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The asymmetric synthesis of aziridines

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Contents

1. Introduction

The ability of aziridines to undergo highly regio- and stereoselective ring-opening reactions renders them of great value in organic synthesis.[1] This ability has not gone unnoticed in nature, where a number of molecules possessing an aziridine ring have been shown to exhibit potent biological activity, which is intimately associated with the reactivity of the strained heterocycle. For example, mitomycin A, B and C, together with porfiromycin and mitiromycin,[2] represent an important class of naturally-occurring *mitosanes*, isolated from soil extracts of *Streptomyces verticillatus* (Figure 1).[3]

These mitosanes exhibit both antitumour and antibiotic activity, their antitumour properties resulting from their ability to cross-link DNA.[2] Structure–activity relationships have identified the aziridine ring as being essential for such antitumour activity, and a vast amount of work has concentrated on synthesising derivatives of these natural products with increased potency.[4] A further class of biologically active aziridine derivatives which were isolated from *Streptomyces griseofuscus* S42227 by Nagaoka and co-workers in 1986 are the azinomycins (Figure 2).[5] Again, these aziridines are naturally occurring metabolites which demonstrate activity against a wide range of tumours.

A number of synthetic aziridines have also been shown to exhibit useful biological properties. For example, 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acid **1**[6] is a potent, irreversible inhibitor of the bacterial enzyme diaminopimelic acid epimerase whilst 2-(3-carboxypropyl)aziridine-2-carboxylic acid **2**[7] is an irreversible inhibitor of glutamate racemase (Figure 3).

Novel antitumour agents related to mitosanes and mitomycins have recently been synthesised and demonstrated to possess activity against a variety of cancers.[8] Thus aziridines are worthy targets for the synthetic organic chemist, and it is essential that efficient methods exist for the facile synthesis of a range of structurally diverse aziridines, with the added requirement that any available methods should also allow *enantioselective* aziridine formation.

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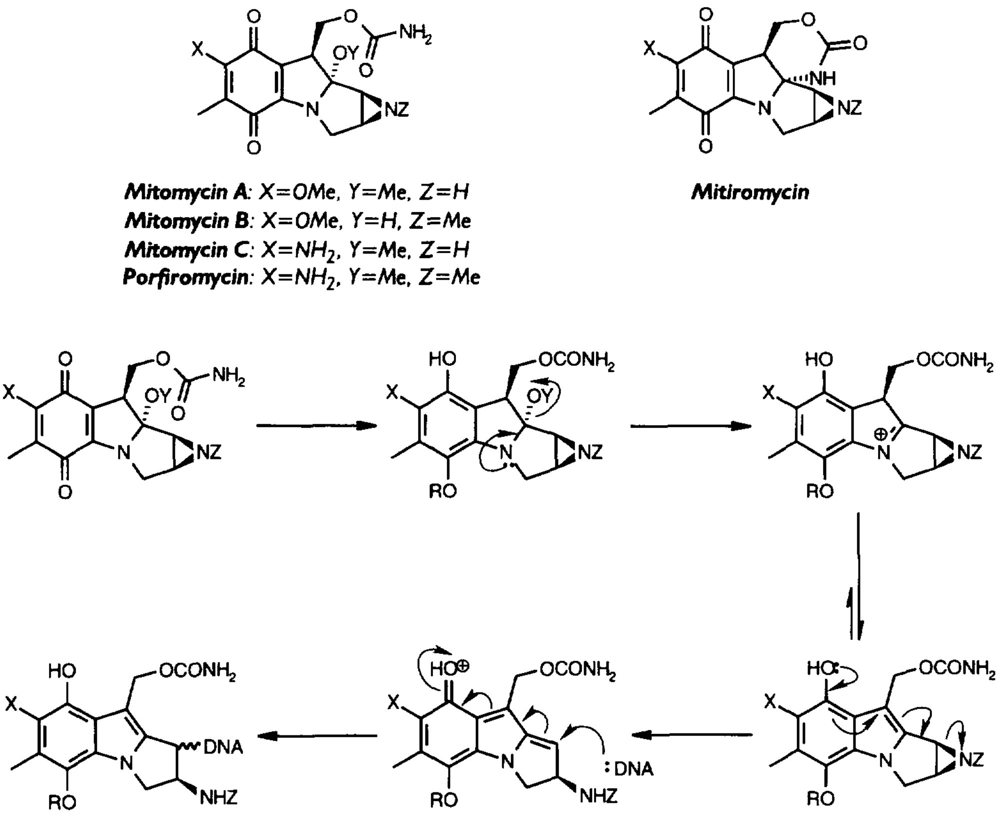
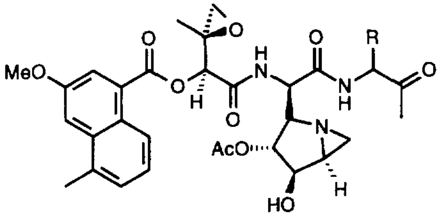


Mitomycin A: X=OMe, Y=Me, Z=H
Mitomycin B: X=OMe, Y=H, Z=Me
Mitomycin C: X=NH$_2$, Y=Me, Z=H
Porfiromycin: X=NH$_2$, Y=Me, Z=Me

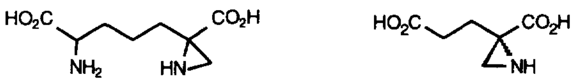
Mitiromycin

Figure 1. Naturally occurring biologically active aziridines and mode of action of mitomycins.



Azinomycin A: R=H; **Azinomycin B**: R=CHO

Figure 2. Biologically active azinomycins.



1

2

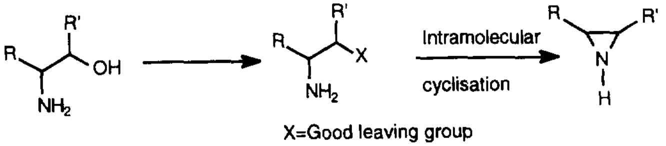
Figure 3. Biologically active synthetic aziridines.

Exisiting literature reviews[1] provide an introduction to general aspects of aziridine synthesis and reactions. The remit of this report is to review general methods for the asymmetric synthesis of aziridines from readily available starting materials. Reference will also be made to methodology for the synthesis of racemic aziridines when an asymmetric protocol has been subsequently developed.

2. Synthesis of aziridines

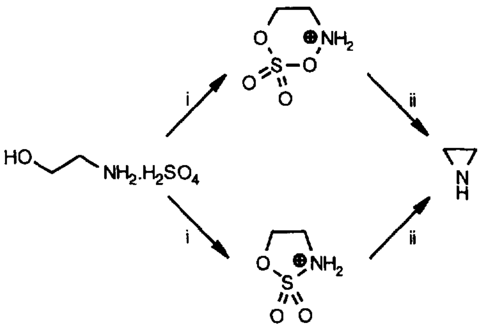
2.1. *From amino alcohols*

A conceptually obvious synthesis of aziridines utilizes 1,2-amino alcohols as precursors: the reaction can be readily achieved when the hydroxyl functional group is converted to a nucleofuge. Intramolecular nucleophilic displacement reaction by either the amide anion or the amine lone pair then yields the aziridine ring (Scheme 1). By using enantiopure amino alcohols, asymmetric synthesis of monochiral (i.e. enantiomerically-pure) aziridines is possible and because the methods to prepare achiral and enantiopure aziridines are, to all intents and purposes, identical, a consideration of the general methods is appropriate.



Scheme 1. General synthesis of aziridines from aminoalcohols.

Early examples of this synthetic transformation to prepare achiral aziridines were reported by Wenker[9] and Gabriel.[10] For example, Wenker converted ethanolamine to ethylene imine *via*, it was claimed, 'β-aminoethyl sulphuric acid' (Scheme 2). Given the modern insight of the reactivity of cyclic sulfates and sulfamidates, however, the intermediate of the reaction might reasonably be considered to be the cyclic sulfamidate of ethanolamine.



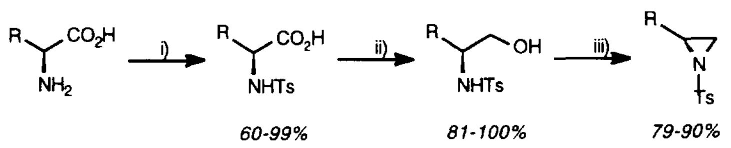
i) H_2SO_4, heat, 71%; ii) Caustic soda, 27%

Scheme 2. Wenker's aziridine synthesis.

Although efficient for simple amino alcohols, this method is unsatisfactory for tertiary alcohols for which elimination occurs to produce an alkene in preference to cyclization. The employment of high pressure technology allows lower temperatures to be used.[11] The reaction is generally stereospecific and relies upon the ability of the amine and leaving group to adopt a *trans* coplanar relationship. If enantiomerically-pure amino alcohols are utilised, this method yields enantiopure aziridines.[12]

Gabriel[10] demonstrated the utility of 2-haloamines for aziridine synthesis. Their intramolecular nucleophilic ring-forming reaction is similar to the Wenker method and is also stereospecific. More recent methods for the conversion of the alcohol moiety of amino alcohols to powerful nucleofuges exploit displacement of oxyphosphonium species.[1] As examples, treatment of an aminoalcohol with Ph_3P plus either Br_2,[13] CCl_4[14] or DEAD,[15] have been widely employed to effect aziridine ring-closure. Other phosphorus reagents employed in such reactions are diphenylphosphinic chloride[16] and diethoxytriphenylphosphine, $[Ph_3P(OEt)_2]$ (*vide infra*).[17] When diphenylphosphinic chloride is employed with enantiopure unprotected amino alcohols, a one-pot version of the recently described method for the asymmetric synthesis of *N*-diphenylphosphinyl activated aziridines is possible.[18]

Enantiomerically-pure 1,2-amino alcohols required for the asymmetric version of the above reactions are frequently obtained in enantiomerically-pure form *via* the reduction of enantiopure 2-amino acids, which are commercially available;[19] indeed, in many cases, the aminoalcohols themselves are commercially available. Where only the aminoacid is available, the efficiency of aziridine formation is, in some cases, hampered by the difficulty in isolating the intermediate amino alcohols, due to formation of water soluble metal complexes. To circumvent this problem, the reduction of *N*-Ts amino acids (rather than the aminoacid itself) has been described; this modification allows the synthesis of enantiopure *N*-Ts aziridines in a one-pot reaction.[20] This method, therefore, permits a high yielding route for the synthesis of enantiopure *N*-Ts aziridines derived from a wide range of 2-amino acids (Scheme 3).

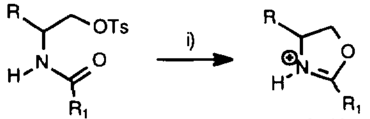


R = Alkyl, benzyl, $CH_2OTBDPS$, $MeS(CH_2)_2$

i) TsCl, EtN^iPr_2; ii) $LiAlH_4$; iii) TsCl, Et_3N, DMAP

Scheme 3. Improved synthesis of enantiopure *N*-Ts aziridines.

Unfortunately, this method cannot be extrapolated to the synthesis of *N*-acyl or *N*-carbamoyl aziridines.[21] In these cases, a more favourable nucleophilic attack by the carbonyl oxygen leads to formation of a 5-membered oxazolonium intermediate *via* loss of TsO^-, rather than the required aziridine (Scheme 4). These species then frequently react to yield either oxazoline or elimination products rather than cyclized materials.



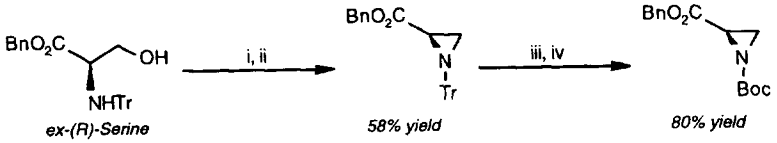
(11)

i) Base

Scheme 4. Oxazoline formation.

Thus, the preparation of (for instance) *N*-BOC aziridines from aminoalcohols is rather tedious, requiring a temporary amine protection; in particular, the use of a trityl blocking group has been efficacious (Scheme 5).[22] Thus *N*-Tr amino alcohols on treatment with TsCl and pyridine yield the tosylates. Further treatment with Et_3N in refluxing THF then yields the *N*-trityl aziridines which can be deprotected under acidic conditions and then reprotected *in situ* with di-*tert* butyl dicarbonate to furnish the *N*-Boc aziridines in good yield.

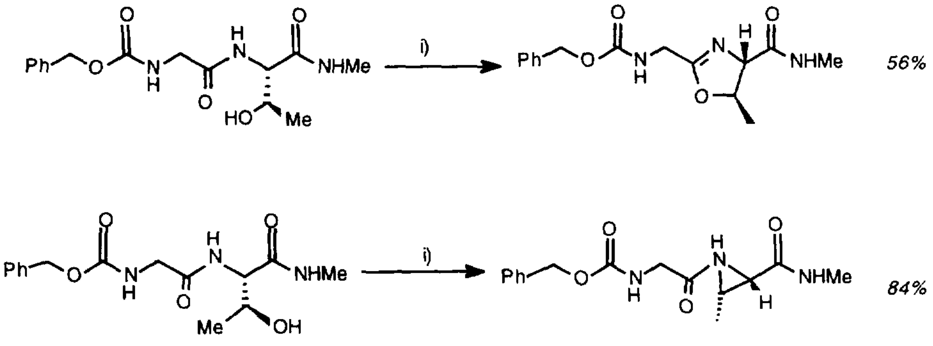
With *certain* peptide-containing *N*-acyl amino alcohols, however, it has proved possible to synthesise *N*-acyl aziridines in preference to oxazolines by using a Mitsunobu reaction.[23] Thus, although *allo*-threonine derivatives produce oxazolines in good yields under Mitsonubu conditions employing diiso-



i) TsCl, pyridine; ii) Et_3N; iii) TFA; iv) Boc_2O

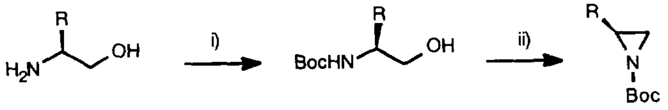
Scheme 5. Indirect synthesis of *N*-Boc aziridines.

propylazodicarboxylate (DIAD) and triphenylphosphine, threonine derivatives successfully produce the required aziridines in good overall yields (Scheme 6).



Scheme 6. Aziridine *versus* oxazoline formation.

This difference in reactivity of threonine and *allo*-threonine is unique to their reaction under Mitsunobu conditions and is not observed in the analogous cyclisations with Burgess reagent (*N*-(triethylammoniosulfonyl)carbamate)[24] or *via* sulphonate displacement. In the latter reactions, oxazoline formation always predominates. The extension of these Mitsunobu conditions for the synthesis of a range of *N*-Boc protected aziridines has recently been reported,[25] although with some *N*-Boc amino alcohols, aziridine formation is still not observed (Scheme 7).



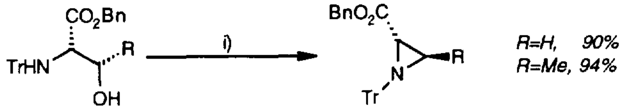
i) Boc_2O; ii) PPh_3, DEAD, THF or $CHCl_3$

R	Yield %
CH_2OBn	73
$CH_2CH_2CO_2Bn$	74
$CH_2CH_2CHMe_2$	82
CH_2Ph	86
$CH_2CH_2CONH_2$	nd[a]
Me	nd[a]

[a] Not determined

Scheme 7. Direct synthesis of certain *N*-Boc aziridines.

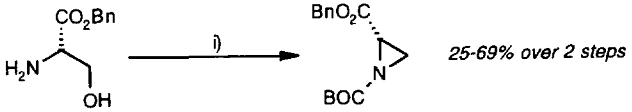
Direct entry to optically active benzyl-*N*-trityl-L-aziridine-2-carboxyic esters may be achieved by treatment of the benzyl esters of *N*-trityl-(*S*)-serine or *N*-trityl-(*S*)-threonine with sulfuryl chloride and triethylamine at −50°C.[26] It has been concluded that a bulky substituent on nitrogen and a non-sterically hindered carboxylate protecting group are essential for favourable cyclisation to occur, affording the required aziridines in good yield (Scheme 8).



i) SO_2Cl_2, Et_3N, -50°C

Scheme 8. Direct synthesis of *N*-Tr aziridines.

As mentioned previously, diethoxytriphenylphosphine (DTPP) effects one-pot activation and cyclization of amino alcohols to aziridines: the method was recently put to use by Baldwin *et al.*, with O-t-butyl-(*S*)-serine as the aminoalcohol in question (Scheme 9).[17]



i) DTPP, toluene, 24 hours; ii) Boc_2O, DMAP, MeCN

Scheme 9. Improved synthesis of *N*-Boc aziridines.

A drawback to this methodology is the fragile nature of DTPP, which is explosive; furthermore, in this case, the reaction was capricious, the yield of cyclisation being variable. *In situ* *N*-protection of the aziridine thus formed then allowed efficient entry to the *N*-Boc-(*S*)-aziridine-2-carboxylic acid derivatives in an efficient manner and without appreciable racemisation. These procedures are an improvement upon Okawa's original lengthy procedure for synthesis of enantiopure aziridine-2-carboxylic esters[27] and are reported to proceed with similar efficiency to his original procedure. The aziridine-2-carboxylic acids thus prepared have recently proved useful synthetic intermediates for the synthesis of (2*S*)-aziridine-2-carboxylic acid containing peptides.[28]

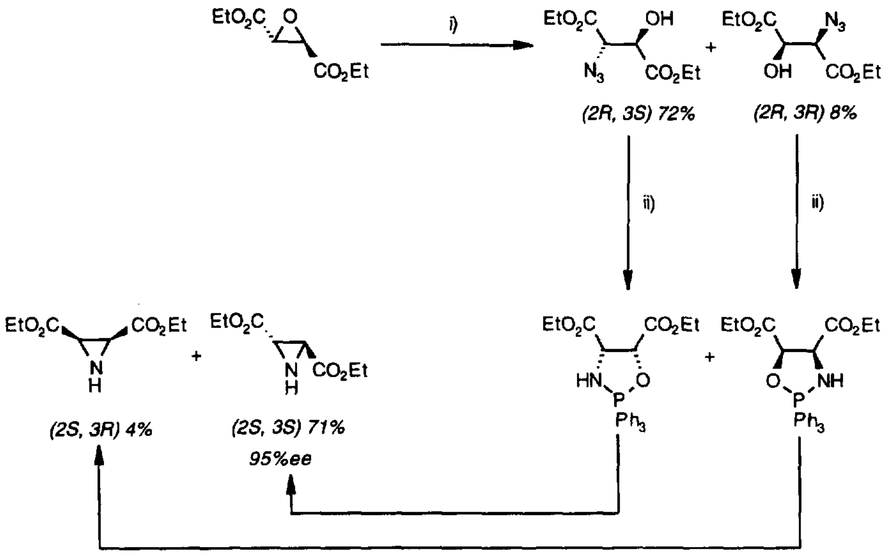
2.2 *From epoxides*

The regiospecific ring opening of epoxides by azide ion has frequently been exploited to enable the synthesis of aziridines.[29] Reduction of the azide moiety of the first-formed azido alcohol, for example with triphenylphosphine in the Staudinger reaction,[30] yields first an imino phosphorane and then an oxazaphospholine intermediate which is normally not be isolated prior to thermally-induced cyclisation to yield an aziridine. When enantiomerically-pure epoxides are used in this reaction sequence, access to non-racemic aziridines is feasible. For example, the method has been applied to the synthesis of all possible isomers of 1H-aziridine-2-carboxylic acids[31] and aziridine-2,3-dicarboxylic acid (Scheme 10).[32]

The ready availability of enantiomerically pure epoxides from allylic alcohols *via* the Sharpless asymmetric epoxidation[33] allows the routine preparation of all possible stereoisomers of a given hydroxymethylaziridine (Scheme 11).

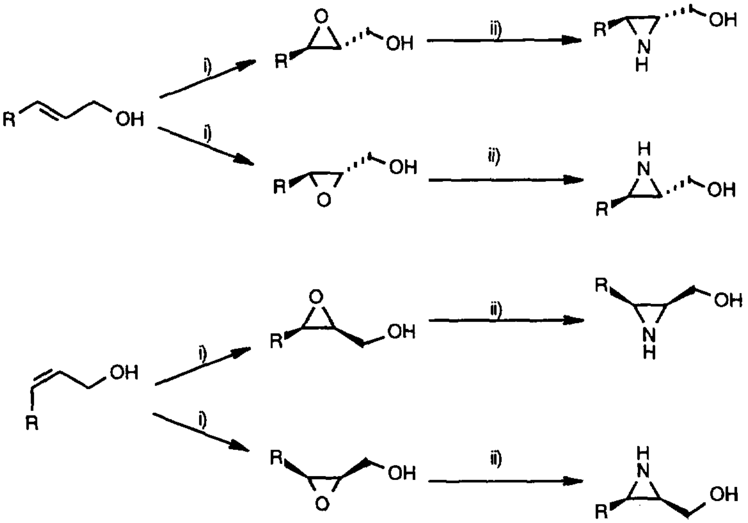
This generation of aziridines from epoxides using the Staudinger reaction has been widely used in preparation of carbohydrate-derived aziridines.[34,30b]

The formation of chiral episulfonium intermediates from chiral epoxides also allows for conversion of chiral epoxides to chiral aziridines, with an overall retention of configuration, resulting from double inversion *via* sequential S_N2 reactions. The overall yields for the transformation from epoxide to aziridine are generally good to excellent (66–94%) (Scheme 12).[35]



i) TMSN$_3$; ii) PPh$_3$

Scheme 10. Synthesis of *N*-Ts aziridines *via* Staudinger reaction.



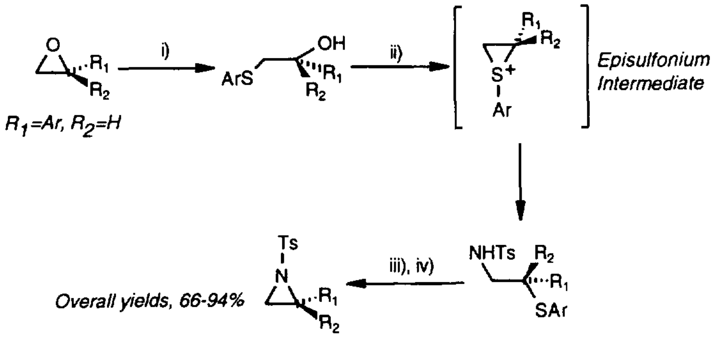
i) Sharpless asymmetric epoxidation; ii) NaN$_3$, PPh$_3$

Scheme 11. Synthesis of all possible stereoisomers of a hydroxymethyl aziridine.

2.3. *From alkenes*

*2.3.1.*Via *cyclic sulfate formation*

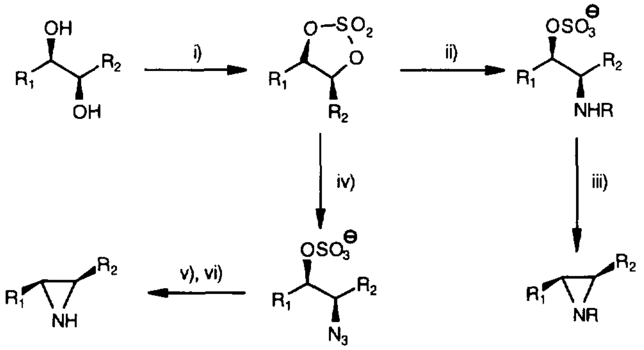
In a reaction sequence exactly analogous to the azide opening/Staudinger sequence shown above, cyclic sulfates obtained from asymmetric dihydroxylation products are easily transformed into aziridines as shown in Scheme 13.[36,37] Two pathways are possible for the conversion of the cyclic sulfate intermediate to aziridines: both involve two consecutive nucleophilic displacement reactions with the final displacement reaction being intramolecular. Thus, facile entry to a range of enantiopure



i) ArSNa; ii) $TsNH_2$; BF_3OEt_2; iii) $Me_3O^+BF_4^-$; iv) NaH

Scheme 12. Synthesis of *N*-Ts aziridine *via* episulfonium intermediate.

N-protected and *N*-unprotected aziridines is possible in excellent overall yields using amine and azide nucleophiles respectively.



i) a) $SOCl_2$, b) $RuCl_3$, $NaIO_4$; ii) RNH_2, THF; iii) *n*-BuLi or $LiAlH_4$ or NaOH; iv) LiN_3, THF; v) $LiAlH_4$; vi) KOH (20%)

SYNTHESIS OF AZIRIDINES FROM CYCLIC SULFATES VIA AMINE ADDITION

R_1	R_2	RNH_2	Overall Yield	% ee / de[b]
(*R*)-Cyclohexyl	H	$PhCH_2NH_2$	78 (77)[a]	>96 (*S*)
(*R*)-Cyclohexyl	H	$Ph(CH_2)_3NH_2$	81 (79)	>96 (*S*)
(*R*)-Cyclohexyl	H	(*S*)-2-Aminobutane	(79)	>96 (*SS*)
(*R*)-n-Butyl	(*R*)-n-Butyl	$PhCH_2NH_2$	62	67 (*SS*)
(*R*)-Phenyl	(*R*)-Phenyl	(*S*)-2-Aminobutane	(82)	>96 (*SSS*)

[a] Yields in parenthesis represent yields from treatment with $LiAlH_4$ and NOT BuLi; [b] From nmr studies

SYNTHESIS OF N-H AZIRIDINES FROM CYCLIC SULFATES VIA AZIDE ADDITION

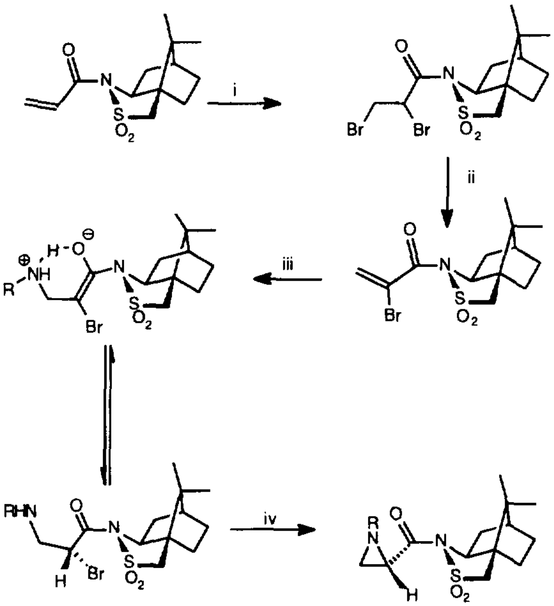
R_1	R_2	Overall Yield	% ee[a]
(*R*)-Cyclohexyl	H	80	>96 (*S*)
(*R*)-n-Butyl	(*R*)-n-Butyl	88	67 (*SS*)

[a] From ^1H and ^{13}C studies of Mosher's amide

Scheme 13. Application of the Sharpless AD reaction to the synthesis of aziridines.

2.3.2. Via *Gabriel–Cromwell reaction*

1,2-Dibromo alkanes, prepared *via* addition of bromine to alkenes, can be elaborated to yield racemic aziridines on treatment with amines.[38] An asymmetric Gabriel–Cromwell reaction of primary amines with enantiomerically-pure 2-bromocarboxylates, leading to *N*-alkylaziridines has been described;[39] best results were obtained utilizing camphor sultam as a stoichiometric chiral controller (Scheme 14).[39]



i) Br_2; ii) Et_3N; iii) RNH_2; iv) Et_3N

R=Bn, 86%; R=p-MeO-C_6H_4, 89%; R=H, 60%

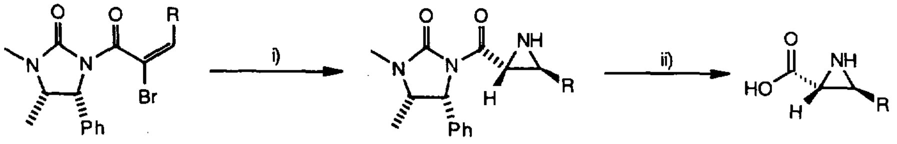
Scheme 14. Aziridines *via* asymmetric Gabriel–Cromwell reaction of bromoacryloyl camphorsultam.

A very similar stoichiometric reagent controlled-strategy utilises chiral alkenoylimidazolidin-2-ones to prepare 1H-aziridines (Scheme 15).[40] In this case, attack of ammonia from the C_β-*si* face of the 2'-bromo derivative establishes the asymmetry; the chiral auxiliary can be removed in a non-destructive manner as the final step of the synthesis *via* treatment of the substrate with lithium benzoxide at 0°C.

A conceptually similar reaction involves the addition of diphenylsulfilimine to an electron-deficient alkene yielding intermediates, which on treatment with base eliminates diarylsulphide leaving aziridine in good yields of upto 70%.[41] If monochiral sulfilimines are used in this reaction, access to monochiral aziridines is possible. Although the overall yield of reaction shown in Scheme 16 was excellent (96%), the maximum ee obtained, despite extensive experimentation, was mediocre (32.6%).[42]

2.3.4. Via *nitrene addition*

Aziridination utilizing direct nitrene addition to alkenes, the reaction conceptually closest to the peracid epoxidation of alkenes, has been improved over recent years by the development of new, mild conditions for nitrene generation. For example, whereas 2,4-dinitrobenzenesulfenylnitrene was traditionally prepared by oxidation of 2,4-dinitrobenzenesulfenamide with lead tetraacetate,[43] a considerably milder alternative has recently been developed which exploits *N*-bromosuccinimide as a mild oxidant.[44] Both electron-rich and cyclic alkenes can be aziridinated with this nitrene to allow entry to *N*-(2,4-dinitrobenzenesulfenyl) aziridines. This class of aziridines is particularly attractive due to the mild conditions underwhich *N*-deprotection can be achieved.[45]

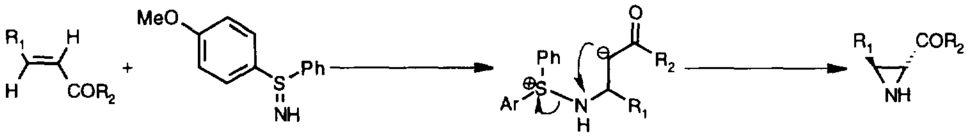


i) NH_3, DMSO; ii) $PhCH_2OLi$, 0°C

R	Time	Solvent	Conversion	(R,S) / (S,R) / cis[a]	Yield of (2'R,3'S) aziridine[b]
Me	1.5	DMSO	95	92/8/trace	84
Me	1.5	MeOH	20	67/-/33	-
Et	2	DMSO	86	90/10/trace	75
n-Pr	2.5	DMSO	88	90/10/-	75
Ph	24	DMSO	3	-	-

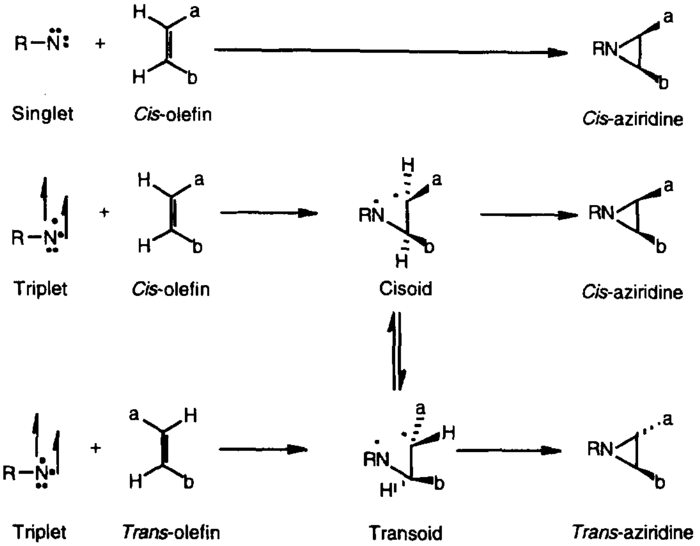
[a] Determined via nmr and HPLC analysis; [b] Yield after purifiction by column chromatography

Scheme 15. Aziridines *via* asymmetric Gabriel–Cromwell reaction of bromoacryloyl oxazolidinones.



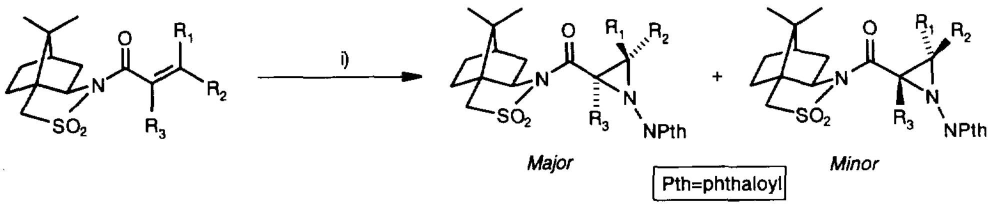
Scheme 16. Synthesis of aziridines *via* sulfilimines.

The addition of *free* nitrenes to an alkene is, however, generally not well stereochemically-controlled, mixtures of *cis*- and *trans*- aziridines being formed.[46] This is due to the rapid interconversion of the singlet and triplet nitrene states (Scheme 17).



Scheme 17. Synthesis of aziridines *via* nitrene addition to alkenes.

Thus even when the nitrene is generated solely in the singlet state (which adds stereospecifically), concurrent decay to the triplet nitrene (1/30 times as fast as addition) leads to loss of stereospecificity. Since the photolytic generation of nitrenes produces two thirds singlet nitrene and one third triplet nitrene, this further limits the stereospecificity of aziridination. Thus, the use of free nitrenes to prepare non-racemic aziridines has not been widespread. However, recent work by Vederas and co-workers[47] has illustrated that lead tetraacetate oxidation of *N*-aminophthalimides in the presence of chiral α,β-unsaturated acid derivatives bearing an appropriate chiral auxiliary at the carbonyl centre allows for the synthesis of *N*-phthalimidoaziridine adducts (12–94% yield) with 33% to >95% diastereofacial selectivity (Scheme 18). It is likely that in this case the reaction no longer preceeds *via* an aminonitrene intermediate, but instead *via* an *N*-acetoxyaminophthalimide intermediate.[48] Thus *syn* attack occurs at the *re* face of the α-carbon to produce the observed diastereoselectivity. By using the antipode of the chiral sultam, it is possible to achieve access to the antipode of the chiral aziridine. Titanium mediated alcoholysis of the sultam aziridine then affords ready access to the parent carboxylic acid, especially if allyl alcohol is used in the hydrolysis reaction. NMR analysis using chiral shift analysis confirmed that no epimerisation occurred during the hydrolytic cleavage process.



i) N-Acetoxyaminophthalimide

R1	R2	R3	Total % yield	% De[a]
H	H	H	94	78
H	Me	H	61	33
H	Ph	H	90	80
Me	Me	H	67	>95[b]
H	H	Me	12	70

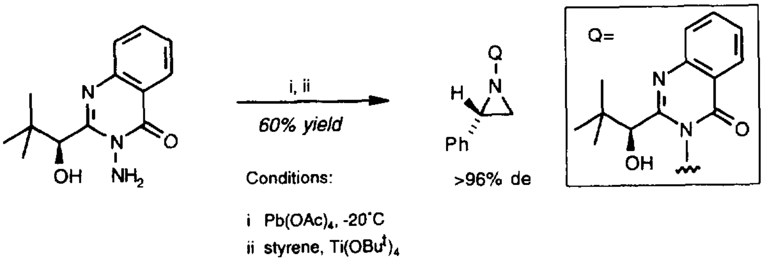
[a] From ^{1}H nmr of crdue reaction mixture; [b] Other isomer not detected

Scheme 18. Aziridination of acryloyl camphorsultam.

In an analogous process in which the controlling asymmetry is present in the aziridinator, rather than the alkene, chiral quinazolin-4(3H)-ones have been shown to effect highly stereoselective aziridination of alkenes.[49] Thus, *tert*-leucine-derived quinoxazolinone aziridinates styrene, butadiene and indene with complete diastereoselectivity in the presence of alkyl titanates; in the absence of the Lewis acid there is no selectivity. The active species is again an *N*-acetoxy species, generated *in situ* by reaction of the precursor quinoxazoline with lead *tetra*acetate (Scheme 19).

These methods therefore offer asymmetric versions of the previously reported reactions with olefins[50] and supplement previously reported chiral variants of this reaction.[51] A related reaction, involving aziridination of electron-deficient alkenes by *N*-acyl-*N*-hydroxyanilines, effects an asymmetric preparation of *N*-arylaziridines.[52] Thus, reaction of *N*-pivaloylhydroxylamines with acrylates in the presence of chiral phase-transfer catalysts dervied from cinchona alkaloids yields aziridines of undisclosed absolute stereochemistry in moderate to poor ee (16–51% ee). Alkenyl silanes may also be aziridinated with good selectivity using the protocol.[53]

The development of effective chiral catalysts for the *enantioselective* transfer of nitrenes and equivalents to alkenes has occupied the recent attention of many researchers. It is true to say, however, that no *generally* effective procedure has yet appeared. Porphyrin and salen-based systems



Scheme 19. Aziridination using chiral quinoxazolinones.

that are effective for alkene epoxidation have only limited utility as aziridination catalysts.[54] Recent reports[55] have shown that (*N*-(*p*-toluenesulphonyl)imino)phenyliodinane (PhI=NTs) can aziridinate alkenes in the presence of catalytic quantities of low-valent metal complexes and recently a variety of catalysts capable of effecting asymmetric aziridination have been reported.[56] These include benzylidene derivatives of 1,2-diaminocyclohexane (Chiral ligand 1)[56c] and chiral 4,4′-disubstituted *bis*(oxazolines) (Chiral ligand 2)[56a,b] (Scheme 20). Binaphthyl salen-manganese(III) complexes have also been examined, by Katsuki *et al.*, as potential aziridinating catlysts.[57]

Jacobsen *et al.* have recently gleaned significant data concerning the origins of the selectivity seen in aziridination reactions using chiral ligand 1 from the X-ray structural analysis of a crystal of a styrene–copper complex.[58] The crystal structure clearly shows that there are two dominant non-bonded interactions between the substarte and the metal complex, a face–face interaction of the arenes and an edge–face arene interaction. This explains why non-aromatic alkenes do not show selectivity in aziridination reactions.

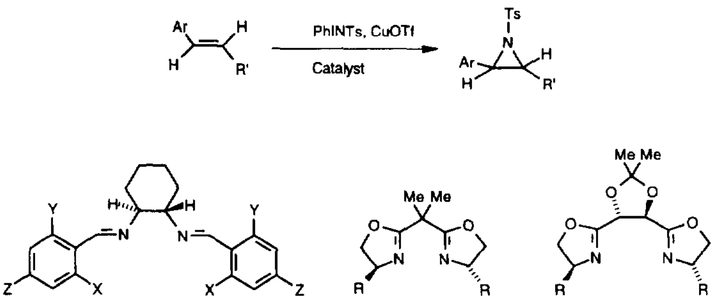
More recently the *bis*-oxazoline ligand used by Evans has been altered by extending the tether between the two oxazoline rings.[59] It was envisaged that the tartrate derived *bis*-oxazoline ligand (chiral ligand 3) would enable the alkyl groups (R) to exert greater steric influence. However, although initial attempts to aziridinate styrene in this way gave excellent yields of conversion of 85%, the enantiomeric excess was a disappointing 18%. The search for more efficient chiral ligands to optimise these results is ongoing, as is a full mechanstic analysis of this synthetic process.[60]

Regioselective copper catalysed nitrene addition to one alkene of 1,3-dienes has also been reported as an efficient method for entry to vinyl aziridines.[61] The more electron rich double bond is preferentially aziridinated. However, when the double bonds are electronically similar, selectivity is governed by steric effects and good regioselectivity may still be achieved. The reaction is poorly enantioselective when carried out in the presence of asymmetric, tartaric acid-derived *bis*oxazoline ligands (Scheme 21).[62]

In an interesting version of self-regeneration of chirality, aziridines have been shown to catalyse the asymmetric aziridination of alkenes with PhI=NTs.[63]

2.4. *From azirines*

Azirines are unsaturated aziridines, and, as such, they represent intermediates for the synthesis of aziridines. They can be prepared from oximes either *via* the Neber reaction[64] or by treatment with Grignard reagents.[65] A recent report has highlighted an elaboration of the former method for access to optically active azirines,[66] which in turn allows access to optically active *cis*-aziridine carboxylates, which are difficult to access by other routes. Thus the Neber reaction is applied, employing a chiral tertiary base such as dihydroquinidine in toluene. After reaction for 6 hours at room temperature, this allows access to a chiral azirine in good yield, presumably *via* a tightly bound complex of the alkaloid base with the ketoximine tosylate. Synthesis of the aziridine is then completed by reduction of the azirine with sodium borohydride with no loss of chirality as detected by GLC of

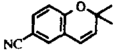
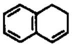
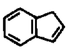
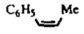
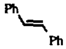


Chiral ligand 1
Optimum results when X=Y=Cl, Z=H

Chiral ligand 2
Optimum results when R=Ph

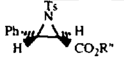
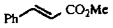
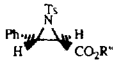
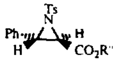
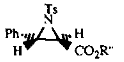
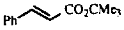
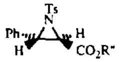
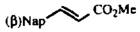
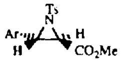
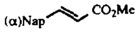
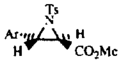
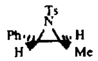
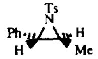
Chiral ligand 3
New generation of catalysts

CHIRAL LIGAND 1 X=Y=Cl, Z=H

Substrate	Yield of aziridine	% Ee[a]	Aziridine configuration
	75	>98	(3*R*, 4*R*) - (+)[b]
	70	87	(1*R*, 2*S*) - (+)[b]
	50	58	(1*R*, 2*S*) - (-)[b]
	79	67 (cis)	(1*R*, 2*S*) - (-)[b]
	79	66	(*R*) - (-)[b]
	nd	30	nd[c]

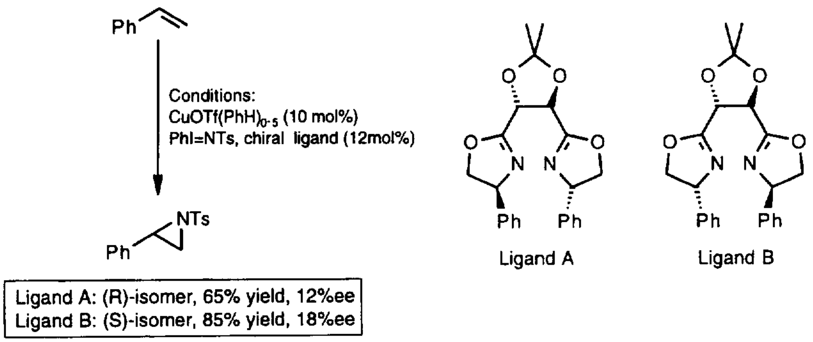
[a] Determined by HPLC analysis; [b] Sign in brackets corresponds to sign of $[\alpha]_D$; [c] Not determined

CHIRAL LIGAND 2 R=Ph

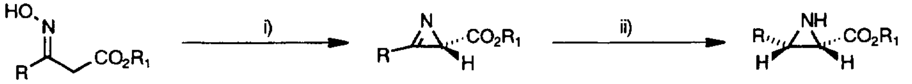
Substrate	R	Solvent	Yield	Ee	Product
	CMe$_3$	MeCN	16	19	
	Ph	MeCN	21	70	
	Ph	C$_6$H$_6$	63	94	
	Ph	C$_6$H$_6$	64	97	
	Ph	C$_6$H$_6$	60	96	
	Ph	C$_6$H$_6$	73	96	
	Ph	C$_6$H$_6$	76	95	
	CMe$_3$	MeCN	62	70	
	CMe$_2$Ph	MeCN	56	38	
	CMe$_3$	Styrene	89	63	

Scheme 20. Synthesis of enantiopure aziridines *via* metal-catalysed nitrene addition to alkenes.

the camphanoyl derivative. Interestingly, no optically active azirine could be attained with sparteine, brucine or strychnine (Scheme 22).



Scheme 21. Modified ligands for nitrene addition to alkenes.



i) TsCl, Chiral tertiary base; ii) NaBH$_4$

R	R$_1$	Base	Yield of azirine from *N*-Ts oxime	ee[a]
Me	Me	Quinidine	40	81 (*R*)
Me	Et	Quinidine	43	82 (*R*)
Me	Et	Quinine	38	55 (*R*)
Me	^{t}Bu	Quinidine	29	44 (*R*)
n-Pr	Et	Quinidine	72	80 (*R*)
Bz	Et	Quinidine	85	80 (*R*)
Bz	Et	Quinine	58	57 (*S*)

[a] As determined from ^{1}H nmr using Yb(tfc)$_3$ as chiral shift reagent, by shift difference of C$_2$ and C$_4$ protons

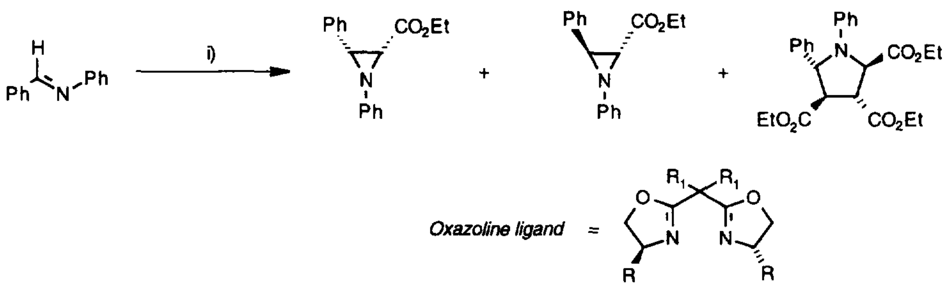
Scheme 22. Asymmetric synthesis of azirines and aziridines *via* Neber reaction.

Application of synthetic procedures,[67] which have been optimised with racemic azirines, may now allow for the asymmetric synthesis of fluorinated aziridines, for example, *via* the addition of CF$_3$SiMe$_3$ to the optically active azirines.

2.5. *From imines*

It has recently proved possible to elaborate traditional methods which have been used for the synthesis of *racemic* aziridines from imines to allow for *asymmetric synthesis* of aziridines from imines. Enantiocontrol is generally obtained by using chiral imines, chiral nucleophiles or chiral catalysts. For example, copper catalysed diazoacetate decomposition in the presence of an imine represents a complementary alternative to nitrene addition to alkenes for the synthesis of aziridines. A preliminary study for racemic synthesis has indicated that the efficiency of the reaction is strongly dependant upon the nature of the imine nitrogen substituent and favours *N*-aryl substituents.[68] The use of a *bis*-oxazoline copper (I) complex as a chiral catalyst has proved useful for introducing enantiocontrol into this process (Scheme 23).[69] However, the combined yield of the isomeric aziridines produced in this way was lower than for the racemic process and this methodology will require further optimisation before it will be generally useful.

Furthermore, the nucleophilic addition of a range of anions bearing α-leaving groups to *N*-Ar or *N*-



i) N_2CHCO_2Et, *bis*-oxazoline and catalytic $[CuPF_6(CH_3CN)_4]$, CH_2Cl_2

Ligand	Yield, *cis*	*cis* / *trans*	ee (*cis*) / ee (*trans*)	Yield Pyrrolidine
R=Ph, R_1=Me	37	4	44 / 35	10
R=Ph, R_1,R_1=H, CN	19	3	15 / 7	11
R=^{t}Bu, R_1=H	10	2	11 / 2	5
R=H, R_1=Me	65	>10	-	<5

Scheme 23. Enantiomerically enriched aziridines from imines and diazoesters.

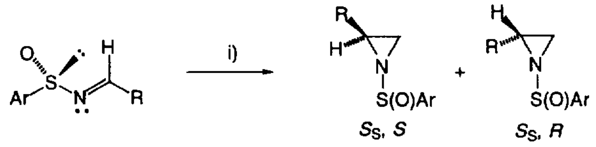
alkyl imines have also been reported as plausible synthetic routes to *N*-Ar or *N*-alkyl aziridines[70] and as such offer the potential for an asymmetric route to aziridines. Asymmetric variants of this reaction have indeed been developed and concentrate on introducing enantiocontrol to the synthetic process either *via* the imine or *via* the nucleophile. For example, the addition of methylene ylids to enantiomerically pure sulfinimines provides a useful method for the asymmetric synthesis of aziridines.[71] Best results are obtained when *S*-t-butylsulfinimines are used,[72] when diastereoselectivities are occasionally good. (Scheme 24). Even when the selectivity is low, the diastereomeric sulfinylaziridines are chromatographically separable. Interestingly, when dimethylsulfonium methylide is used in place of dimethyloxosulfonium methylide, the diastereoselectivity is reversed.

In a similar vein, condensation of enantiopure sulfinimines with the lithium enolate of methyl-α-bromoacetate[73] or of methyl-α-bromopropionate[74] allows entry to *cis*-*N*-(*p*-toluenesulfinyl)aziridine-2-carboxylates in yields of 60–77%. Diastereoselectivities of upto 98% in favour of the *cis*-diastereomer are achieved, with better selectivity being observed with the latter enolate (Scheme 25).

A chair-like transition state is proposed in which the sulfinyl group is also coordinated to the lithium cation. Both the enolate and the *N*-sulfinylimine are required to have the *E*-configuration in the transition state. However, sulfinimines are known to possess relatively low barriers to inversion,[75] and it has, therefore, been argued that the lithium cation may coordinate to both the nitrogen and oxygen of the transition state to lock the imine in the necessary *E*-geometry. By employing the opposite sulfinimine enantiomer, selective entry to the enantiomeric aziridine may be achieved. This procedure is simplified practically by the ready availability of both enantiomers of the sulfinyl group from Andersens reagent,[76] and has allowed for the synthesis of natural products.[77]

A chiral auxiliary based approach has also been reported for introduction of chirality onto the imine substrate.[78] In this way, tartrate derived auxiliaries attached to imines have allowed facile entry to a range of *cis*-aziridines on condensation with lithium or zinc enolates (Scheme 26). It has been observed that lithium enolates afford the (2*R*,3*S*) aziridine diastereomer whereas zinc enolates afford the (2*S*,3*R*) diastereomer, presumably as a consequence of the different co-ordinating abilities of the lithium and zinc metals.[78a]

The moderate yield obtained for this transformation is attributed to self condensation of the metal enolate.

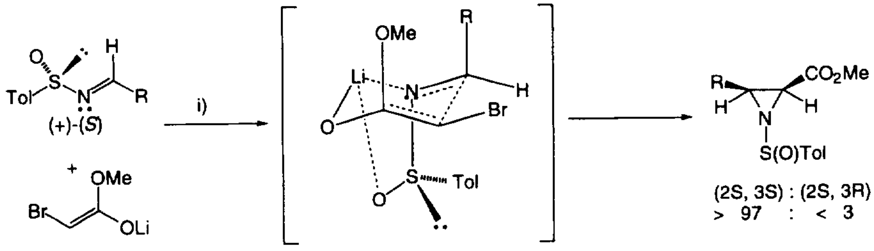


i) $Me_3S(O)Cl$, NaHMDS, THF, -78°C

Sulfinimine, R=	Base	(S_SS) / (S_SR)[a]	Yield[b]
Ph	n-BuLi	75 : 25	62
Ph	LDA	75 : 25	15
Ph	NaH	61 : 39	75
Ph	NaHMDS	79 : 21	68
Ph	LiHMDS	73 : 27	53
Ph	KHMDS	70 : 30	54
n-Pr	NaHMDS	84 : 16	68
1-Naphthyl	NaHMDS	85 : 15	57

[a] From ^1H nmr of crude product. [b] Isolated yield

Scheme 24. Addition of dimethyloxosulfonium methylide to enantiomerically pure imines.



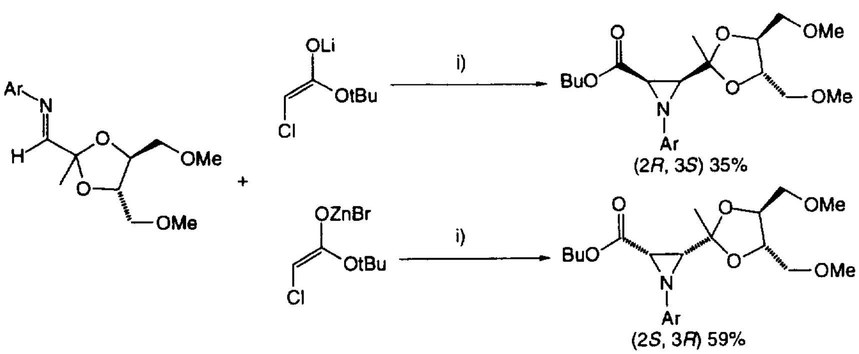
i) -78°C, THF, 2 hours

R	T (°C) / time (h)	(2S, 3S) : (2S, 3R)	Yield
Ph	-78 / 2.5	97 : 3	65
Ph	-78 to rt / 3	90 : 10	77
Ph-OMe-*p*	-78 / 2.5	99 : 1	74
i-Pr	-78 / 2.5	99 : 1	64

Scheme 25. Enantiopure sulfinimines produce aziridines in an enantioselective manner.

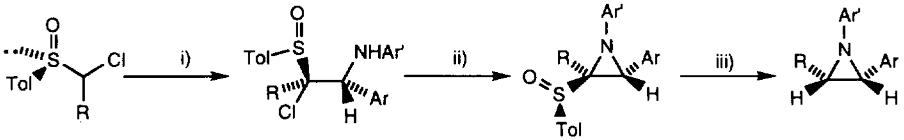
Alternatively, asymmetric routes have been developed which introduce enantioselectivity *via* the addition of chiral nucleophiles onto achiral imines. Chiral sulfoxides can again be employed, for example, when the (*S*)-1-chloroalkyl-*p*-tolyl sulfoxide is condensed with a non-chiral imine, subsequent intramolecular displacement of the chloride leaving group allows for entry to the *cis*-aziridine with maintenance of enantiomeric integrity (Scheme 27).[79]

Subsequent removal of the sulfinyl group has proved possible upon treatment with a Grignard reagent. Chiral enolates also make for useful chiral nucleophiles: for example, Gennari has used chiral boron reagent enolates (Scheme 28).[80] In this way, entry to the *cis*-aziridine with enantiomeric excesses of 94–99% are achieved. A mechanistic rationale for this synthetic operation assumes that the



i) 3 equivalents of enolate, THF, -78°C to ambient temperature

Scheme 26. Tunable enantioselective *aza*-Darzens reaction.



i) LDA, ArCH=NAr', ii) ^tBuOK, iii) R-Met, H_2O

R	Ar	Ar'	Yield chloroamine[a]	Yield S(O)Tol aziridine
$Me(CH_2)_9$	Ph	Ph	94	87
$Me(CH_2)_9$	$Cl-C_6H_4$	Ph	84	93
$Me(CH_2)_9$	Ph	$Br-C_6H_4$	88	98
$CH_2=CHCH_2CH_2$	Ph	Ph	76	83
Me	Ph	Ph	91	92
Me	$Cl-C_6H_4$	Ph	74	90

[a] The enantiomeric excess of the sulfinyl starting material was 97% ee. The enantiomeric excess of the chloroamine derivative was improved to 100% ee by recyrstallisation from $CHCl_3$ / hexane.

Scheme 27. Enantiomeric synthesis of *cis*-aziridines *via* chiral sulfoxides.

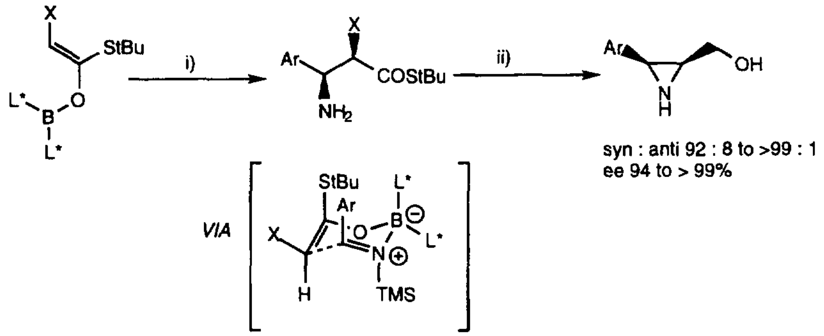
imine adopts the *E*-geometry and that the *re*-face of the imine is attacked by the enolate nucleophile in a chair-like transition state.

An aza-Darzens reaction of the chiral enolate derived from bromoacylcamphorsultam with *N*-(diphenylphosphinyl)aryl- and *tert*-butylmethanimines has also been recently reported as a means of asymmetric access to 2-carboxyaziridines.[81] Thus, deprotonation of bromoacyl camphorsultam at −78°C using LHMDS in THF generates the corresponding bromoenolate to which a solution of the imine in THF is immediately added. Enantiomerically-pure *cis*-aziridinecarboxylates may then be obtained in acceptable yields by basic hydrolysis of these sultams (Scheme 29).

2.6. Resolution

If an asymmetric route to an enantiomerically-pure aziridine cannot be achieved, the possibility still exists to effect a resolution of the racemic aziridine mixture. This can either be achieved chemically or enzymatically. For example, the resolution of a range of mono and disubstituted aziridines has been achieved using optically active host compounds derived from tartaric acid (Figure 4).[82]

Enantiomeric excesse of up to 100% are reported. Alternatively, lipase catalysed alcoholysis of aziridine carboxylates is possible to allow preparation of optically active aziridine carboxylates in

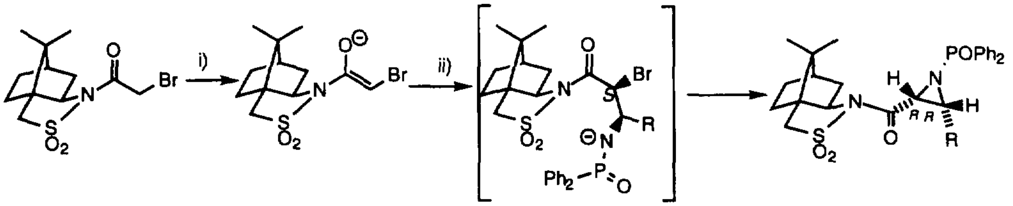


i) ArCH=NTMS; ii) LiAlH$_4$, THF, 0°C

X	Ar	*Syn* : *Anti* of amine	% Ee of *syn*[a]	% Yield
Br	Ph	>99 : 1	97	80
Br	*p*-MeS-C_6H_4	> 99 : 1	>99	77
Cl	Ph	92 : 8	94	89
Cl	*p*-MeS-C_6H_4	94 : 6	95.7	85

[a] *Via* ^{1}H nmr of Mosher's amide

Scheme 28. Asymmetric Mukaiyama aldol reaction to prepare aziridines.



Reagents and conditions : i) LHMDS, THF, -78°C; ii) RCH=NP(O)Ph$_2$, THF, -78°C

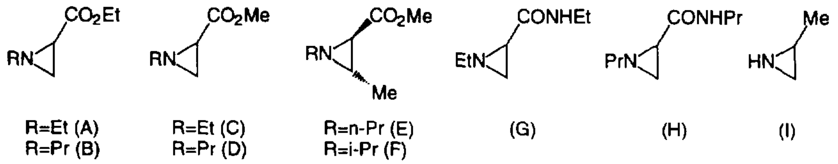
Imine, R=	Yield of aziridine attached to sultam	Yield of aziridine carboxylic acid
Ph	71	64
4-BrC_6H_4	65	61
4-MeOC_6H_4	74	*
2-$O_2NC_6H_4$	72	67
4-$O_2NC_6H_4$	77	60
2-Naphthyl	73	67
Fluoren-2-yl	68	*
2-Furyl	71	*
^{t}Bu	40	47

* products unstable under hydrolysis conditions

Scheme 29. Asymmetric aziridine synthesis *via* aza-Darzens reaction of bromoacylcamphorsultam.

good yield.[83] Whereas PPL- or CCL-catalysed alcoholysis of *N*-alkyl and *N*-aryl aziridines occurs smoothly at 40°C to afford enantiopure derivatives, *N*-acyl and *N*-carboxyalkyl aziridines only afford products from alcoholysis of the amide bond, under all conditions investigated (Scheme 30).

Further limitations to this method are that *N*-tosyl and *N*-mesyl aziridines are left unchanged



R=Et (A)
R=Pr (B)

R=Et (C)
R=Pr (D)

R=n-Pr (E)
R=i-Pr (F)

(G)

(H)

(I)

HOST A

HOST B

Aziridine	Host	Yield	% ee[a]
A	A	34	100
B	A	32	b
C	B	43	64
D	B	44	100
E	A	28	100
F	A	33	100
G	A	42	b
H	A	74	b
I	B	30	b

[a] Determined *via* ^{1}H nmr spectroscopy using Eu(hfc)$_3$. b Ee not determined

Figure 4. Novel tartaric acid derived ligands.

even after exposure to the enzymes for 10 days. This method is, however, complementary to that of Bucciarelli and co-workers who have described the resolution of *N*-substituted aziridine-2-carboxylates and *N*-substituted aziridine-2,3-dicarboxylates with good to excellent stereochemical purity by enzymatic hydrolysis catalysed by the lipase from *Candida cylindracea*.[84]

3. Concluding remarks

This review has outlined recent developments in methods for the asymmetric synthesis of aziridines from readily available starting materials. Although considerable progress has been made in recent years, there is still potential for further progress and as such aziridines remain synthetic targets of immense interest. The synthetic uses of aziridines have been alluded to throughout this report, both as versatile intermediates for the synthesis of amino acids,[85] β-lactams,[86] pyrrolidines[87] and polymers,[88] and as chiral auxiliaries for asymmetric alkylation[1a,89] and aldol transformations.[1a,89] Enantiopure aziridines are currently receiving attention in a new synthetic role as chiral ligands, and have recently proved valuable as alternative chiral ligands for enantioselective dihydroxylation and cyclopropanation reactions[90] and for palladium catalysed allylic substitution reactions.[91] Enantiopure aziridines are also currently of interest as enzyme substrates[92] and enzyme inhibitors.[93]

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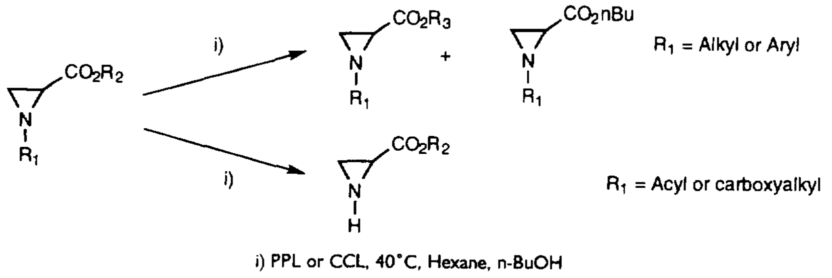

R_1	R_2	Lipase	Reaction time (Days)	Ee substrate	Ee product	Yield
Me	Me	PPL	2	62.3	66	95
^{i}Pr	Me	PPL	42	5	54.5	50
^{i}Pr	Me	CCL	4	21	32	61
^{i}Pr	CH_2CF_3	PPL	12	10	95	73
^{i}Pr	CH_2CF_3	CCL	5	91	68	90
^{t}Bu	Me	PPL	14	5	0	42
^{t}Bu	Me	CCL	14	5	17	70
^{t}Bu	CH_2CF_3	PPL	28	23	75	75
^{t}Bu	CH_2CF_3	CCL	20	53	47	79
Bn	Me	PPL	20	6	54	80
Bn	Me	CCL	20	0	7	82

Scheme 30. Lipase-mediated resolution of aziridines.

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