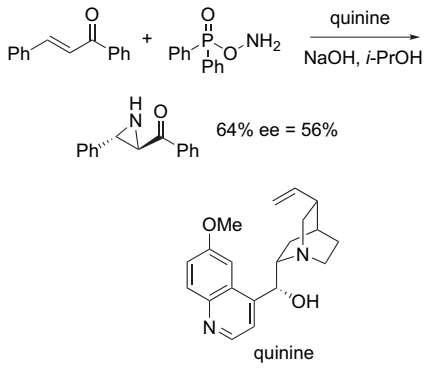
An unprecedented example of a highly chemo- and enantioselective organocatalytic aziridination of α,β-unsaturated aldehydes with acylated hydroxycarbamates was reported by Cordova et al., in 2007.[169] This reaction was catalysed efficiently by simple chiral pyrrolidine derivatives and led to the corresponding 2-formylaziridines in good-to-high yields with diastereoselectivities of



Scheme 120. Aziridinations of olefins with *N*-chloro-*N*-sodio carbamate mediated by cinchona alkaloids.

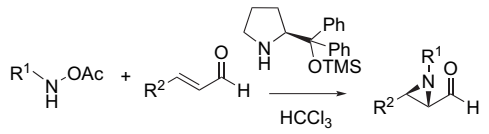


Scheme 121. Aziridination of chalcones with aminimide derived from (+)-Tröger's base.

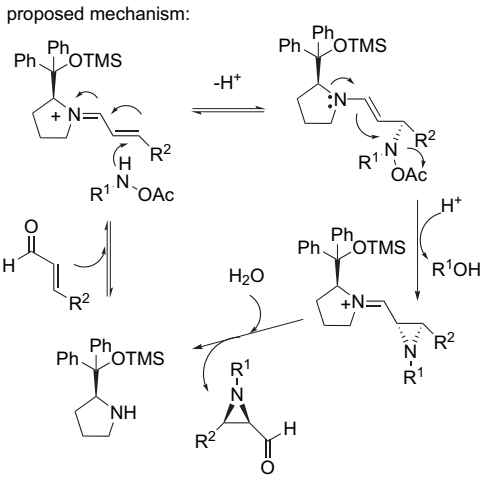


Scheme 122. Aziridination of chalcone with aminimide derived from quinine.

up to 90% de and enantioselectivities of up to 99% ee, as shown in Scheme 123. These authors have proposed a mechanism, depicted in Scheme 123, in which an efficient shielding of the *Si* face of the chiral iminium intermediate by the bulky phenyl groups of the organocatalyst led to the stereoselective *Re*-facial nucleophilic conjugate attack on the β carbon atom of the electrophile by the amino group of the acylated hydroxycarbamate. Next, the chiral enamine intermediate generated performed a 3-*exo*-tet nucleophilic attack on the now electrophilic nitrogen atom, and acetic acid was released. The intramolecular ring closure pushed the equilibrium in the forward direction and made this step irreversible.



R^1 = *n*-Pr, R^2 = Cbz: 62% de = 82% ee = 99%
R^1 = *n*-Bu, R^2 = Cbz: 70% de = 66% ee = 96%
R^1 = Bn, R^2 = Boc: 68% de = 66% ee = 92%
R^1 = Me, R^2 = Boc: 54% de = 66% ee = 90%
R^1 = CH_2-CH=CH_2, R^2 = Cbz: 68% de = 72% ee = 96%
R^1 = Et, R^2 = Cbz: 60% de = 66% ee = 97%
R^1 = $(CH_2)_3OBz$, R^2 = Boc: 60% de = 66% ee = 98%
R^1 = $(CH_2)_2CO_2Bn$, R^2 = Cbz: 62% de = 66% ee = 84%
R^1 = CH_2-*p*-$NO_2C_6H_4$, R^2 = Cbz: 66% de = 74% ee = 92%



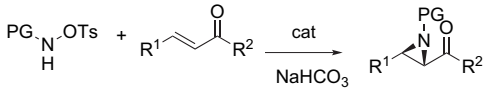
Scheme 123. Aziridination of α,β-unsaturated aldehydes with acylated hydroxycarbamates mediated by chiral pyrrolidine.

In 2008, a closely related strategy was applied by Melchiorre et al. to the asymmetric aziridination of α,β-unsaturated ketones by using a chiral primary amine salt, which was prepared by combining the easily available 9-amino(9-deoxy)*epi*-hydroquinine with D-*N*-Boc-phenylglycine.[170] Therefore, both linear and cyclic α,β-unsaturated ketones reacted with tosylated hydroxycarbamates in these conditions to afford the corresponding aziridines with almost complete diastereocontrol and very high enantioselectivity of up to 99% ee (Scheme 124). These results showed the ability of this chiral organocatalyst salt to promote an asymmetric domino iminium–enamine intramolecular sequence.

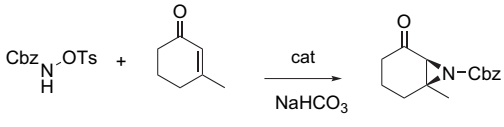
3.2. Aziridination via carbene transfer to imines

Although most of the methods for obtaining chiral aziridines by using a chiral catalyst proceeded through the transfer of a nitrogen

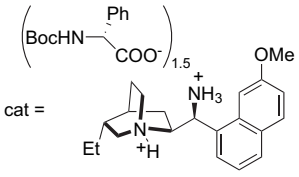
group to an olefin, a number of methods based on the less-studied enantioselective transfer of a carbenoid to an imine have been successfully developed in recent years.[171]



R^1 = *n*-Pent, R^2 = Me, PG = Cbz: 93% de = 90% ee = 96%
R^1 = *n*-Pent, R^2 = Me, PG = Boc: 82% de > 90% ee = 99%
R^1 = R^2 = Me, PG = Cbz: 96% de > 90% ee = 93%
R^1 = Me, R^2 = Et, PG = Cbz: 94% de = 90% ee = 98%
R^1 = CO_2Et, R^2 = Me, PG = Cbz: 85% de > 90% ee = 73%
R^1 = Ph, R^2 = Me, PG = Cbz: 85% de > 90% ee = 99%
R^1 = *p*-$NO_2C_6H_4$, R^2 = Me, PG = Cbz: 92% de > 90% ee = 99%
R^1,R^2 = $(CH_2)_3$, PG = Cbz: 86% de > 90% ee = 98%

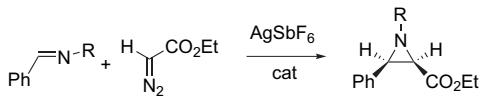


84% ee = 73%

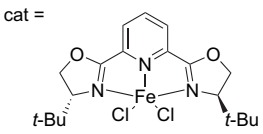


Scheme 124. Aziridinations of α,β-unsaturated ketones with tosylated hydroxycarbamates mediated by chiral primary amine salt.

3.2.1. Carbene methodology. The formation of aziridines upon transition metal-catalysed decomposition of diazo compounds in the presence of imines is well established. In particular, the reaction of ethyl diazoacetate with imines mediated by a Lewis acid is normally selective for the formation of the *cis*-aziridine. In 2003, Tilley et al. studied the enantioselective reaction of ethyl diazoacetate with *N*-aryl imines catalysed by a novel chiral benzyl bisoxazoline complex of coordinatively unsaturated monomeric rhodium(II).[172] This reaction proceeded selectively, giving a 75:25 ratio of the corresponding *cis*- and *trans*-aziridines, albeit with poor enantioselectivity (≤11% ee). On the other hand, the use of a chiral iron–pybox complex to catalyse these reactions was demonstrated by Hossain et al. to be more efficient.[173] Indeed, when $AgSbF_6$ was used as an initiator, the reaction of ethyl diazoacetate with *N*-aryl imines afforded the corresponding *cis*-aziridines in enantioselectivity of up to 49% ee in the presence of the *tert*-butyl-pybox iron complex depicted in Scheme 125. The role of the Ag^+ ion was assumed to create an open site on iron for coordination of the imine to the Lewis acid.

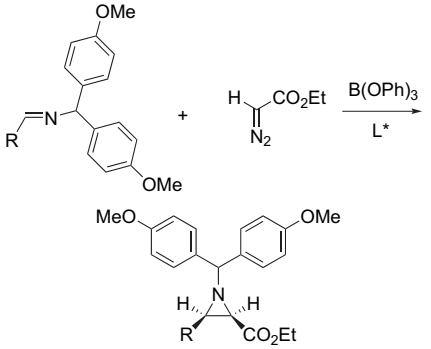


R = Ph: 47% ee = 49%
R = $CHPh_2$: 39% ee = 28%

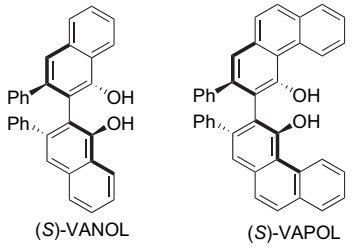


Scheme 125. Fe-catalysed aziridination of *N*-aryl imines with ethyl diazoacetate mediated by *tert*-butyl-pybox.

The studies recently developed by Wulff et al. based on the use of the vaulted chiral biaryl ligands, VANOL and VAPOL, are among the most successful contributions to date for the enantioselective aziridination of imines with ethyl diazoacetate. Therefore, the asymmetric catalytic aziridination of *N*-dianisylmethylimines with ethyl diazoacetate was developed with chiral catalysts prepared from triphenylborate and both the vaulted binaphthol (VANOL) and vaulted biphenanthrol (VAPOL) ligands.[174] These reactions produced the corresponding *N*-dianisylmethyl-protected 3-substituted aziridinyl-2-carboxylate esters in high yields and high asymmetric inductions of up to 97% ee combined with a high diastereoselectivity for the *cis*-aziridines. These two catalysts were both highly enantioselective, and the catalyst loading could be lowered to 0.25 mol % in some cases. Some results are collected in Scheme 126.



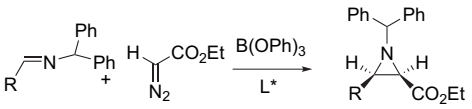
with L* = VAPOL:
R = Cy: 86% *cis:trans* = 97:3 ee = 84%
R = *t*-Bu: 70% *cis:trans* = 98:2 ee = 75%
R = Ph: 92% *cis:trans* = 97:3 ee = 95%
R = *o*-$MeOC_6H_4$: 86% *cis:trans* = 98:2 ee = 89%
R = *p*-BrC_6H_4: 95% *cis:trans* = 98:2 ee = 93%
R = *p*-$NO_2C_6H_4$: 97% *cis:trans* = 98:2 ee = 97%
R = 1-Naph: 91% *cis:trans* = 98:2 ee = 97%
with L* = VANOL:
R = Cy: 69% *cis:trans* = 98:2 ee = 77%
R = *t*-Bu: 77% *cis:trans* = 98:2 ee = 87%
R = Ph: 91% *cis:trans* = 98:2 ee = 96%
R = *p*-$MeOC_6H_4$: 86% *cis:trans* = 97:3 ee = 89%
R = *p*-BrC_6H_4: 89% *cis:trans* = 97:3 ee = 97%
R = *p*-$NO_2C_6H_4$: 88% *cis:trans* = 95:5 ee = 96%
R = 1-Naph: 92% *cis:trans* = 98:2 ee = 94%



Scheme 126. Boron-catalysed aziridination of *N*-dianisylmethylimines with ethyl diazoacetate mediated by VANOL and VAPOL ligands.

In 2008, the scope of this methodology was extended to a wide range of *N*-benzhydryl imines, including electron-poor aromatic benzhydryl imines as well as primary, secondary and tertiary aliphatic benzhydryl imines.[175] The use of catalysts prepared from $B(OPh)_3$ and either the VANOL or VAPOL ligand gave essentially the same profile of asymmetric inductions with enantioselectivities ranging from 77 to 94% for all the substrates (Scheme 127).

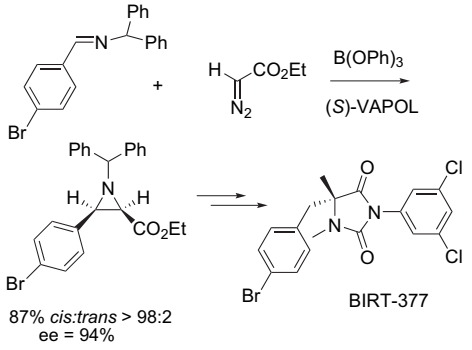
The synthetic utility of this methodology has been illustrated by the same workers in the asymmetric catalytic synthesis of a leukointegrin LFA-1 antagonist, BIRT-377, which has been developed as an agent for the treatment of inflammatory and immune disorders.[176] As shown in Scheme 128, the synthesis was achieved



with L* = VAPOL:
R = 1-Naph: 76% *cis:trans* = 97:3 ee = 93%
R = Ph: 82% *cis:trans* = 98:2 ee = 94%
R = *o*-MeOC$_6$H$_4$: 63% *cis:trans* = 91:9 ee = 91%
R = *p*-Tol: 80% *cis:trans* = 98:2 ee = 92%
R = *o*-BrC$_6$H$_4$: 37% *cis:trans* = 62:38 ee = 82%
R = *p*-BrC$_6$H$_4$: 78% *cis:trans* = 95:5 ee = 90%
R = *p*-NO$_2$C$_6$H$_4$: 79% *cis:trans* = 94:6 ee = 79%
R = *p*-MeOC$_6$H$_4$: 51% *cis:trans* = 86:14 ee = 86%
R = 3,4-(OAc)$_2$C$_6$H$_3$: 87% *cis:trans* = 100:0 ee = 89%
R = *n*-Pr: 40% *cis:trans* = 93:7 ee = 81%
R = Cy: 73% *cis:trans* = 98:2 ee = 81%
R = *t*-Bu: 72% *cis:trans* = 100:0 ee = 87%
with L* = VANOL:
R = 1-Naph: 80% *cis:trans* = 98:2 ee = 93%
R = Ph: 87% *cis:trans* = 100:0 ee = 93%
R = *o*-MeOC$_6$H$_4$: 67% *cis:trans* = 92:8 ee = 90%
R = *p*-Tol: 79% *cis:trans* = 98:2 ee = 94%
R = *o*-BrC$_6$H$_4$: 43% *cis:trans* = 66:34 ee = 82%
R = *p*-BrC$_6$H$_4$: 86% *cis:trans* = 95:5 ee = 94%
R = *p*-NO$_2$C$_6$H$_4$: 86% *cis:trans* = 100:0 ee = 89%
R = *p*-MeOC$_6$H$_4$: 61% *cis:trans* = 97:3 ee = 87%
R = 3,4-(OAc)$_2$C$_6$H$_3$: 84% *cis:trans* = 100:0 ee = 93%
R = *n*-Pr: 54% *cis:trans* = 93:7 ee = 77%
R = Cy: 79% *cis:trans* = 98:2 ee = 82%
R = *t*-Bu: 89% *cis:trans* = 100:0 ee = 85%

Scheme 127. Boron-catalysed aziridination of *N*-benzhydryl imines with ethyl diazoacetate mediated by VANOL and VAPOL ligands.

through a *cis*-aziridine, prepared by the reaction of ethyl diazoacetate with an *N*-benzhydryl imine in the presence of the VAPOL catalyst.

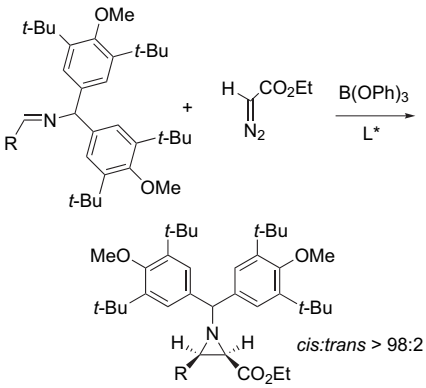


87% *cis:trans* > 98:2
ee = 94%

Scheme 128. Synthesis of BIRT-377.

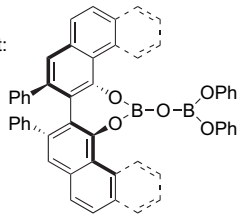
According to mass spectral analysis and mechanistic studies, it was demonstrated that the active catalyst of this process was a pyroborate species, involving one ligand molecule and two boron atoms (Scheme 129).[175] In order to obtain an insight into how the imine interacted with the catalyst, these workers have screened the diarylmethyl *N*-substituents on the imine.[177] This study has revealed that the 3,5-di-*tert*-butyldianisylmethyl group gave exceptionally high asymmetric inductions, along with high yields and almost complete *cis* stereoselectivity, as shown in Scheme 129.

In addition, this highly efficient asymmetric aziridination methodology could be successfully applied to other diazo compounds, such as diazomethyl vinyl ketones, which were reacted with a series of *N*-benzhydryl imines in the presence of the VAPOL catalyst.[178] As shown in Scheme 130, the corresponding *cis*-vinyl



with L* = VAPOL:
R = 1-Naph: 93% ee = 99%
R = Ph: 98% ee = 99%
R = *p*-MeOC$_6$H$_4$: 87% ee = 98%
R = *p*-Tol: 95% ee = 99%
R = *o*-Tol: 97% ee = 99%
R = *o*-BrC$_6$H$_4$: 84% ee = 96%
R = *p*-BrC$_6$H$_4$: 99% ee = 99%
R = *p*-NO$_2$C$_6$H$_4$: 92% ee = 96%
R = Et: 62% ee = 93%
R = Cy: 89% ee = 89%
R = *t*-Bu: 60% ee = 78%
with L* = VANOL:
R = 1-Naph: 96% ee = 98%
R = Ph: 97% ee = 98%
R = *p*-MeOC$_6$H$_4$: 90% ee = 98%
R = *p*-Tol: 98% ee = 98%
R = *o*-Tol: 96% ee = 96%
R = *o*-BrC$_6$H$_4$: 83% ee = 90%
R = *p*-BrC$_6$H$_4$: 99% ee = 98%
R = *p*-NO$_2$C$_6$H$_4$: 91% ee = 97%
R = Et: 57% ee = 87%
R = Cy: 87% ee = 84%
R = *t*-Bu: 76% ee = 80%

active cat:

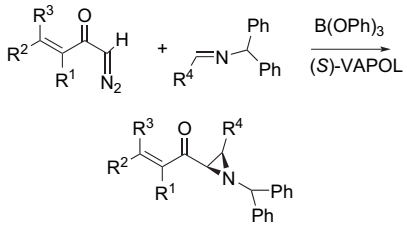


Scheme 129. Boron-catalysed aziridination of 3,5-di-*tert*-butyldianisylmethylimines with ethyl diazoacetate mediated by VANOL and VAPOL ligands.

aziridinyl ketones were isolated in high yields and with high degrees of asymmetric induction of up to 100% ee.

While catalysts derived from linear biaryls such as BINOL gave very poor-to-moderate enantioselectivity for the aziridination of benzylidene benzhydrylamines with ethyl diazoacetate,[179] Wipf and Lyon have demonstrated that increasing the steric bulk at the 3,3′-positions of BINOL exerted an improved facial control in the reaction.[180] Therefore, these authors have studied a series of 3,3′-disubstituted BINOL derivatives as chiral ligands for the aziridination of benzhydryl imines with ethyl diazoacetate. It was demonstrated that the introduction of bulky arene substituents, in particular the 2-phenylnaphthalene moiety, into the 3- and 3′-positions of the binaphthol scaffold led to a significant improvement in the level of chiral induction of up to 78% ee, as shown in Scheme 131.

In contrast to all the preceding aziridinations, which are *cis*-selective, Maruoka et al. reported, in 2008, a *trans*-selective asymmetric aziridination of diazoacetamides with *N*-Boc imines

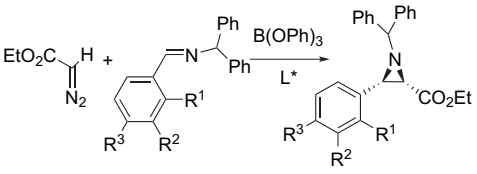


$R^1 = R^3 = H$, $R^2 = R^4 = Ph$: 79% *cis:trans* > 98:2 ee = 95%
$R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = o$-Tol: 45% *cis:trans* > 98:2 ee = 91%
$R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = o$-BrC_6H_4: 55% *cis:trans* = 92:8 ee = 93%
$R^1 = R^3 = H$, $R^2 = Ph$, R^4 = 2-F-5-C_6H_3: 64% *cis:trans* = 93:7 ee = 95%
$R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = m$-$NO_2C_6H_4$: 78% *cis:trans* > 98:2 ee = 94%
$R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = p$-Tol: 71% *cis:trans* > 98:2 ee = 100%
$R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = p$-BrC_6H_4: 51% *cis:trans* = 93:7 ee = 96%
$R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = p$-$NO_2C_6H_4$: 80% *cis:trans* > 98:2 ee = 95%
$R^1 = R^3 = H$, $R^2 = Ph$, R^4 = 2-Naph: 84% *cis:trans* > 98:2 ee = 98%
$R^1 = R^3 = H$, $R^2 = Ph$, R^4 = Cy: 90% *cis:trans* = 83:7 ee = 93%
$R^1 = H$, $R^2 = R^3 = Me$, $R^4 = Ph$: 76% *cis:trans* = 94:6 ee = 98%
$R^1 = H$, $R^2 = R^3 = Me$, $R^4 = p$-Tol: 83% *cis:trans* > 98:2 ee = 96%
$R^1 = H$, $R^2 = R^3 = Me$, $R^4 = p$-BrC_6H_4: 76% *cis:trans* = 95:5 ee = 98%
$R^1 = H$, $R^2 = R^3 = Me$, $R^4 = p$-$NO_2C_6H_4$: 67% *cis:trans* = 87:13 ee = 96%
$R^1 = H$, $R^2 = R^3 = Me$, R^4 = Cy: 75% *cis:trans* = 91:9 ee = 94%
$R^1 = R^3 = H$, $R^2 = Me$, $R^4 = Ph$: 85% *cis:trans* = 96:4 ee = 96%
R^1,R^2 = $(CH_2)_4$, $R^3 = H$, $R^4 = Ph$: 40% *cis:trans* = 86:14 ee = 82%

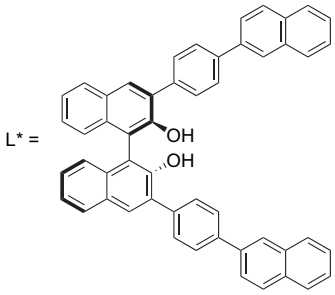
Scheme 130. Boron-catalysed aziridination of *N*-benzhydryl imines with diazomethyl vinyl ketones mediated by VAPOL ligand.

organocatalysed by an axially chiral dicarboxylic acid.[181] Screening of the reaction between benzaldehyde *N*-Boc imine and *N*-phenyldiazoacetamide using various axially chiral dicarboxylic acids having 3,3′-diaryl substituents led to the identification of the 3,3′-dimesityl substituted dicarboxylic acid depicted in Scheme 132 as the optimal catalyst, providing the corresponding *trans*-aziridine exclusively in good yield and high enantioselectivity (92% ee). The scope of this trans-selective aziridination was further extended to a wide range of substrates with excellent general enantioselectivities (89–99% ee), good yields and complete trans selectivity, as shown in Scheme 132. In order to explain the trans selectivity, the authors have speculated that it arose from the preference of a rotamer in which the carboxamide group and the aryl group of the *N*-Boc imine adopted an antiperiplanar orientation. Synclinal orientation would be destabilised by the steric repulsion (Scheme 132). The hydrogen bonding between the amide N–H bond and the Boc group might act as a secondary factor.

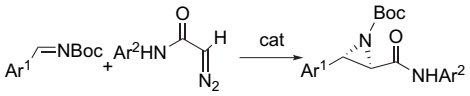
3.2.2. Sulfur ylide-mediated aziridination. As an extension of his methodology for epoxide synthesis, Aggarwal has developed an aziridination procedure based on asymmetric carbene transfer via a chiral in situ-generated sulfonium ylide.[182] This procedure



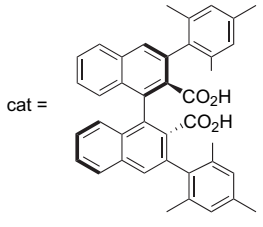
$R^1 = R^2 = R^3 = H$: 55% *cis:trans* = 99:1 ee = 54%
$R^1 = R^2 = H$, $R^3 = Br$: 76% *cis:trans* = 99:1 ee = 78%
$R^1 = R^2 = H$, $R^3 = NO_2$: 66% *cis:trans* = 99:1 ee = 55%
$R^1 = H$, R^2,$R^3 = OCH_2O$: 57% *cis:trans* = 99:1 ee = 55%
$R^1 = OSO_2$-(*o*-NO_2)C_6H_4, $R^2 = R^3 = H$: 39% *cis:trans* = 60:40 ee = 55%

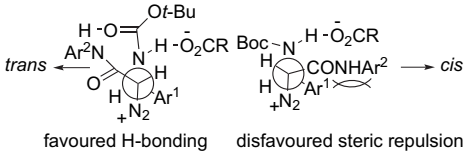


Scheme 131. Boron-catalysed aziridination of *N*-benzhydryl imines with ethyl diazoacetate mediated by bulky BINOL-derived ligand.



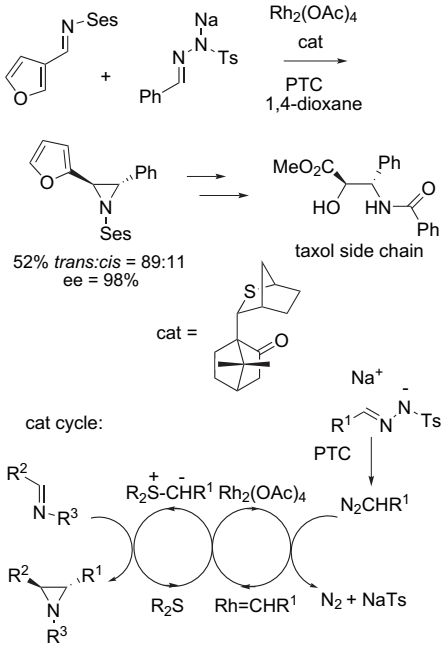
$Ar^1 = Ar^2 = Ph$: 61% ee = 97%
$Ar^1 = p$-Tol, $Ar^2 = Ph$: 51% ee = 99%
$Ar^1 = m$-Tol, $Ar^2 = Ph$: 52% ee = 98%
Ar^1 = 2-Naph, $Ar^2 = Ph$: 66% ee = 99%
$Ar^1 = p$-$PivOC_6H_4$, $Ar^2 = Ph$: 49% ee = 96%
$Ar^1 = m$-$MeOC_6H_4$, $Ar^2 = Ph$: 55% ee = 96%
$Ar^1 = p$-FC_6H_4, $Ar^2 = Ph$: 31% ee = 89%
$Ar^1 = m$-ClC_6H_4, $Ar^2 = Ph$: 50% ee = 91%
$Ar^1 = Ph$, $Ar^2 = p$-$MeOC_6H_4$: 61% ee = 97%
Ar^1 = 2-Naph, $Ar^2 = p$-$MeOC_6H_4$: 71% ee = 99%
$Ar^1 = p$-$PivOC_6H_4$, $Ar^2 = p$-$MeOC_6H_4$: 57% ee = 97%
$Ar^1 = Ph$, $Ar^2 = p$-ClC_6H_4: 60% ee = 97%
Ar^1 = 2-Naph, $Ar^2 = p$-ClC_6H_4: 70% ee = 99%





Scheme 132. Organocatalysed *trans*-aziridination of diazoacetamides with *N*-Boc imines.

consists of the generation of a carbene via a diazo decomposition with $[Rh_2(OAc)_4]$, its association to a chiral sulfide and subsequent transfer to an appropriate imine.[183] This highly efficient sulfur ylide methodology has been used to construct the taxol side chain with a high degree of enantioselectivity via a *trans*-aziridine.[184] Therefore, the reaction of the *N*-Ses imine depicted in Scheme 133 with the tosylhydrazone salt derived from benzaldehyde in the presence of a phase-transfer catalyst (PTC), $Rh_2(OAc)_4$ and catalytic quantities (20 mol %) of a chiral sulfide led to the corresponding aziridine in good yield and an 89:11 *trans*/*cis* diastereoisomeric ratio (Scheme 133). The expected *trans*-aziridine was obtained with an enantiomeric excess of 98% and was further converted into the desired final taxol side chain. A catalytic cycle was proposed involving the decomposition of the diazo compound in the presence of the rhodium complex to yield the metallocarbene. This was then transferred to the chiral sulfide, forming a sulfur ylide, which underwent a reaction with the imine to give the expected aziridine, returning the sulfide to the cycle to make it available for further catalysis (Scheme 133).

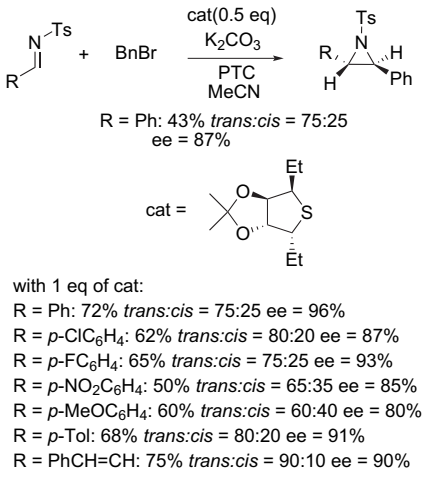


Scheme 133. Synthesis of taxol side chain.

Finally, Huang et al. have reported the synthesis of a novel chiral C_2-symmetric sulfide from L-tartaric acid and its application to an asymmetric tandem reaction between benzyl bromide and tosylimines to form the corresponding aziridines.[185] In this case, the sulfide reacted with benzyl bromide in the presence of potassium carbonate to generate the corresponding chiral sulfonium ylide in situ, which then reacted with an *N*-tosyl imine to yield the aziridine. In the presence of a catalytic amount of the sulfide (0.5 equiv) the aziridine was isolated in moderate yield with a dominant *trans*-isomer and high enantioselectivity, as shown in Scheme 134. Increasing the amount of sulfide from 0.5 to 1 equiv allowed both better yields and enantioselectivities of up to 96% ee.

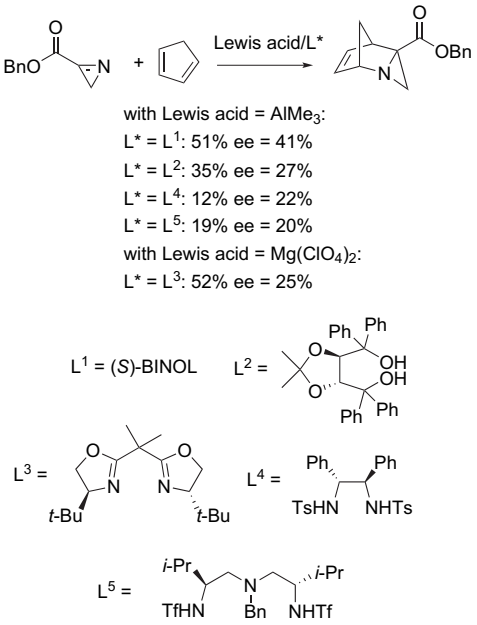
3.3. Miscellaneous reactions

In 2003, Somfai and Timén developed the first catalytic enantioselective aza-Diels–Alder reactions involving azirines as dienophiles.[186] In this study, a wide range of Lewis-acidic metals and chiral ligands were screened together with benzyl-2*H*-azirine-3-carboxylate as dienophile and cyclopentadiene. Of all the Lewis



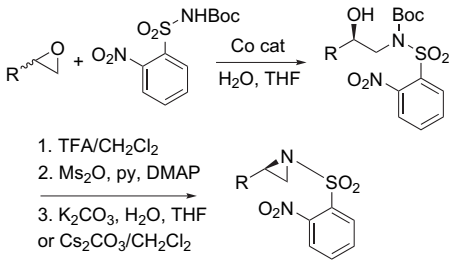
Scheme 134. Sulfur ylide-mediated aziridination.

acids screened, $AlMe_3$, together with, especially, oxygen-containing ligands, such as (*S*)-BINOL, TADDOL or bisoxazoline, but also with nitrogen-containing ligands, such as bis-sulfonamides, proved to be most successful, providing the corresponding aziridine with moderate enantioselectivity of up to 41% ee (Scheme 135).

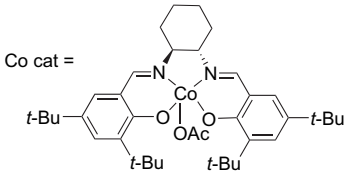


Scheme 135. Lewis-acid-catalysed aza-Diels–Alder reaction of azirine with cyclopentadiene.

In 2004, Kim and Jacobsen developed a new and practical route to highly enantio-enriched aziridines from racemic epoxides, which was actually constituted by three successive reactions, with the intermediate products isolated by simple filtration of the crude reaction mixtures.[187] The first step of the sequence consisted of the kinetic resolution of a racemic epoxide with a sulfonamide in the presence of a chiral [(salen)Co] complex, yielding the corresponding enantiopure 1,2-amino alcohol derivative, which was isolated by filtration of the crude material through silica gel. This product was then transformed into the corresponding *N*-nosyl aziridine by successive removal of the Boc group, conversion into the *O*-mesylate and then cyclisation with K_2CO_3 or Cs_2CO_3. A series of chiral aziridines was thus synthesised in almost complete enantioselectivity and in high yields, as shown in Scheme 136.

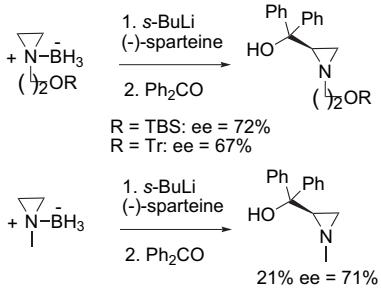


R = Cy: 86% ee > 99%
R = *n*-Bu: 79% ee > 99%
R = *t*-Bu: 67% ee > 99%
R = CO_2Me: 69% ee > 99%
R = CH_2Cl: 75% ee > 99%
R = $(CH_2)_2CH{=}CH_2$: 58% ee > 99%
R = Ph: 81% ee = 99%
R = *m*-ClC_6H_4: 82% ee > 99%
R = *o*-ClC_6H_4: 81% ee > 99%
R = *p*-ClC_6H_4: 85% ee > 99%
R = *m*-$MeOC_6H_4$: 80% ee > 99%
R = *m*-$NO_2C_6H_4$: 72% ee > 99%



Scheme 136. Synthesis of aziridines by kinetic resolution of epoxides.

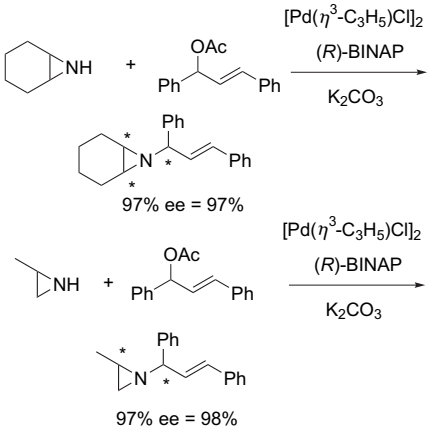
In 2003, Vedejs et al. studied the stereochemistry of aziridine borane lithiation, demonstrating that it occurred *syn* to the borane subunit.[188] Moreover, the enantioselective lithiation of stable borane complexes was performed in the presence of (−)-sparteine as the chiral ligand of lithium, providing the corresponding lithioaziridines, which were subsequently trapped with electrophiles. The corresponding free aziridines were isolated with good enantioselectivities of up to 72% ee (Scheme 137).



Scheme 137. Syntheses of aziridines by enantioselective borane lithiations.

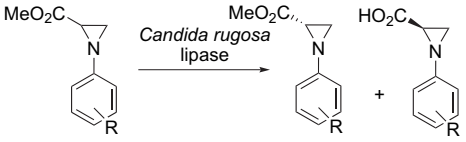
The conventional methods to prepare enantiomerically aziridines have mostly provided these products in their *N*-protected forms. In 2004, Yudin et al. explored routes from unprotected aziridines to their *N*-allylated derivatives.[189] In this context, these authors found that unprotected aziridines underwent facile palladium-catalysed allylic amination with allyl acetates in the presence of K_2CO_3, providing the corresponding aziridines in high yields. When the reaction was carried out in the presence of (*R*)-BINAP as the chiral ligand of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, it yielded the corresponding aziridines with excellent enantioselectivity of up to 98% ee, as shown in Scheme 138.

When an asymmetric route to an enantiomerically pure aziridine cannot be achieved, the possibility still exists to perform a kinetic resolution of the racemic aziridine mixture. This can either



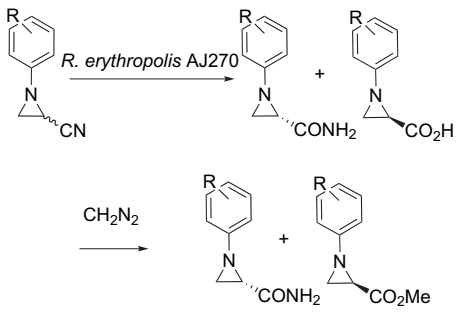
Scheme 138. Syntheses of aziridines by Pd-catalysed allylic aminations.

be achieved chemically or enzymatically. In recent years, several examples of the enzymatic resolution of aziridines have been successfully developed. As an example, Kumar et al. have demonstrated that *N*-arylaziridine-2-carboxylates could be enzymatically resolved using the lipase from *Candida rugosa* to afford optically active aziridine carboxylates in moderate-to-high enantiomeric purity, as shown in Scheme 139.[190]



R = H: 48% ee = 84%
R = 4-Br: 50% ee = 99%
R = 4-NO_2: 45% ee = 12%
R = 4-Me: 48% ee = 70%
R = 4-F: 44% ee = 7%
R = 4-Me,3-Br: 46% ee = 15%
R = 4-MeO: 46% ee = 79%

Scheme 139. Enzymatic resolution of *N*-arylaziridine-2-carboxylates.

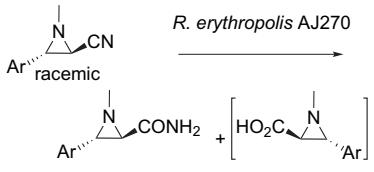


R = H: 45% (carboxamide) ee (carboxamide) > 99% + 47% (ester) ee (ester) = 91%
R = 4-F: 48% (carboxamide) ee (carboxamide) > 99% + 50% (ester) ee (ester) = 94%
R = 4-Cl: 46% (carboxamide) ee (carboxamide) = 95% + 49% (ester) ee (ester) = 87%
R = 4-Br: 25% (carboxamide) ee (carboxamide) > 99% + 74% (ester) ee (ester) = 67%
R = 4-MeO: 28% (carboxamide) ee (carboxamide) = 96% + 22% (ester) ee (ester) > 99%
R = 4-Me: 50% (carboxamide) ee (carboxamide) > 99% + 50% (ester) ee (ester) > 99%
R = 3-Me: 45% (carboxamide) ee (carboxamide) = 97% + 50% (ester) ee (ester) = 90%

Scheme 140. Resolution of *N*-arylaziridine-2-carbonitriles by biotransformations.

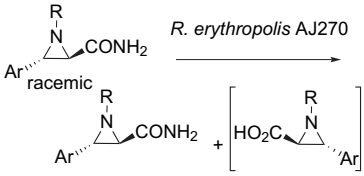
In 2007, Wang et al. demonstrated that, catalysed by the *Rhodococcus erythropolis* AJ270 whole-cell catalyst under very mild conditions, biotransfromations of racemic *N*-arylaziridine-2-carbonitriles proceeded efficiently and enantioselectively to produce highly enantiopure (*S*)-*N*-arylaziridine-2-carboxamides and (*R*)-*N*-arylaziridine-2-carboxylic acids in excellent yields (Scheme 140).[191] The latter carboxylic acids were converted by treatment with diazomethane into the corresponding methyl esters.

As an extension of this methodology, several racemic *trans*-3-arylaziridine-2-carbonitriles were efficiently transformed into their corresponding enantiopure (2*R*,3*S*)-3-arylaziridine-2-carboxamides in similar conditions (Scheme 141).[192]



Scheme 141. Resolution of *trans*-3-arylaziridine-2-carbonitriles by biotransformations.

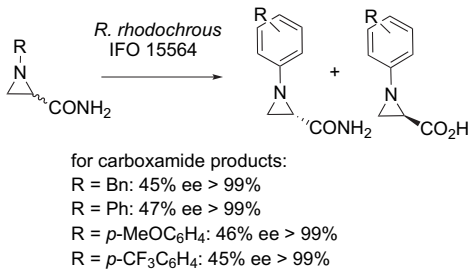
While the nitrile hydratase exhibited low selectivity against nitrile substrates, the amidase was highly enantioselective towards 3-arylaziridine-2-carboxamides. Indeed, the conditions described above could be applied to the resolution of a number of racemic *trans*-3-arylaziridine-2-carboxamides, as shown in Scheme 142.[192]



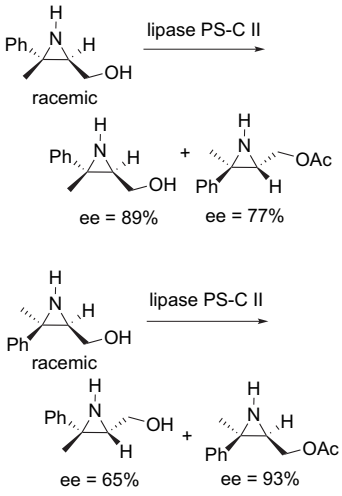
Scheme 142. Resolution of *trans*-3-arylaziridine-2-carboxamides by biotransformations.

In the same context, enantiopure *N*-benzyl- and *N*-arylaziridine-2-carboxamides were obtained by Gotor et al. through kinetic resolution of their corresponding racemates by treatment with *Rhodococcus rhodochrous* IFO 15564 (Scheme 143).[193]

In addition, Sakai et al. have reported the lipase-catalysed resolution of (2*R**,3*S**)- and (2*R**,3*R**)-3-methyl-3-phenyl-2-aziridinemethanols.[194] Therefore, upon treatment with lipase PS-C II, (2*R**,3*S**)-3-methyl-3-phenyl-2-aziridinemethanol gave enantio-enriched (2*R*,3*S*)-3-methyl-3-phenyl-2-aziridinemethanol and its corresponding acetate, while a similar reaction of (2*R**,3*R**)-3-methyl-3-phenyl-2-aziridinemethanol afforded enantio-enriched (2*R*,3*R*)-3-methyl-3-phenyl-2-aziridinemethanol and its corresponding acetate (Scheme 144).



Scheme 143. Resolution of *N*-benzyl- and *N*-arylaziridine-2-carboxamides by biotransformations.



Scheme 144. Enzymatic resolution of 3-methyl-3-phenyl-2-aziridinemethanol.

4. Conclusions

This review updates the recent developments in asymmetric aziridination covering the literature from 2003. For a long time, asymmetric approaches towards chiral aziridines appeared to be less developed than the analogous reactions leading to other three-membered heterocycles such as epoxides or cyclopropanes. In recent years, however, great advances have been made, which now allow the preparation of chiral aziridines by various synthetic strategies in an efficient manner, affording products in excellent yields and enantioselectivities. In addition to describing the large number of highly efficient processes based on the use of various chiral auxiliaries, this review has demonstrated that the most important achievements in asymmetric aziridination are the spectacular expansion of novel chiral catalysts, including the especially attractive chiral organocatalysts, which have been recently applied to this type of reaction. Indeed, a collection of new chiral Lewis-acid catalysts and organocatalysts have provided new opportunities for these enantioselective reactions. In particular, a number of novel chiral catalysts have been developed to induce chirality in the nitrene transfer to olefins. Moreover, special mention has been made to the VANOL and VAPOL catalysts, which have been applied to the borane-catalysed carbene transfer to imines. On the other hand, several chiral organocatalysts have been successfully applied to both carbene transfer to imines and nitrene transfer to alkenes.

The asymmetric aziridination reaction is therefore well represented as an important tool for organic synthesis. Indeed, enantiopure aziridines attract considerable interest, due to their potential use as intermediates for the synthesis of complex molecules on the one hand, and the interesting biological activities of numerous aziridine-containing alkylating agents or natural products on the other.

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Biographical sketch

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