Recent Synthetic Applications of Chiral Aziridines

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Abstract: Due to their ready availability in chiral form, and propensity to undergo regio- and stereoselective ring opening, aziridines have found widespread use in asymmetric synthesis. This review attempts to summarise the breadth of use of chiral aziridines in synthesis that has recently been reported. Particular emphasis is put on the effect of substituents on ring openings, rearrangements and use as chiral ligands and auxiliaries.

Key words: aziridine, asymmetric synthesis, ring opening, rearrangements, regioselectivity

1 Introduction

Chiral aziridines have found widespread use in organic synthesis.[1–4] The highly strained three membered ring readily opens with excellent stereo- and regiocontrol to afford a wide variety of more stable ring opened or ring expanded chiral amines. In addition, aziridines can function as sources of chirality in stereocontrolled reactions and have found use both as ligands and auxiliaries in asymmetric synthesis.[1,2] Since the use of aziridines is ubiquitous in modern organic synthesis, the aim of this review is to present recent noteworthy applications of chiral aziridines in synthesis to illustrate their breadth of use, rather than to be completely exhaustive. Particularly, research conducted since the review by Tanner in 1994[2] through 1999 shall be presented here. Racemic examples will only be mentioned if they shed insight into chiral extensions of the same chemistry. The asymmetric synthesis of aziridines will not be specifically discussed and the reader is directed to recently published summaries.[5–7]

2 Stereoselective Ring Opening of Aziridines

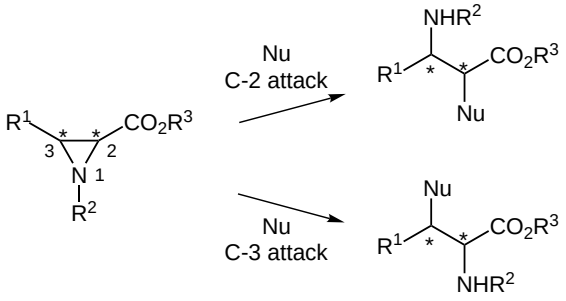
Chiral aziridines readily undergo regio- and stereoselective ring opening to relieve ring strain allowing access to amines with predictable α and β stereochemistry. The increasing synthetic accessibility of chiral aziridines[5–7] has propelled their use in ring opening reactions in organic synthesis. In general, two types of aziridine can be considered: activated and unactivated. The former contain substituents capable of stabilising the developing negative charge on nitrogen during nucleophilic ring opening. The latter, also known as simple aziridines are generally unsubstituted or with alkyl substitution on nitrogen and usually require acid catalysis to facilitate ring opening.

2.1 Aziridine-2-carboxylates

Activation of the aziridine nitrogen by an electron-withdrawing group (e.g. acyl, carbamoyl, sulfonyl), by protonation, or by Lewis acids promotes either C-2 attack to give β-amino acid derivatives or C-3 attack to give α-amino acid derivatives (Scheme 1). Stereoselectivity is generally high and the regioselectivity depends on the ring substituents, with the majority of nucleophiles reacting at C-3.

2.1.1 Hydrogenolysis

With C-3 aryl substituted aziridines, hydrogenolysis was used to regiospecifically cleave the benzylic C–N bond.

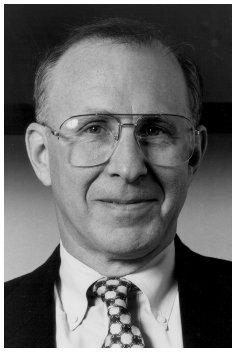


Scheme 1

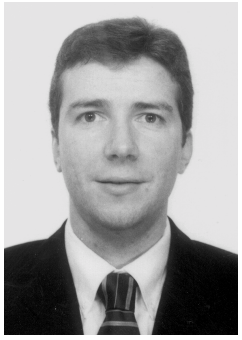
Such ring opening does not affect the C-2 stereochemistry of the aziridine which is maintained in the product α-amino acid derivative. Transfer hydrogenation has been used to open unactivated or sulfonyl activated phenyl aziridine carboxylates[8–12] and phenyl aziridine cyanides.[13] It is noteworthy and uncommon in aziridine chemistry that nitrogen activation was not always necessary. In the case of geminal disubstituted aziridines the new benzylic stereocentre arises from either inversion or retention of configuration on reduction. The stereoselectivity was substrate dependent for aziridine esters (2*S*,3*R*)-**1** and (2*R*,3*S*)-**4**, but was also influenced by solvent (Scheme 2).[11] The retention product always predominated for trisubstituted aziridine esters **1** with CH_2Cl_2 giving the best selectivity. For the tetrasubstituted aziridine esters **4**, use of hexane as solvent with methyl ester gave predominantly the inversion product, while CH_2Cl_2 gave predominantly the retention product with *t*-butyl ester. While this behaviour was not fully understood the affinity of nitrogen for the catalyst in the presence of other chelating functionality and solvent was proposed to be a factor.

When no benzylic aziridine carbon centre was present, hydrogenolysis occurred at C-2 for monosubstituted aziridine-2-carboxylate (2*R*,1'*S*)-**7** to give β-amino ester *(S)*-**8**. However, the corresponding aziridine alcohol (2*R*,1'*S*)-**9** gave C-3 opening to produce chiral amino alcohol (2*R*,1'*S*)-**10**.[14] Chiral β-amino ester *(S)*-**12** was prepared using *N*-tosyl aziridine-2-carboxylate (2*S*,3*S*)-**11** but the *N*-benzyl derivatives could not be used in this C-3 methyl substituted case as debenzylation proved faster than ring opening.[14] With the trityl group on nitrogen, no reaction occurred.

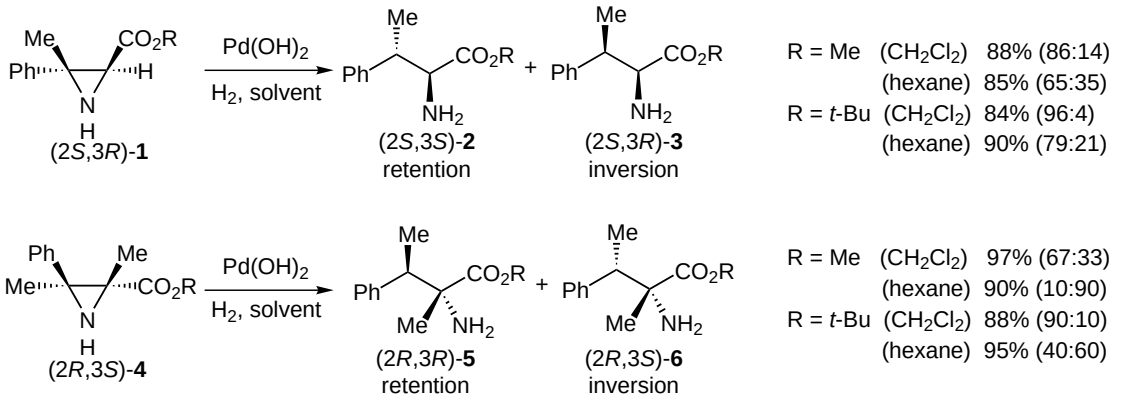
Biographical Sketches



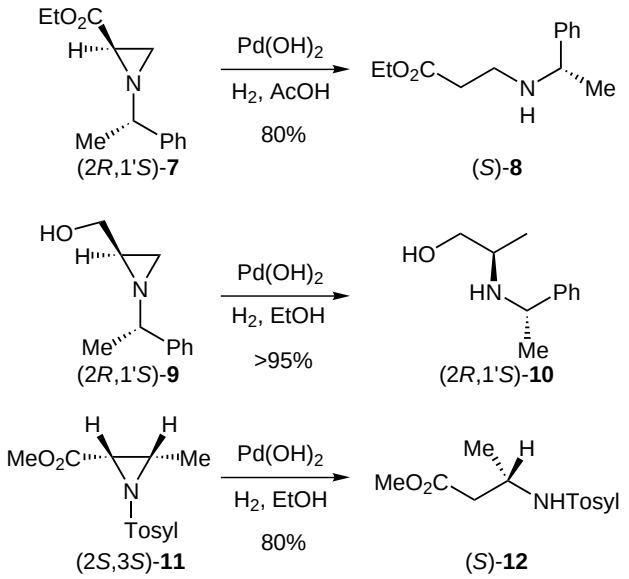
Franklin A. Davis was born in Des Moines, Iowa. He received his B.S. degree in 1962 from the University of Wisconsin and was awarded a Ph.D. in organic chemistry from Syracuse University in 1966 where he worked with Donald C. Dittmer. After two years with Michael J. S. Dewar as a Welch Postdoctoral Fellow at the University of Texas he joined the faculty at Drexel University in 1968. He was the George. S. Sasin Professor of Chemistry until 1995 when he joined the Chemistry Department at Temple University. In 1980 he received the Philadelphia ACS Section Award and was a Fellow of the Japan Society for the Promotion of Sciences in 1992. Dr. Davis is a member of the executive committees of the Fluorine and Organic Divisions of the American Chemical Society where he served as Program Chair (1988–1991) and Chair (1994) of the Organic Division. His major research interests are in the areas of asymmetric synthesis and the development of new methodologies for stereoselective transformations. In particular he is interested in the application of sulfur–nitrogen reagents to the synthesis of bioactive primary amines; e.g. protein and nonprotein α- and β-amino acids, asymmetric oxidations and the regio- and stereoselective fluorination of organic molecules. Other interests include natural product synthesis and heterocyclic chemistry.



William McCoull was born in Glasgow, Scotland in 1971, received his B.A. in Chemistry in 1993 and D.Phil. in 1996, both from the University of Oxford under the supervision of Prof. J. E. Baldwin and Dr. R. M. Adlington. He conducted postdoctoral studies firstly with Prof. J. D. Winkler at the University of Pennsylvania, Philadelphia, USA in 1997 and then with Prof. F. A. Davis at Temple University, Philadelphia, USA in 1998–1999. Currently, he is working in the medicinal chemistry department at AstraZeneca in Cheshire, UK. His research interests include synthetic methodology, total synthesis and all aspects of medicinal chemistry.



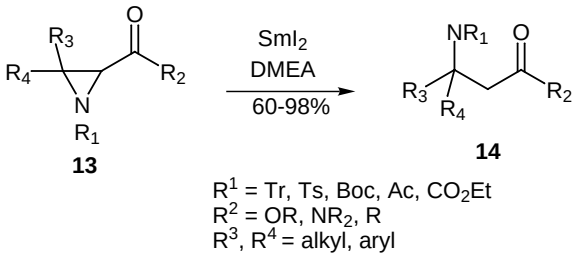
Scheme 2



Scheme 3

2.1.2 Reductive Ring Opening Through Electron Transfer

Samarium(II) iodide has been used as a reducing agent to cleave α to the carbonyl of aziridines **13** containing 2-acyl, 2-carboxylate or 2-carboxamide functionality to give β-amino carbonyl compounds **14** in excellent yields (Scheme 4).[15,16] Use of *N*,*N*-dimethylethanolamine (DMEA) as the proton source instead of MeOH or EtOH was essential to prevent competing nucleophilic ring-opening reactions. It was not necessary to activate nitrogen with an electron-withdrawing group and the trityl group could be used. Although stereochemistry was preserved β to the carbonyl, the stereochemistry at the α position cannot be controlled in this process. Magnesium in methanol can also be employed as the electron transfer reagent which extended the applicability of this type of reduction to include 2-cyano, 2-halomethyl and 2-(phenylsulfonylmethyl)aziridines.[17] In the latter two cases, elimination of halide or phenylsulfonyl resulted in an alkene product.

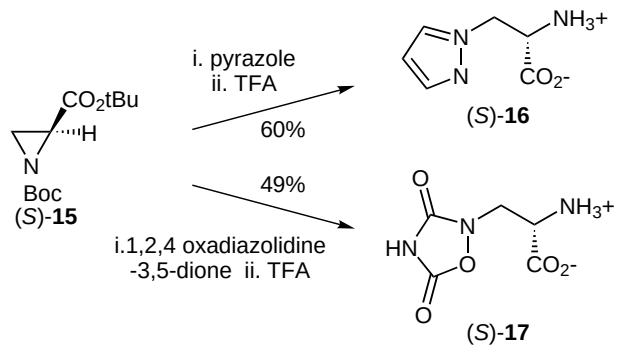


Scheme 4

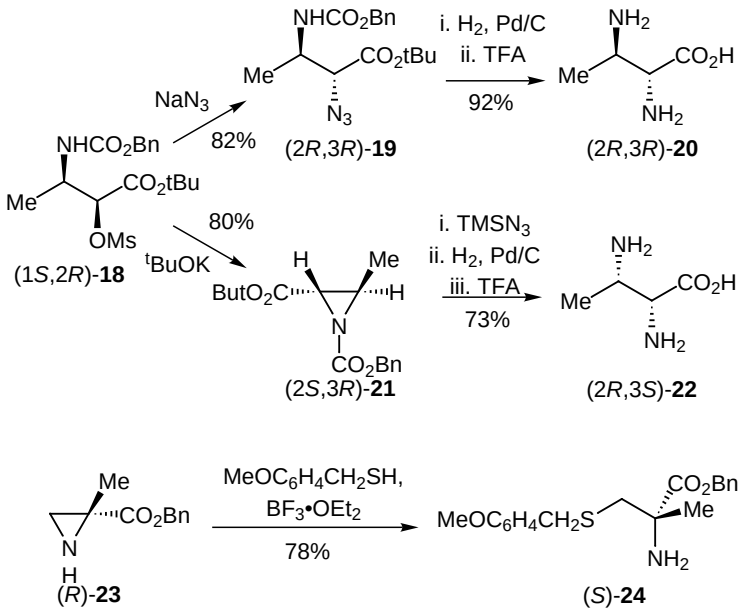
2.1.3 Heteronucleophile Ring Opening

The reaction of heteronucleophiles with aziridine-2-carboxylates generally proceeded at C-3, as exemplified by the synthesis of the less common α-amino acids *(S)*-β-pyrazolylalanine **16** and *(S)*-quisqualic acid **17** using nitrogen nucleophiles with Boc activated aziridine *(S)*-**15** (Scheme 5).[18]

Amine nucleophiles have also been utilised for the asymmetric synthesis of diazepine derivatives[19,20] and 2,3-diaminobutanoic acids.[21] In the latter case, the aziridine precursor (1*S*,2*R*)-**18** was prepared using Sharpless asym-



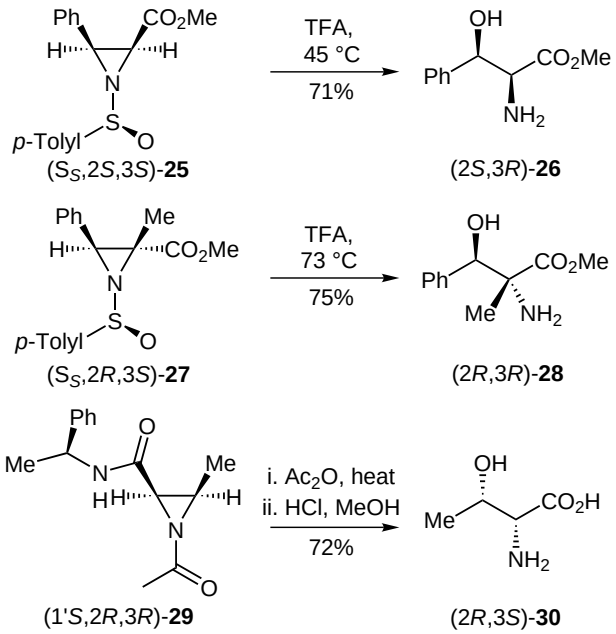
Scheme 5



Scheme 6

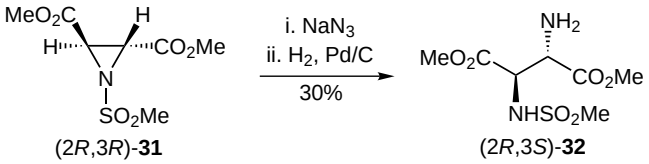
metric aminohydroxylation (AA) methodology, which could be converted directly to (*2R,3R*)-diaminobutanoic acid (**20**) (Scheme 6).[21] Alternatively, **18** was cyclised to aziridine (*2S3R*)-**21** which was in turn ring opened with azide and reduced to give (*2R,3S*) diaminobutanoic acid (**22**). The versatility of this synthesis was extended in that the two remaining stereoisomers were prepared analogously by starting with the AA product from the alternative alkene geometric isomer. *N*-Phthalimidoaziridines and N–H aziridines reacted cleanly with thiols in the presence of BF_3•OEt_2 to give β-thiosubstituted α-amino esters.[22,23] Chiral non-racemic α-methylcysteine (*S*)-**24** was prepared by this method (Scheme 6).[24]

The introduction of oxygen functionality β to the carboxylate group, as present in substituted serine derivatives, was achieved using acid promoted ring opening. When chiral aziridines (S_S,2*S*,3*S*)-**25** and (S_S,2*R*,3*S*)-**27** were prepared with the sulfinyl group on nitrogen, ring opening and nitrogen deprotection were performed in one step to afford β-phenylserine (2*S*,3*R*)-**26** and the α-methylated analogue (2*R*,3*R*)-**28** (Scheme 7).[9,10] Alternatively, when nitrogen was activated with an acetyl group as in (1'*S*,2*R*,3*R*)-**29**, deacetylation from both oxygen and nitrogen was necessary after ring opening to afford D-threonine (2*R*,3*S*)-**30**.[25]



Scheme 7

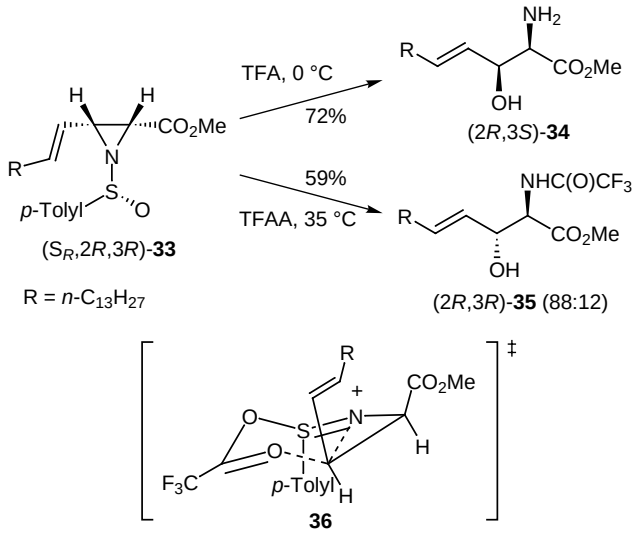
Dicarboxylate aziridines have been reacted with a variety of nucleophiles (HCl, BnSH, NaN_3, TFA, MeOH) to afford β-substituted aspartates (Scheme 8).[26] Higher yields were obtained when the aziridine was activated, particularly with *N*-methylsulfonyl and regioselectivity was not an issue with such C_2-symmetric aziridines which are available from enzymatic resolution of racemic material.[26]



Scheme 8

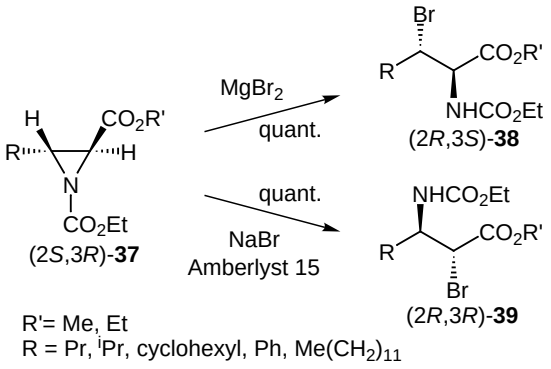
Virtually all aziridine ring openings proceed via S_N2 mechanism. One notable exception was the TFAA in-

duced ring opening of aziridine (S_R,2*R*,3*R*)-**33**.[27] Treatment of **33** with aqueous TFA gave the expected S_N2 C-3 ring opening to afford L-*threo* sphingosine precursor (2*R*,3*S*)-**34** but TFAA predominantly affords (2*R*,3*R*)-**35**, a precursor to L-*erythro* sphingosine with the opposite chirality of C-3 ring opening (Scheme 9). A [3,3] stereospecific rearrangement of the activated sulfoxide complex **36** was proposed to explain this result.



Scheme 9

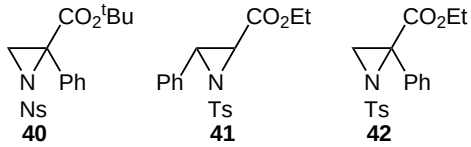
Halogen nucleophiles gave ring opening regioselectivity dependent on the nucleophilic reagent rather than aziridine substrate control (Scheme 10). The conventional C-3 opening proceeded in near quantitative yields for a variety of C-3-alkyl aziridines (2*S*,3*R*)-**37** when $MgBr_2$ was used but with NaBr (or NaI) C-2 opening generally predominated.[28] A secondary branch in the alkyl group was necessary for optimal regioselectivity at C-2 and phenyl gave a 1:1 regiochemical mixture under the latter conditions. Removal of the halogen using radical reduction allowed the preparation of either α- or β-amino acid derivatives.



Scheme 10

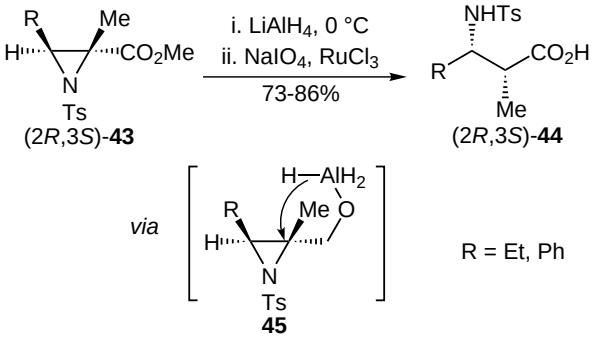
2.1.4 C-2 Directed Ring Opening

Aromatic functionality can override the general preference for C-3 ring opening. In racemic examples, azirdine **40** incorporated hydroxy functionality at C-2 on treatment with aqueous TFA and in a useful comparison aziridines **41** and **42** were both treated with $NaBH_4$ and $NiCl_2$ in MeOH (Scheme 11). The former underwent reduction at C-3 while the latter was reduced at C-2, i.e. always at the benzylic position.[29]



Scheme 11

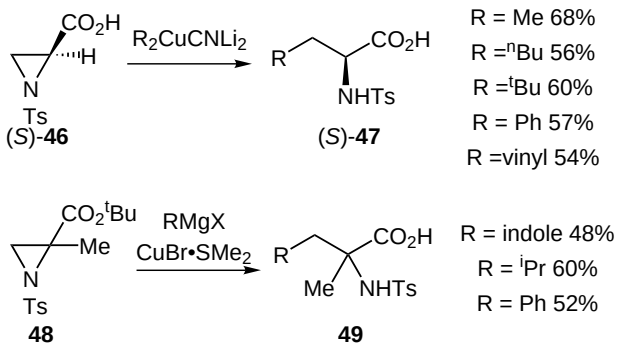
The regiochemistry of ring opening can also be directed towards C-2 through chelation of the nucleophilic agent.[30,31] Treatment of ester (2*R*,3*S*)-**43** with $LiAlH_4$ first reduced the ester to alkoxide **45** which directed the delivery of hydride to open the aziridine at C-2 (Scheme 12).[31] After a reoxidation procedure β-amino acids (2*R*,3*S*)-**44** were obtained.



Scheme 12

2.1.5 Carbon Nucleophile Ring Opening

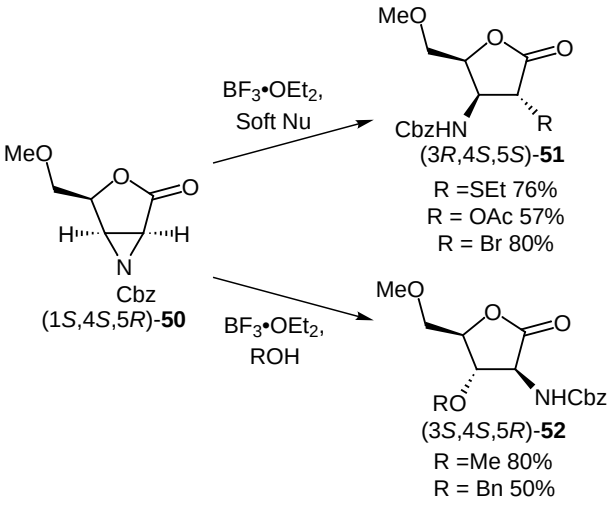
The use of organometallics to open chiral aziridine-2-carboxylates appears an excellent route for the synthesis of α-amino acids, but the competing reaction at the ester functionality is problematic. While organocuprate reagents have obviated this problem, regioselectivity in ring opening was poor.[32] Hydrolysis of the ester to an acid, then treatment with higher order cuprates overcame this regioselectivity problem for unsubstituted aziridine *(S)*-**46** (Scheme 13).[33] Introduction of a C-3 methyl substituent caused a lack of selectivity except in the case of the sterically undemanding acetylide nucleophile.[33] In accordance with the expected steric effect of methyl substitution at C-2 in aziridine **48**, cuprates afford C-3 attack with complete control of regioselectivity (Scheme 13).[34]



Scheme 13

2.2 Aziridine-2-lactones

A comparative study of aziridine-2-carboxylates and aziridine-2-lactones has shown the latter to react with soft nucleophiles at C-2 compared to the general C-3 reactivity of the former (Scheme 14).[35,36] Such regioselectivity was explained by orbital control where in aziridine-2-lactone (1*S*,4*S*,5*R*)-**50**, the calculated LUMO coefficient for C-2 was substantially greater than for C-3. While this is also true for aziridine-2-carboxylates, the flexible ester side chain sterically prevents C-2 attack. The nature of the *N*-activating group did not affect the regioselectivity. With hard nucleophiles such as alcohols, charge control directed regioselectivity in both systems to attack at aziridine C-3 although lactone opening in **50** preceded aziridine ring opening and re-lactonization occurred during chromatography to afford (3*S*,4*S*,5*R*)-**52**.



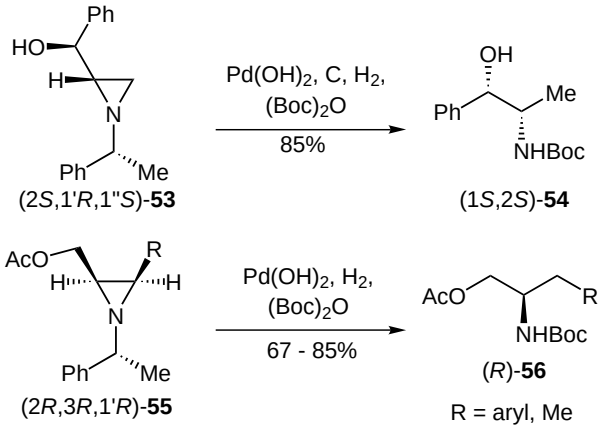
Scheme 14

2.3 Non-carboxylate Aziridines

While the use of aziridine-2-carboxylates appealingly gives direct access to amino acid derivatives, regioselectivity and chemoselectivity problems have led to widespread use of non-carboxylate containing aziridines for amino acid synthesis and other purposes.

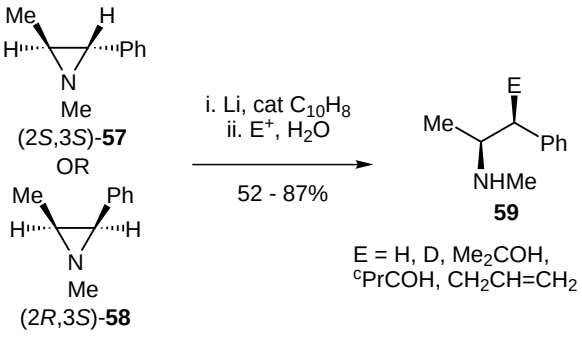
2.3.1 Reductive Ring Opening

Selective hydrogenolysis at the aziridine benzylic position has been used for the preparation of phenyalanine derivatives[37,38] and in alkaloid synthesis.[39] In the absence of a benzylic aziridine carbon, reductive cleavage of the 2-substituted azirdine (2*S*,1'*R*,1"*S*)-**53** occurred at the less hindered C-3 position (Scheme 15).[40] 2,3-Disubstituted derivatives (2*R*,3*R*,1'*R*)-**55** were also cleaved at C-3 when either aryl or methyl substituents were attached at this position.[38] The presence of $(Boc)_2O$ activated the aziridine to facilitate ring cleavage which occurred prior to removal of the α-methylbenzyl group.



Scheme 15

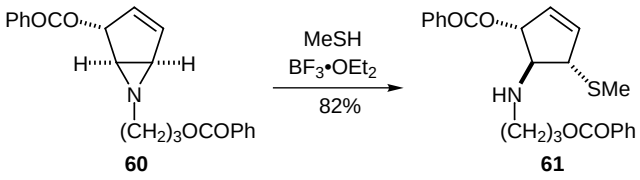
Reductive benzylic centre opening of aziridines has been achieved using lithium in the presence of catalytic napthalene.[41] Activation of nitrogen was not found necessary and the intermediate dianion was quenched with a variety of electrophiles to afford amines **59** (Scheme 16). The C-3 aziridine stereocentre was preserved but the benzylic anion derived from (2*R*,3*S*)-**58** underwent inversion to the less hindered intermediate derived from (2*S*,3*S*)-**57** hence the product stereochemistry β to nitrogen was independent of that in the starting aziridine.



Scheme 16

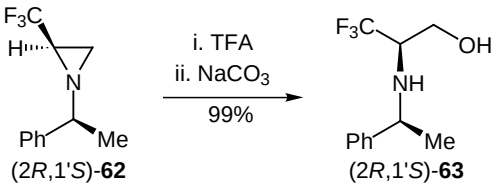
2.3.2 Heteronucleophilic Ring Opening

Depending on the nucleophile, Lewis acids or suitable nitrogen activation can be chosen to facilitate aziridine ring opening. Thiols have been used without Lewis acids or nitrogen activation to react exclusively at a benzylic aziridine centre to produce β-amino thiols.[42,43] Introduction of hydroxy,[44] chloro,[45] and azide[45] functionality was also performed at the benzylic position in the presence of acid. Furthermore, unsaturation has also been used to direct regioselective ring opening. Lewis acids facilitate reaction at the more stable carbocation centre as in the conversion of aziridine **60** to amino thiol **61** with MeSH and BF_3•OEt_2 (Scheme 17)[46] and alkoxy nucleophiles have been used likewise.[47]



Scheme 17

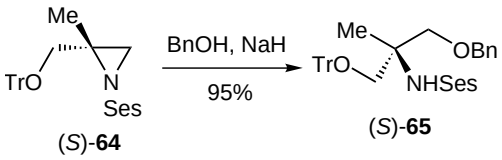
In saturated systems, heteronucleophilic attack generally proceeded exclusively at the least hindered aziridine carbon. Chiral *N*-α-methylbenzyl aziridines such as **62** were easily prepared and ring opened with acetates to provide amino alcohols **63** (Scheme 18)[48] and propane-1,3-diols.[49] Imidazole has been used to ring open an *N*-acylaziridine with complete control of regioselectivity, but dibenzyl phosphate was less selective at ambient temperatures.[50]



Scheme 18

An optimised procedure for ring opening of 2,2-disubstituted aziridine *(S)*-**64** used β-trimethylsilylethanesulfonyl (Ses) as an activating group for nitrogen (Scheme 19).[51,52] This gave better regioselectivity for reaction with alkoxides than Lewis acid activation and avoided deacylation problems caused by other activating groups such as amides or carbamates. The Ses protecting group was easily removed after elaboration of product *(S)*-**65** using TBAF. Other nucleophiles including thiols were applicable to this protocol.

Amines were found to ring open aziridines in the presence of 10–20 mol% of $Yb(OTf)_3$ to give 1,2-diamines.[53] Protection of the aziridine nitrogen was necessary to avoid

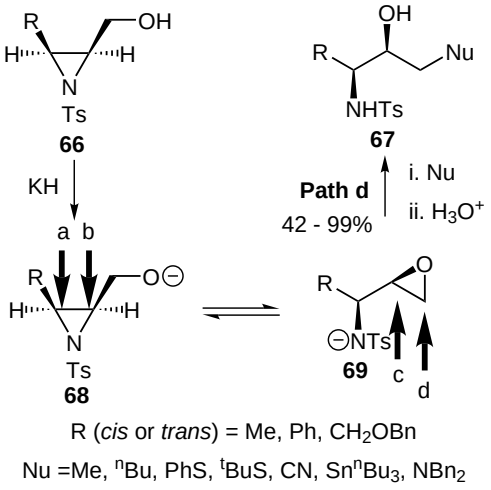


Scheme 19

oligomer formation and while disubstituted aziridines gave excellent yields, trisubstituted aziridines gave only moderate diamine formation.[53] When 5 mol% $Sn(OTf)_2$ or $Cu(OTf)_2$ was used as Lewis acid, only aromatic amines exhibited aziridine ring opening and an ion complex intermediate was postulated.[54] Lewis acids were found unnecessary when methanol was used as solvent and the reaction proceeded until the amine nucleophile was trialkylated.[55,56]

2.3.3 Aza-Payne Reaction

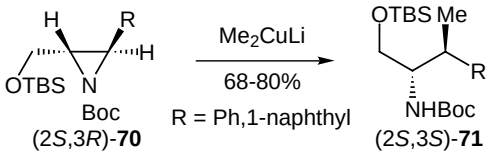
The aza-Payne[57] rearrangement of aziridine-2-methanols **66** can give rise to two potential intermediates, the oxa-anionic species **68** or the aza-anionic species **69**, when treated with base (Scheme 20).[58] Intermediate **69** was predicted computationally and found experimentally to predominate. Consequently, on reaction with nucleophiles, regioselective attack by pathway d out of the four possible reaction pathways a–d occurred exclusively to give amino alcohol **67** in a stereo- and regioselective manner. Higher order cuprate reagents were used to incorporate alkyl, amine and stannyl nucleophiles, and TMSCN with Lewis acid to incorporate cyanide while thiols were used without other additives. In the absence of a suitable activating group on nitrogen, the aza-Payne rearrangement does not occur on formation of an oxo-anionic species.[59] When a strong base is not used then direct attack of the aziridine ring by the external nucleophile (pathway a/b) has been observed.[60]



Scheme 20

2.3.4 Carbon Nucleophile Ring Opening

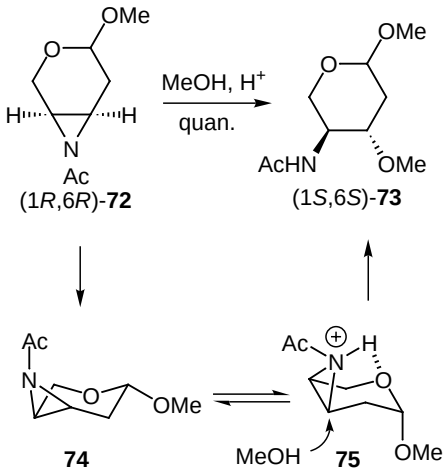
Organocopper reagents are the organometallic reagent of choice for ring opening of aziridines.[30,61–65] Usually lower order cuprates, derived from organolithium or Grignard reagents are used as in the preparation of β-arylalanine derivative (2*S*,3*S*)-**71** (Scheme 21).[37] Attack occurred at the least hindered aziridine carbon unless an additional activation was present such as the benzylic centre in (2*S*,3*R*)-**70**. Both organolithium[66,67] and Grignard[68] reagents have also been used, but this required robust *N*-tosyl protection. Lithium anions derived from 1,3-dithianes have also been used for the preparation of 2-tosylaminocarbonyl compounds.[69]



Scheme 21

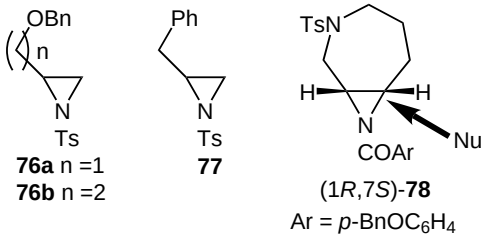
2.3.5 Heteroatom Directed Ring Opening

Neighbouring groups have been used to facilitate and direct aziridine ring opening. Acid catalysed methanolysis of aziridine (1*S*,6*R*)-**72** gave only (1*S*,6*S*)-**73** as the regio- and stereocontrolled product (Scheme 22).[70] Protonation of the aziridine nitrogen in conformer **75** was stabilized by an intramolecular hydrogen bond to the endocyclic oxygen thus favouring diaxial attack through this conformer.



Scheme 22

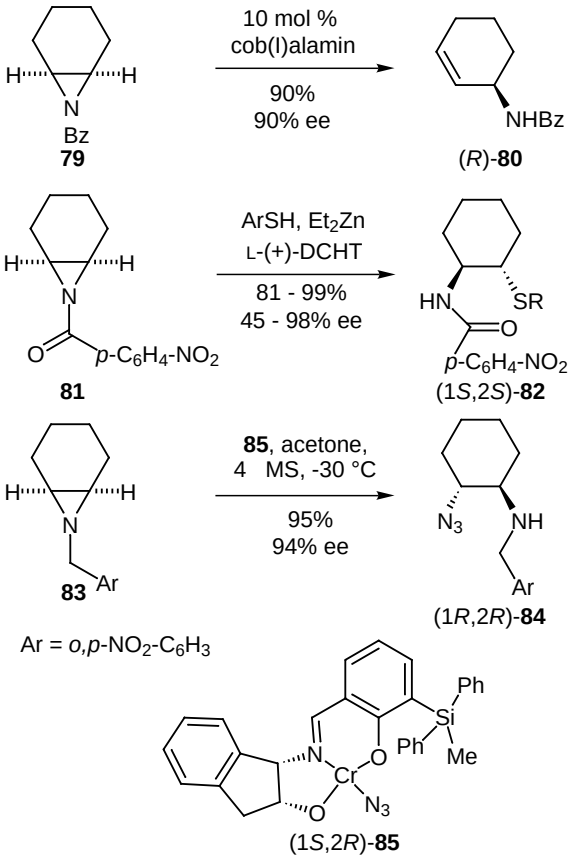
A bridging Lewis acid also explains why $AlMe_3$ facilitated addition of PhC≡CLi to aziridines **76a/b** but not to **77** since the latter does not contain a coordinating heteroatom substituent (Scheme 23).[71] In the absence of the $AlMe_3$ there was negligible reaction. The tosylamide nitrogen in **78** directed acid catalysed attack by water to the position shown and was not dependent upon the presence of a Lewis acid or the nature of the aziridine nitrogen activating group.[72,73] An electronic effect was used to explain this behaviour where nucleophilic attack occurs at the carbon with the larger positive charge distribution.



Scheme 23

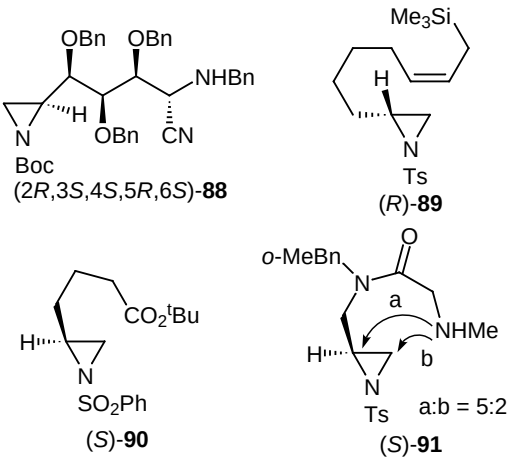
2.3.6 Ligand Catalysed Asymmetric Ring Opening

Chiral catalysts have been used to effect asymmetric ring opening of achiral aziridines.[74–78] The ee's produced varied from poor to excellent and were generally dependent on the structure of the aziridine, catalyst, solvent and nucleophile. Isomerisation of aziridine **79** using catalytic cob(I)alamin in MeOH afforded optically active amine *(R)*-**80** in 90% yield and 90% ee (Scheme 24).[74] Aziridine **81** was converted to β-amido thiol (1*S*,2*S*)-**82** in an opti-



Scheme 24

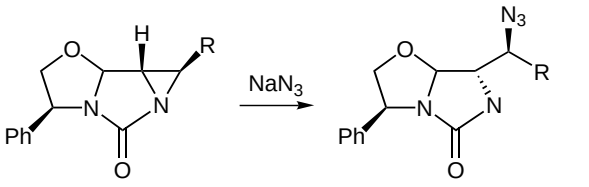
mised 98% yield and 93% ee using a crucial 1:3:1:4.8 ratio of **81**:Et_2Zn:L-(+)-DCHT (dicyclohexyl tartrate):thiol in toluene.[76] Aliphatic thiols gave poor ee's and the reaction could not be performed with catalytic amounts of zinc complex. Grignard reagents have also been used with chiral copper catalysts to desymmetrise *N*-sulfonylaziridines.[77] *N*-Alkyl substituted aziridine **83** was ring opened to afford amine (1*R*,2*R*)-**84** using the tridentate Schiff base chromium complex **85**.[78] Unsaturated, acyclic and five membered cyclic *meso* aziridines also gave good yields and enantioselectivities. Amide or carbamate activated aziridines however gave poor enantioselectivites and sulfonyl activated aziridines were unreactive. In an interesting comparison of aziridine versus epoxide reactivity in the same molecule, chiral bases were used to desymmetrise an epoxide while leaving a *N*-diphenylphosphinyl aziridine intact.[79]



Scheme 26

2.3.7 Bridged Aziridines

Bridged aziridines were readily opened by nucleophiles at the least hindered aziridine carbon.[80–82] Regiochemistry can also be controlled by the electroattracting effect of heteroatoms. Aziridines **86a** and **86b** were both ring opened by azide at the same position to form **87a/b** where neither position is sterically more available (Scheme 25).[83] While **86a** was directed by the benzylic nature of one of the aziridine carbons, in **86b** the oxazolidinone was proposed to deactivate the proximal aziridine carbon to nucleophilic attack.



(7*S*,1'*R*)-**86a** R = Ph
(7*S*,1'*R*)-**86b** R = Pr

(7*S*,1'*S*)-**87a** R = Ph, 90%
(7*S*,1'*S*)-**87b** R = Pr, 94%

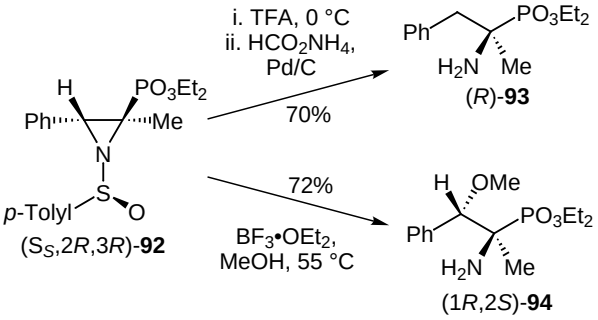
Scheme 25

2.3.8 Intramolecular Ring Opening

The regioselectivity of intramolecular aziridine ring openings was strongly affected by the size of the ring formed and often different from that expected from intermolecular attack. A 6-membered imino sugar was formed from intramolecular cyclisation at the most hindered aziridine carbon of (2*R*,3*S*,4*S*,5*R*,6*S*)-**88** (Scheme 26).[84] Intramolecular allylation occurred to form only 6-membered ring products on treatment of *(R)*-**89** with BF_3•OEt_2 and competing chairlike transition states were used to explain modest diastereoselectivity.[61] Likewise, the ester enolate derived from *(S)*-**90** forms a 5-membered ring with 2:1 ratio of diastereomers.[85] In the case of *(S)*-**91**, the electron attracting effect of the second nitrogen may explain why 7 as well as 6 membered ring formation occurred.[19]

2.4 Aziridine-2-phosphonates

Aziridine-2-phosphonates undergo ring-opening reactions analogous to aziridine carboxylates to form α-amino phosphonate derivatives.[86–88] *trans*-Substituted aziridine phosphonates were found to be more reactive towards nucleophilic ring opening than their *cis* counterparts.[87] *N*-Sulfinyl aziridine (S_S,2*R*,3*R*)-**92** was deprotected and hydrogenolysed as the unactivated aziridine to afford the first asymmetric synthesis of *(R)*-α-methylphosphophenylalanine (**93**) (Scheme 27).[86] Furthermore, methanol was used as a nucleophile to obtain the α,β-trisubstituted phosphonate derivatives in 90% de and (1*R*,2*S*)-**94** was isolated in high yield.

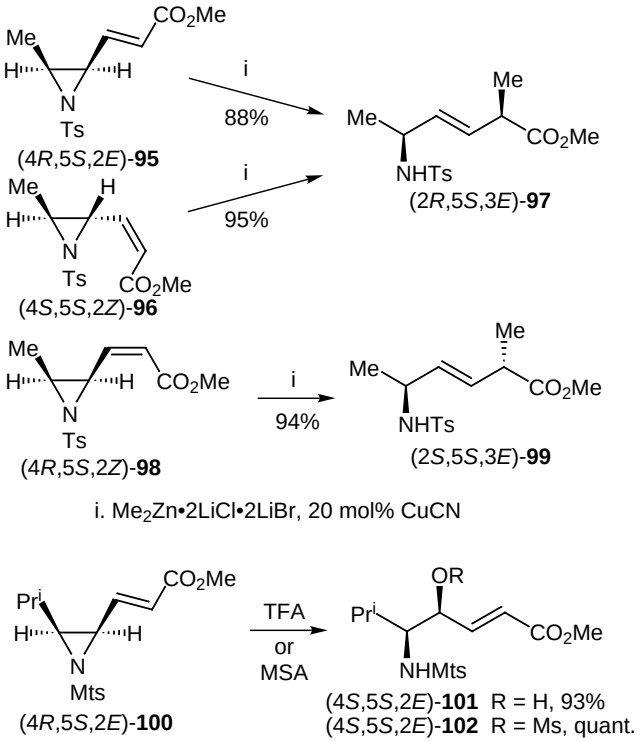


Scheme 27

2.5 Vinyl Aziridines

Vinyl aziridines have been utilised as precursors to *(E)*-alkene isosteres of peptides through reaction with organocopper reagents.[89–91] Excellent diastereoselectivity and high yields were obtained in an *anti*-S_N2' reaction for *N*-acyl, peptidyl, carbamoyl and sulfonyl activated aziridines. Both *(E)*-α,β-enoate **95** and *(Z)*-α,β-enoate **96** gave *(E)*-alkene product (2*R*,5*S*,3*E*)-**97** as a result of a predominant reactive conformer dictated by minimizing allylic 1,3 strain with only minor amounts of products arising from γ-alkylation (Scheme 28).[90] The aziridine stereo-

chemistry in (4*R*,5*S*,2*Z*)-**98** was likewise relayed to control the α-stereocentre in (2*S*,5*S*,3*E*)-**99**. In contrast, oxygenation at the γ-position using TFA or methanesulfonic acid occurred with stereo- and regioselective S_N2 aziridine ring opening of (4*R*,5*S*,2*E*)-**100** (Scheme 28).[92] The diphenylphosphinyl (Dpp) group has also been used to activate vinyl aziridines and resulted in exclusive *anti*-S_N2' attack by dialkyl copper lithium and stannyl cuprate reagents.[93] In densely functionalised vinyl aziridine systems, both S_N2' and S_N2 behaviour has been observed.[94]

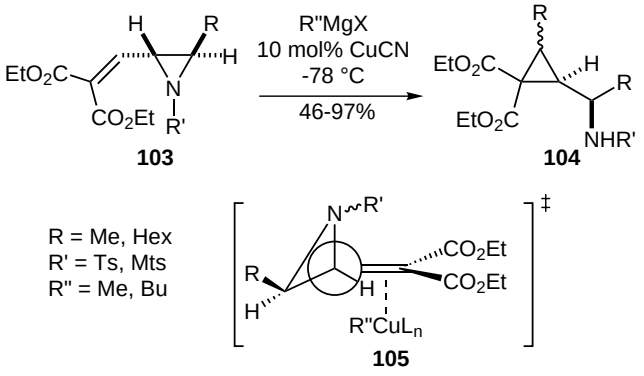


Scheme 28

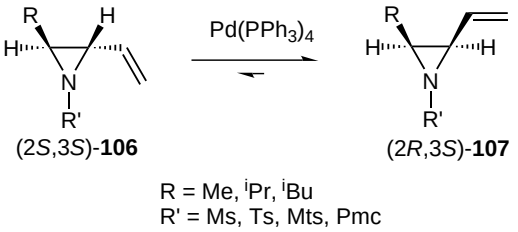
The Michael reaction Initiated Ring Closure (MIRC) reaction has been applied to activated vinyl aziridines **103** for the synthesis of cyclopropanes **104** (Scheme 29).[95] Addition of Grignard reagents catalysed by CuCN gave the highest yields and the *cis* cyclopropane product generally predominated as explained by allylic strain arguments, through the preferred reactive conformer **105**. Increasing the bulk of the aziridine substituents generally gave improved *cis*:*trans* ratios of up to 80% de.

While *cis* or *trans* aziridines are generally prepared independently, in the case of *N*-alkyl/arylsulfonyl-3-alkyl-2-vinylaziridines, palladium(0)-catalysed isomerisation of *trans* isomers allowed preparation of their *cis*-counterparts. In accord with computationally predicted thermodynamic stabilities (2*S*,3*S*)-**106** was isomerised to (2*R*,3*S*)-**107** in ratios generally greater than 95:5 (Scheme 30).[96,97]

Rearrangement of vinyl aziridines has been used in stereoselective alkaloid and seven-membered lactam synthesis

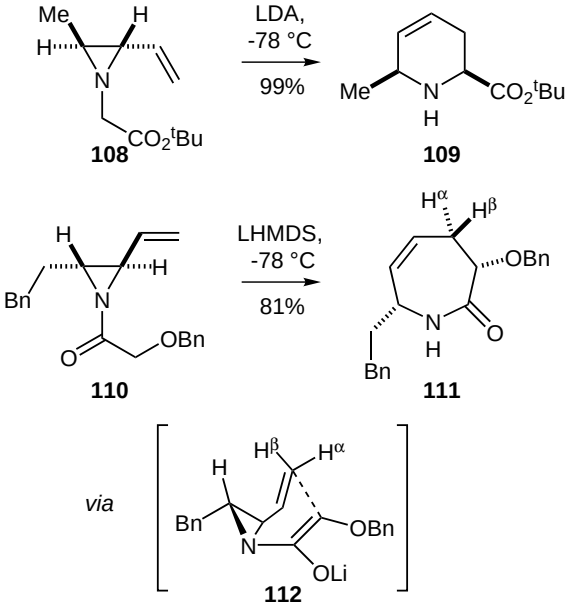


Scheme 29



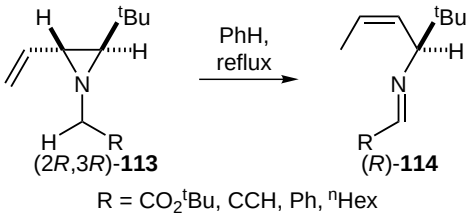
Scheme 30

(Scheme 31).[98–101] Aziridine **108** underwent an aza-[2,3]-Wittig rearrangement[102] to form tetrahydropyridine **109** in excellent yield[99] while **110** afforded lactam **111** in an aza-[3,3]-Claisen through transition state **112** (Scheme 31).[101] Substitution of the alkene also afforded stereocontrol at the β-position. The reaction was less successful for *N*-propargyl vinyl aziridines where competing reaction pathways have been reported.[103]



Scheme 31

Under thermal conditions, vinyl aziridines (2*R*,3*R*)-**113** underwent homodienyl-[1,5]-hydrogen shifts to give chiral imines *(R)*-**114** (Scheme 32).[104] Substitution of the alkene in **113** retarded the reaction while the presence of unsaturation in the R group significantly increased the reaction rate. Accordingly, aza-[2,3]-Wittig precursors such as **108** or **110** are not stored at room temperature else they are decomposed via [1,5]-hydrogen shift.



Scheme 32

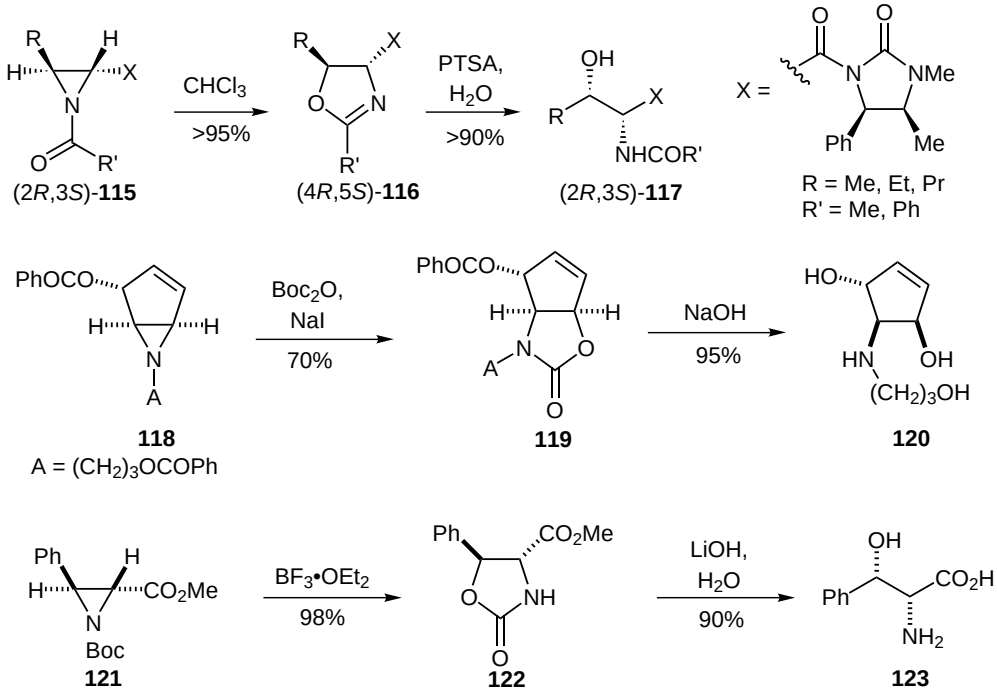
3 Rearrangements and Ring Expansions

3.1 *N*-Acyl Aziridines

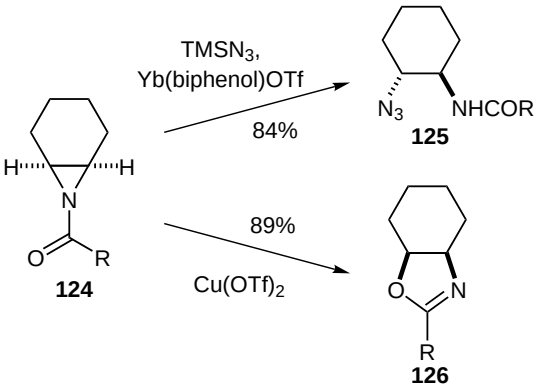
Acyl aziridines readily rearrange to oxazolines under thermal, acidic or nucleophilic conditions.[105–109] Aziridines (2*R*,3*S*)-**115** thermally rearranged to afford oxazolines (4*R*,5*S*)-**116** with complete regio- and stereocontrol (Scheme 33).[105–107] Yields were excellent in chloroform but other solvents gave very slow reactions. Subsequent mild acid hydrolysis yielded β-hydroxy α-amino acid derivatives (2*R*,3*S*)-**117** or in the case of R' being an amino acid and R = Me then threonine, D-serine and D-isoserine containing dipeptides were obtained. Conversion of aziridine **118** to oxazolidinone **119** was facilitated by sodium iodide and subsequent alkaline hydrolysis resulted in formation of amino alcohol **120**.[46] Racemic phenylserine **123** was prepared from aziridine **121** by rearrangement to oxazolidinone **122** then alkaline hydrolysis.[110] The phenyl functionality was key to the rearrangement of the Boc group onto the C-3 aziridine position and methyl or isopropyl substitution at this position afforded poor yields.

The balance of reactivity between direct aziridine ring opening and rearrangement of acylaziridines has been investigated.[111,112] Such reactivity was controlled by judicious choice of "orthogonal" Lewis acids. The oxophilic Lewis acid Yb(biphenol)OTf was postulated to coordinate to the carbonyl oxygen thus activating the aziridine **124** to external nucleophilic attack forming **125** while the more azaphilic Lewis acid $Cu(OTf)_2$ was postulated to coordinate to the amide nitrogen thus catalyzing rearrangement to oxazoline **126** (Scheme 34). In the latter case, a chiral non-racemic example rearranged stereospecifically with retention of configuration.

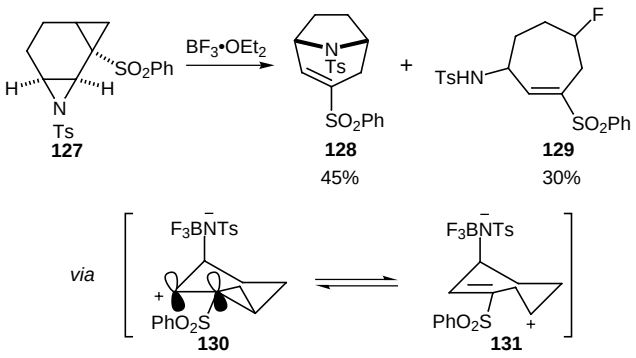
Aziridino cyclopropane **127** underwent rearrangement to the bicyclic tropane alkaloid skeleton **128** using BF_3•OEt_2 (Scheme 35).[113] The cyclopropyl carbinyl cation **130** was initially formed and rearranged to cation **131,** which was trapped by the sulfonamide nitrogen to give **128** or by fluoride to give **129**. When carbamate protection was used on nitrogen, the reduced nucleophilicity of nitrogen resulted in exclusive fluoride trapping.



Scheme 33



Scheme 34



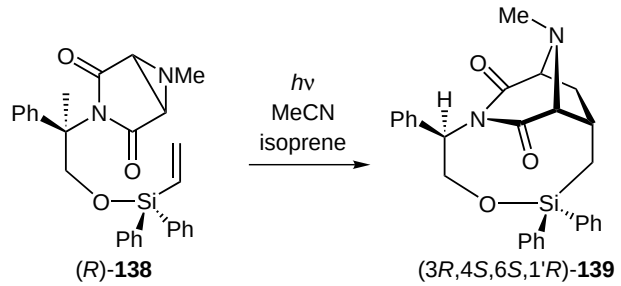
Scheme 35

3.2 Carbonylation Reactions

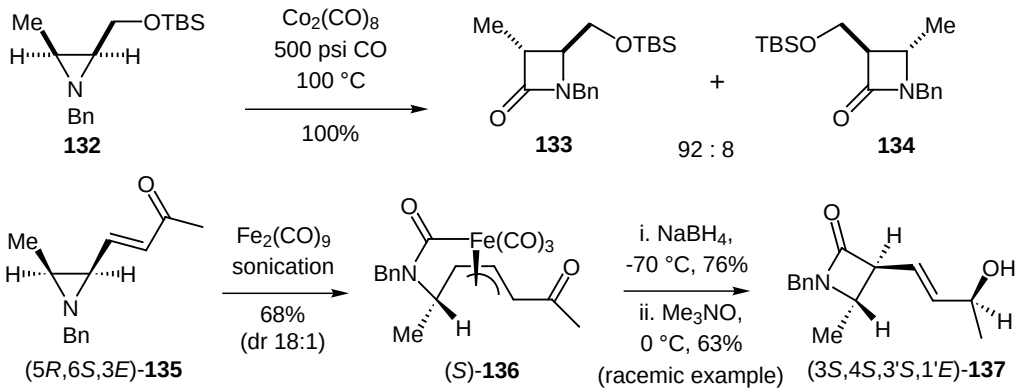
Aziridines are precursors to β-lactams through carbonylative ring expansion reactions.[114] This has been applied to disubstituted *cis* aziridine **132** to quantitatively afford the *trans*-β-lactam products **133** and **134** in 92:8 ratio using dicobalt octacarbonyl as catalyst (Scheme 36).[115] Likewise, the corresponding *trans*-aziridine gave β-lactam products with inversion of stereochemistry. However this procedure failed with aziridine carboxylates which ring opened then eliminated the organometallic species before carbonyl insertion could occur. Use of stoichiometric nonacarbonyldiiron under sonication conditions converted aziridine (5*R*,6*S*,3*E*)-**135** to the exo lactam complex *(S)*-**136** (Scheme 36).[116] Subsequent reduction of the ketone functionality with sodium borohydride proceeded stereoselectively and for racemic examples oxidative decomplexation was performed using Me_3NO to give β-lactams such as (3*S*,4*S*,1*S*, 1'*E*)-**137** in 54–69% yield. A similar ring expansion has also been applied to bicyclic vinyl aziridines.[117]

3.3 Cycloadditions

Aziridines can be precursors to azomethine ylides leading to a wide variety of thermal or photochemical [2+3] cycloaddition reactions. For example five-membered heterocycles have been prepared by reaction of aziridines with heterocumulenes,[118] thiones[119] and even C_{60}.[120] Intramolecular azomethine cycloadditions have been used in alkaloid synthesis[121] and notably in a computationally guided design of a silicon based tether system in aziridine *(R)*-**138** (Scheme 37).[122] Photolysis of **138** afforded the *endo-re* product (3*R*,4*S*,6*S*,1'*R*)-**139** in 64% yield and *re*:*si* ratio of 16:1. With larger tethers, the transition state energy calculations favored a switch to *endo-si* products as was borne out by experiment.



Scheme 37

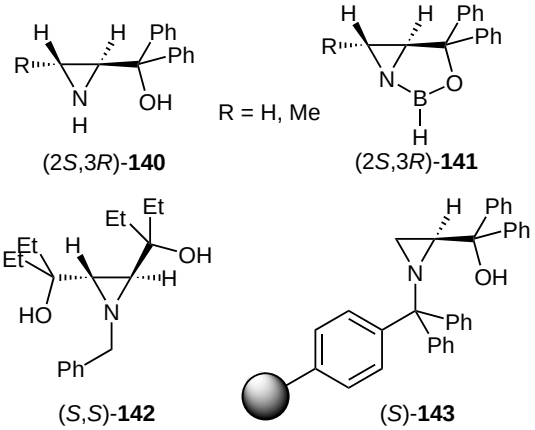


Scheme 36

4 Aziridines as Chiral Ligands and Auxiliaries

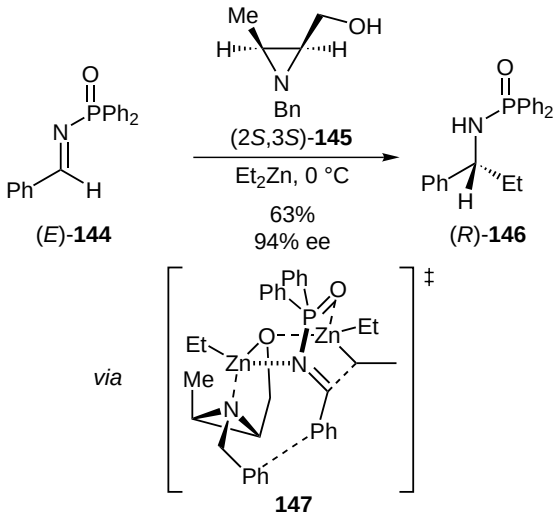
4.1 Chiral Ligands

The concentrated density of stereochemical information located close to a good σ-donor nitrogen makes chiral aziridines attractive ligands for asymmetric catalysis. In an extension of Corey's chiral oxazaborolidines for the enantioselective reduction of prochiral ketones, aziridine 2-carbinols (2*S*,3*R*)-**140** have been used as precatalysts to prepare oxazaborolidines (2*S*,3*R*)-**141** (Scheme 38).[123] When used with borane-dimethylsulfide complex for the reduction of acetophenone to *(R)*-phenylethyl alcohol, enantioselectivities were greater than 90%.



Scheme 38

A range of aziridine 2-carbinols have been screened as catalysts for the enantioselective addition of diethylzinc to aldehydes and aziridine (*S*,*S*)-**142** gave up to 97% ee and good yields.[124] An equally effective *N*-trityl aziridine has been studied and the corresponding polymer supported catalyst *(S)*-**143** prepared.[125,126] High enantioselectivity was retained and the catalyst was recycled without significant loss in enantioselectivity. Aziridine alcohols have also been screened as promoters of enantioselective addition of dialkylzincs to *N*-(diphenylphosphinoyl) imines such as *(E)*-**144** (Scheme 39).[127] Aziridine (2*S*,3*S*)-**145** gave the best enantioselectivity for formation of amine *(R)*-**146**. The aziridine could be recovered in good yield (90%) but use of catalytic quantities resulted in a reduced enantioselectivity. The stereochemical outcome was rationalised by transition state **147** where the C-3 methyl substituent sterically directs attack of the imino bond from one face and a favourable π–π interaction accounted for improved selectivity of *N*-benzyl over *N*-alkyl aziridine promoters. An aziridine carboxylate has also been used as a ligand for rhodium catalysed cyclopropanation with modest enantioselectivity.[128]

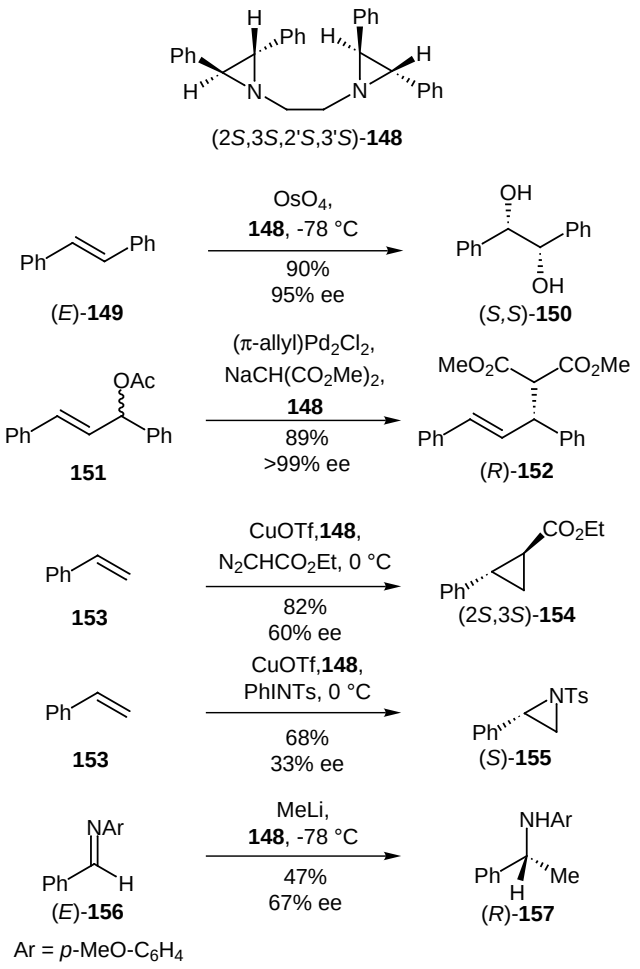


Scheme 39

C_2-Symmetric bis-aziridines have been studied as ligands in a number of metal mediated asymmetric reactions.[129–132] A two carbon tether between the aziridine nitrogens was optimal, regardless of the metal used, to allow five membered chelate formation, and the other aziridine side chains were varied for steric and electronic requirements. Bis-aziridine (2*S*,3*S*,2'*S*,3'*S*)-**148** generally showed the best performance. Osmium mediated asymmetric dihydroxylation of *trans*-stilbene **149** and palladium catalysed allylic alkylation of **151** proceeded in excellent yields and enantioselectivity using **148** (Scheme 40). Copper catalysed cyclopropanation and aziridination of styrene **153** gave poorer ee's but in the former exchange of the phenyl for benzyl substituents on ligand **148** increased the ee to 90%. Addition of organolithium reagents to imines such as **156** gave variable yields and enantioselectivities up to 89%.[133]

4.2 Chiral Auxiliaries

C_2-Symmetric aziridines have been utilised as chiral auxiliaries.[2,134] Amide (2*S*,3*S*)-**158** underwent diastereoselective alkylation when treated with a lithium base then benzyl bromide (Scheme 41). A side-chain oxygen chelates with the lithium cation of a *Z*-enolate and the C_2-symmetry forces the same intermediate if nitrogen inversion occurs. Nonsymmetrical aziridines consequentially resulted in poorer diastereoselectivity as did aziridines lacking side-chain oxygens. However, in aldol reactions, aziridines lacking side-chain oxygens produced better selectivities. Aziridine (2*S*,3*S*)-**161** afforded only *syn*-aldol products **162** and **163** with the former generally predominant as rationalised by a Zimmerman–Traxler transition state (Scheme 41).



Scheme 40

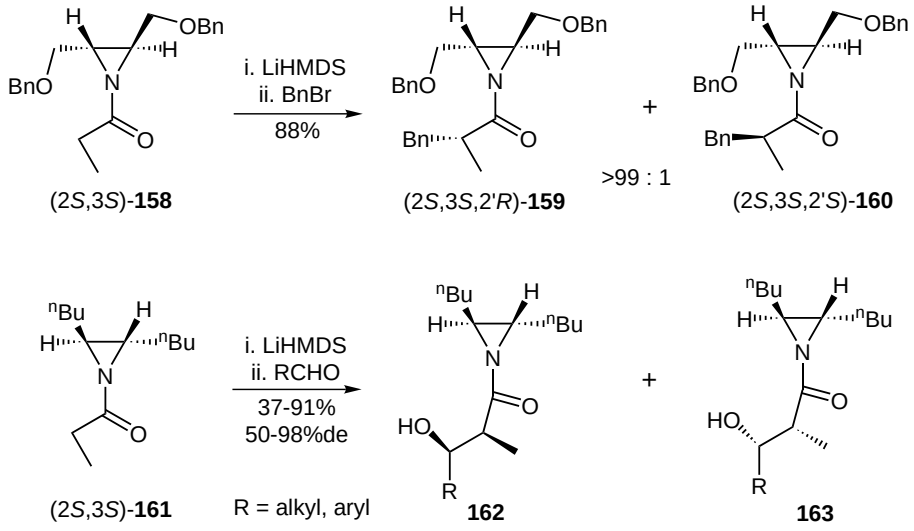
5 Transformations of Aziridine Side Chains

5.1 Reactions of Side Chains Attached to Aziridine Carbons

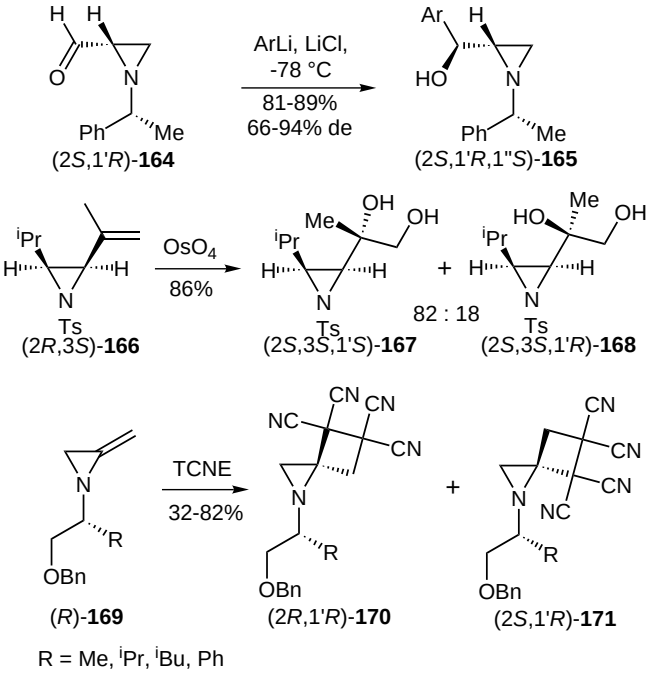
The inherent reactivity of aziridines to nucleophiles limits the amount of chemistry that can be conducted on aziridine side chains. However aziridine carboxaldehyde (2*S*,1'*R*)-**164** is noteworthy in its configurational stability attributable to ring strain of the aziridine. It was found to react with a variety of phenyl, naphthyl, furyl and phenanthryl lithium (ArLi) reagents to afford alcohols (2*S*,1'*R*,1"*S*)-**165** in excellent yields and high diastereoselectivities (Scheme 42).[40] A diastereoselective dihydroxylation of vinyl aziridine (2*R*,3*S*)-**166** has been reported using osmium tetroxide where allylic strain dictated the preferred reactive conformation (Scheme 42).[135] Methylene aziridine *(R)*-**169** underwent [2+2] cycloaddition with tetracyanoethylene (TCNE) to afford 5-azaspiro[3.2]hexanes (2*R*,1'*R*)-**170** and (2*S*,1'*R*)-**171** in up to 68% de (Scheme 42).[136]

5.2 Nitrogen Deprotection

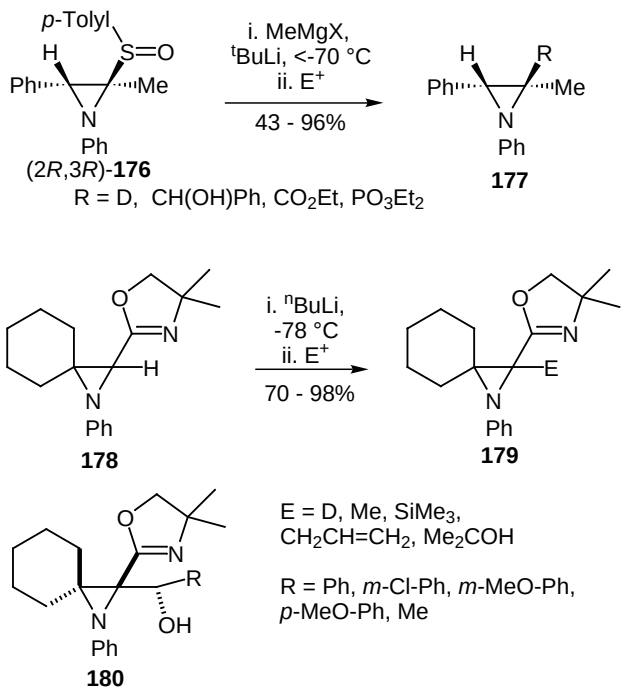
Acyl, carbamoyl or sulfinyl protecting groups on aziridines are generally easily removed. However, aziridines are often prepared or utilised with an arenesulfonyl group attached to nitrogen which is not as readily removed except under harsh conditions.[85,137,138] Samarium iodide has been used for such a purpose with alkyl substituted aziridines[139] but is not a general method since aziridine carboxylates will ring open.[15,16] Lithium in the presence of di-*tert*-butyl biphenyl (DTBB) was found to be of some application, notably facilitating removal of nosyl functionality from aziridine *(S)*-**172** (Scheme 43).[138] Magnesium in methanol under ultrasonic conditions was also found useful to deprotect aziridine carboxylate (2*S*,3*S*)-



Scheme 41

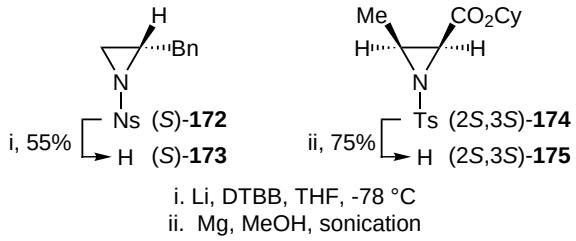


Scheme 42



Scheme 44

174, albeit accompanied by some ring opening.[138] Sodium naphthalenide has recently been reported to deprotect *N*-toluenesulfonyl aziridines for a variety of examples.[137,140] However, 2-carboxylate substitution led to decomposition although 2-amide functionality was tolerated.



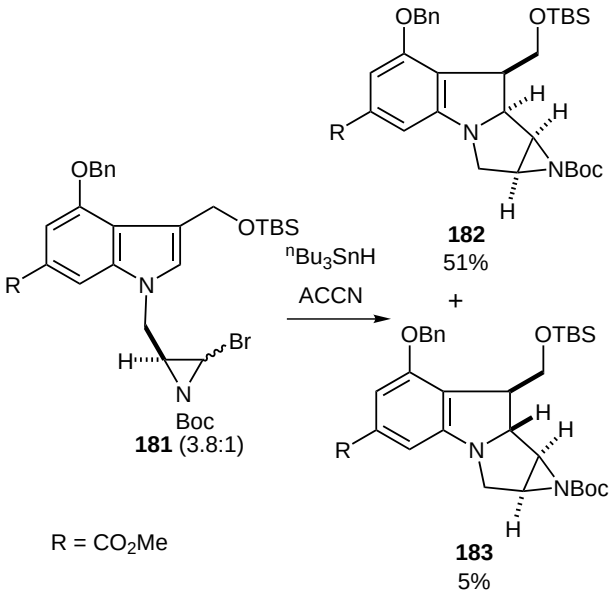
Scheme 43

5.3 Aziridinyl Anions

The use of aziridinyl anions has been reviewed although only a limited number studies have been conducted.[141] Recently aziridine borane complexes have been lithiated and reacted with electrophiles.[142,143] In addition, sulfinyl aziridine (2*R*,3*R*)-**176** was subjected to sulfoxide-lithium exchange and quenched with range of electrophiles, mainly aldehydes and ketones (Scheme 44).[144] Oxazolinyl aziridinyl anions have increased the scope for introducing substituents directly to the aziridine ring (Scheme 44).[145] The aziridinyllithium species was stable at −78 °C and could be quenched by a variety of electrophiles to give aziridine **179**. Notably, reaction with aldehydes was *anti* selective and a range of hydroxy alkyl aziridines **180** were prepared.

5.4 Aziridinyl Radicals

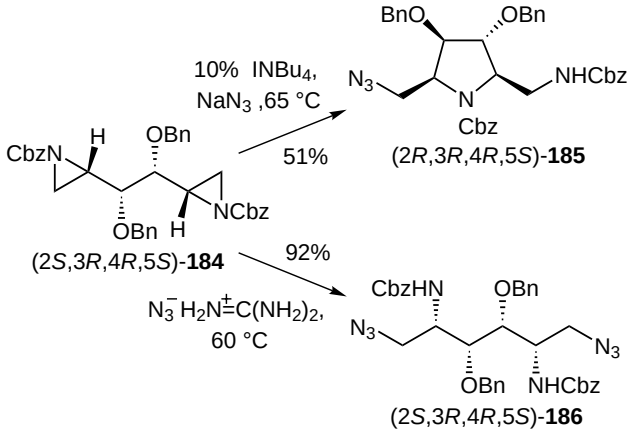
There are few reports of chiral aziridinyl radicals but they have been generated from bromoaziridines.[146,147] Treatment of aziridine epimers **181** with ACCN and Bu_3SnH under high dilution afforded a chiral aziridinyl radical which cyclised onto the indole functionality (Scheme 45). Reductive cyclisation predominated in this system to afford **182** and **183** whereas dimerisation occurred when an electron withdrawing group was attached to the aziridine.



Scheme 45

6 Bis-Aziridines

The role of bis-aziridines as chiral ligands has already been discussed (Section 4.1). In addition, bis-aziridines have been utilised in ring-opening reactions although achieving complete chemoselectivity for a specific pathway has seldom been achieved. Commonly, substituted pyrrolidines can be obtained from intermolecular aziridine ring opening followed by intramolecular *5-exo-tet* aziridine ring opening as in the preparation of (2*R*,3*R*,4*R*,5*S*)-**185** from (2*S*,3*R*,4*R*,5*S*)-**184** (Scheme 46).[148] Use of the guanidinium cation provided a proton donor which stifled the intramolecular step leading to double intermolecular ring opening by azide to give bis-amino derivative (2*S*,3*R*,4*R*,5*S*)-**186**. Benzyl Grignard reagents have also been used to give bis-amino derivatives in copper catalysed bis-opening reactions of a similar Boc activated bis-aziridine.[149]

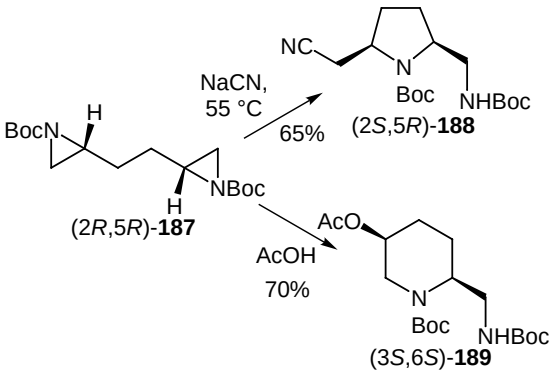


Scheme 46

Bis-aziridine (2*R*,5*R*)-**187** was found to be quite reactive and unstable to prolonged exposure to silica gel.[150] Use of sodium cyanide in an aprotic solvent gave mainly pyrrolidine (2*S*,5*R*)-**188** with some bis-opened product (15%) (Scheme 47).[150] However with more reactive nucleophiles bis-opening became more prevalent. Under acid catalysis bis-aziridine **187** underwent an S_N1 ring opening followed by *6-exo-tet* cyclisation to afford piperidine (3*S*,6*S*)-**189**. Diethylaluminium cyanide has also been found to favour piperidine formation.[151]

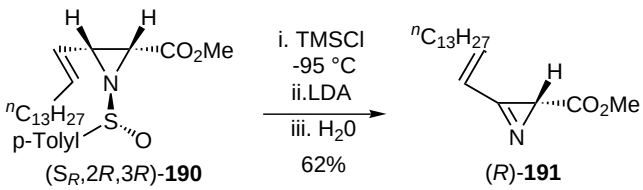
7 Preparation of Azirines

Chiral *N*-sulfinylaziridine (S_R,2*R*,3*R*)-**190** underwent β-elimination of the sulfinyl group when treated with base at low temperature to afford the antibiotic *(R)*-dysidazirine (**191**) (Scheme 48).[152] The rate of deprotonation of both aziridine protons was proposed to be competitive with loss of the C-3 proton leading to product while removal of the C-2 proton leads to decomposition. When the C-2 position is fully substituted, no such competition exists and



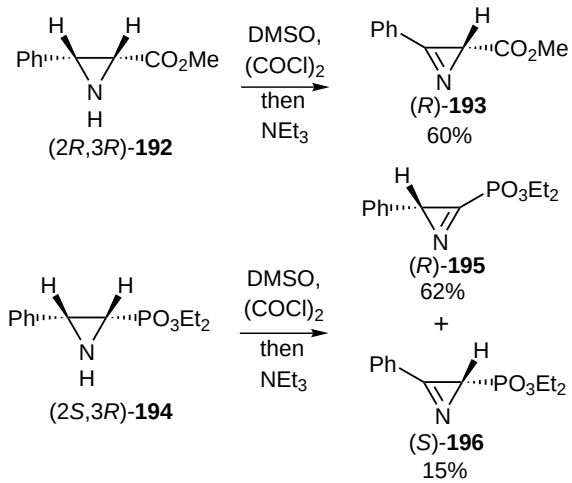
Scheme 47

the reaction yield increased dramatically for an *N*-tosyl derivative.[11] Desilylative elimination of an *N*-quinazoline from a chiral aziridine has also been used to prepare azirines.[13,153]



Scheme 48

An alternative azirine preparation from nitrogen unsubstituted aziridines has been conducted using a Swern oxidation procedure. Aziridine-2-carboxylate (2*R*,3*R*)-**192** afforded only the 2*H*-azirine product *(R)*-**193** while the corresponding aziridine-2-phosphonate (2*S*,3*R*)-**194** afforded both 2*H*-azirine *(S)*-**196** and 3*H*-azirine *(R)*-**195** with the latter predominating (Scheme 49).[87,154] A greater acidifing effect on the geminal aziridine proton by the

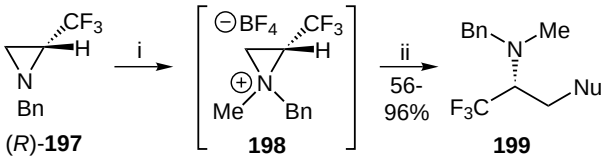


Scheme 49

phosphonate group compared to the carboxylate group was used to explain different elimination pathways for the respective *N*-sulfonium intermediates.[87]

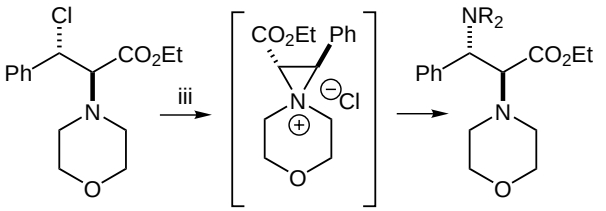
8 Aziridinium Ions

When there is no activating group on the aziridine nitrogen, reactivity towards nucleophiles can be dramatically increased through the formation of an aziridinium ion.[155–158] In the simplest sense, protonation of aziridine *(R)*-**197** using an acid catalyst facilitated ring opening by halogen and chalcogen nucleophiles. *N*-Alkylation to afford aziridinium ion **198** further increased reactivity such that nitrogen and carbon nucleophiles could also be used (Scheme 50).[156] The aziridinium ion **201** could be generated by heating chloroamine **200** and was reacted with a range of primary and secondary amines to give α,β-diamino esters **202** with excellent regioselectivity.[157]



(*R*)-**197** **198** **199**

Nu = PPh_3, H_2O, (Bn)MeNH, $^nBuNH_2$, $NaCH(CO_2Et)_2$, $LiCH_2COPh$



200 **201** **202**

R = H/ ^nBu, ^iPr, ^tBu, Ph, H or-$(CH_2)_4$ or $(CH_2)_2NPh(CH_2)_2$

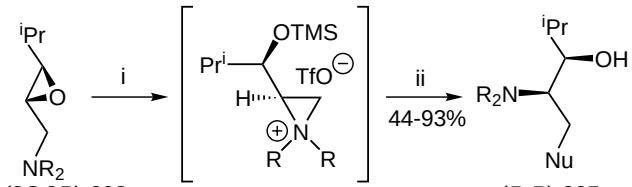
i. MeI, $AgBF_4$ (50%) or Me_3OBF_4 (97%); ii. Nu, 0 °C; R_2NH, 60 °C, K_2CO_3

Scheme 50

The Payne Rearrangement-Nucleophilic Trapping Procedure (PRNTP) was used to prepare amino alcohols (*R*,*R*)-**205** from chiral epoxides (2*S*,3*R*)-**203** via the chiral aziridinium ions **204** (Scheme 51).[155] A wide variety of amine nucleophiles were successfully used, notably amino esters without any loss of stereochemical purity under these conditions.

9 Conclusion

The use of chiral aziridines has been widespread in organic synthesis. Their chemistry has been dominated by facile ring opening with predictable control of regiochemistry and stereochemistry using a variety of nucleophiles. The use of nitrogen activating groups, Lewis acids and formation of aziridinium ions has facilitated greater diversity of ring opening. Rearrangements of aziridines has allowed access to β-lactams and alkaloid skeletons. Furthermore, both chiral ligands and auxiliaries have been derived from aziridines. The breadth of organic chemistry involving chiral aziridines has been demonstrated and their use can only be expected to increase in the future.



(2*S*,3*R*)-**203** **204** (*R*,*R*)-**205**

R = Bn, allyl, piperidinyl, morpholinyl, pyrrolidinyl
Nu = uracils, imidazoles, amines, amides, amino esters

i. TMSOTf, -78 °C; ii. Nu

Scheme 51

Acknowledgement

For our own studies in the area of aziridine-2-carboxylates and aziridine-2-phosphonates we acknowledge the financial support of the National Science Foundation and the National Institutes of Health.

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