ChemComm
FEATURE ARTICLE

Asymmetric routes to substituted piperidines

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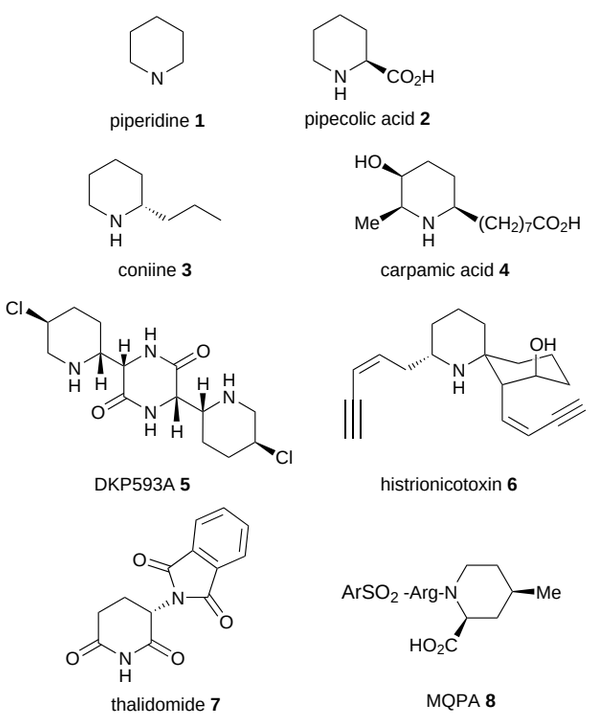
An overview of the main asymmetric routes to substituted piperidines is presented. A wide range of synthetic strategies have been developed, because of the ubiquitous nature of the piperidine sub-unit in natural products, and because of the biological properties of natural and synthetic piperidine derivatives. This review concentrates on general methodologies that provide enantioselective routes to substituted piperidines, but also includes some specific target syntheses that illustrate the power of the methods that have been developed. The three approaches that have been most successful are: the use of the chiral pool, especially amino acids; the use of reagents that utilise a chiral catalyst; and the use of chiral auxiliaries in the asymmetric formation or derivatisation of the piperidine ring.

Introduction

The piperidine ring system **1** is one of the commonest structural sub-units in natural compounds, as exemplified by structures **2**–**6**. Moreover, piperidine alkaloids (*e.g.* **2**–**6**) and synthetic



analogues (*e.g.* **7, 8**) are the focus of great interest in the pharmaceutical industry because they exhibit an extensive range of biological activities. The importance of this ring system makes short, versatile, stereocontrolled routes to substituted piperidines of tremendous potential value. This review outlines some of the recent developments in the asymmetric synthesis of piperidine systems;[1] it does not include resolution methods, although these are still very important, but focusses on the use of the chiral pool, chiral reagents and chiral auxiliaries. The examples selected are those that, in the view of the authors, offer the most reliable and flexible asymmetric routes to piperidines, and/or have the greatest potential for doing so.

Asymmetry from the chiral pool

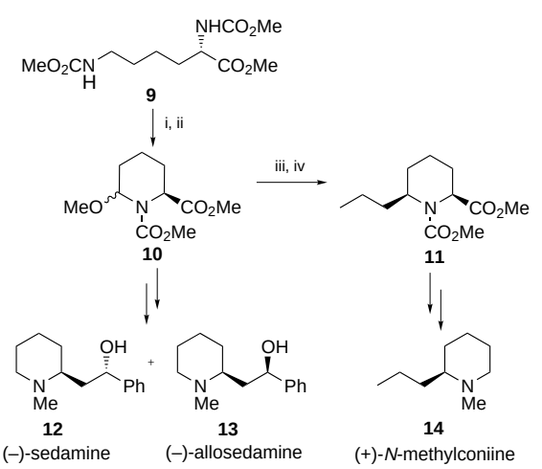
Amino acids

Amino acids are particularly useful precursors for the asymmetric synthesis of piperidine alkaloids for several reasons. Firstly, many amino acids are cheap and homochiral; secondly, they already contain the nitrogen of the alkaloid target; thirdly, they usually lead to 2-substituted piperidines, which is the commonest position for substitution.

Lysine. Lysine is the biosynthetic precursor for many piperidine alkaloids, but there are two main problems with its use in a laboratory synthesis; firstly, the amino groups need to be differentiated and (one of them) converted into a leaving group; secondly, it is not easy to introduce additional substitution (other than the existing carboxylic acid of lysine) into the piperidine ring. Enantiomerically pure forms of pipecolic acid have been prepared from lysine *via* several synthetic pathways. Fujii *et al.* have reported a six step synthesis of L-pipecolic acid in 60% overall yield starting from L-lysine.[2] However, L-pipecolic acid has also been prepared in 39% yield in a one step reaction of L-lysine with disodium nitrosyl pentacyanoferrate(II).[3]

The 6-methoxypipecolate derivative **10**, which is of biological interest, can be synthesised from the lysine derivative **9** by electrochemical oxidation at a platinum electrode.[4] Subsequent conversion of the *cis* isomer into enantiomerically pure (−)-sedamine **12** and (−)-allosedamine **13** was achieved in five further steps as outlined in Scheme 1. (+)-*N*-Methylconiine **14** has also been synthesised from **10** by Shono *et al.*; exclusive formation of the *cis*-disubstituted intermediate **11** was followed by saponification, anodic decarboxylation and reduction to afford the pure enantiomer in good yield (Scheme 1).[5]

Several other methods for the preparation of piperidine derivatives from lysine and various lysine analogues have been

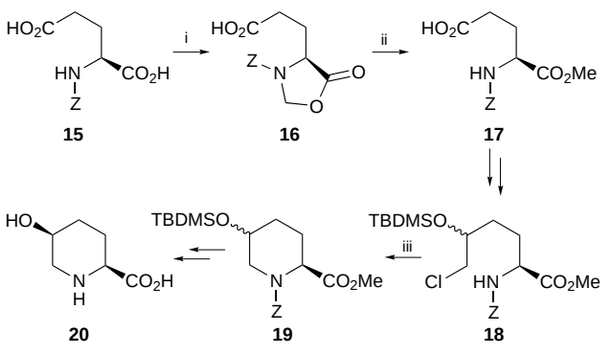


Scheme 1 *Reagents and conditions*: i, −2e⁻, MeOH; ii, MeOH, H_2SO_4; iii, CH_2=$CHCH_2SiMe_3$, $TiCl_4$; iv, H_2, Pd–C

reported,[6,7] including the use of an immobilised analogue of lysine to access piperidine derivatives attached to a polymeric support, providing the opportunity for preparing combinatorial libraries.[8]

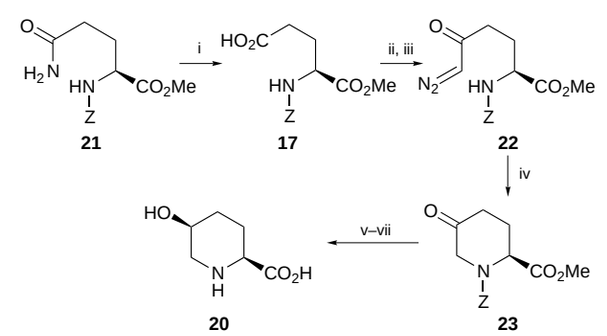
Glutamic acid/glutamine. Glutamic and aspartic acids are attractive chiral building blocks for piperidine targets because the side-chain functionality can be readily derivatised. In both cases, additional carbon(s) need to be introduced, and this can be exploited as a means of introducing additional substituents into the piperidine ring. The side-chain carboxylic acid group is usually retained as a functionalised position, thus providing access to 5-substituted pipecolic acid derivatives in the case of glutamic acid.

For example, Bailey *et al.* have made use of L-glutamic acid in a stereo- and enantio-specific synthesis of the naturally occurring alkaloid, *cis*-5-hydroxy-L-pipecolic acid **20**.[9] The dense functionalisation led to a number of synthetic problems, but treatment of the trialkylsilyl-protected alcohol **18** with NaH in DMF at 85 °C induced an intramolecular cyclisation to form the piperidine unit in 60% yield (Scheme 2).



Scheme 2 *Reagents and conditions*: i, $(CH_2O)_n$, TsOH, benzene, reflux (94%); ii, NaOMe, MeOH, reflux (95%); iii, NaH, DMF, 85 °C (60%)

This route has been subsequently improved in two ways. Firstly, the problematic differentiation of the two carboxylic acid groups in glutamic acid has been overcome by selective hydrolysis of glutamine using *tert*-butyl nitrite, and the development of a rhodium(II) catalyzed carbene N–H insertion reaction has led to a short and efficient route to the piperidine ring. The substitution pattern is amenable to the synthesis of 2,5-disubstituted targets such as DKP593A **5**, and the monomer of this compound has been prepared in protected form (Scheme 3).[10]

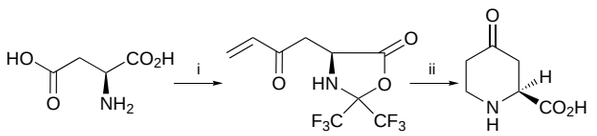


Scheme 3 *Reagents and conditions:* i, Bu^{t}ONO, MeCN, reflux (74%); ii, EtOCOCl; iii, CH_2N_2, Et_2O; iv, $[Rh(OAc)_2]_2$, benzene, reflux; v, $NaBH_4$, MeOH; vi, HO^- (aq); vii, H_2, Pd–C

The α-chiral centre can also be sacrificed after using it to control the stereochemistry elsewhere, such as in the synthesis of (*S*)- or (*R*)-3-hydroxypiperidine from D- or L-glutamic acid,[11] or in the formation of piperidines (and pyrrolidines) from glutamine.[12]

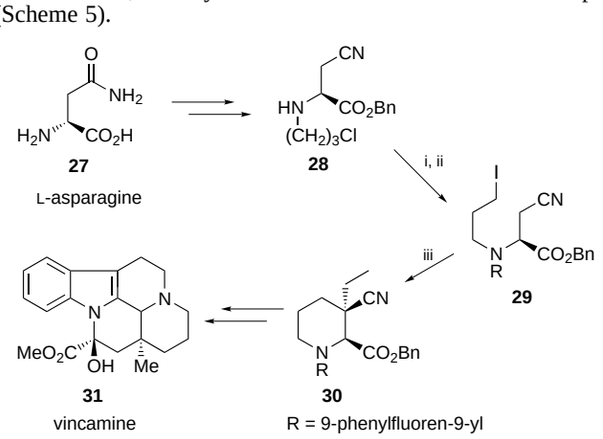
Aspartic acid/asparagine. In the same way that glutamic acid provides a route to 5-substituted pipecolic acids, aspartic acid can be used as a chiral precursor to 4-substituted pipecolic acids. For example, a range of 2,6-disubstituted piperidines can be prepared by extending the side-chain carboxylic acid group of Asp, using the attack of a sulfonamide on a ketone to effect the cyclisation.[12]

Differentiation of the α- and β-carboxylic groups in Asp can be tricky, but they were neatly distinguished in work by Golubev *et al. via* the formation of an oxazolidinone, which could be readily transformed into the hexafluoroacetone protected enone **25**.[13] A Lewis acid catalysed intramolecular Michael addition, followed by deprotection of the vicinal amino and carboxylic functions, gave the 4-oxo-L-pipecolic acid **26** which served as an intermediate in the synthesis of *cis*- and *trans*-4-hydroxy-L-pipecolates (Scheme 4).



Scheme 4 *Reagents and conditions*: i, hexafluoroacetone, then $SOCl_2$, Δ, then CH_2=$CHSnMe_3$, $BnPd(PPh_3)_2Cl$, dimethoxyethane; ii, $BF_3{\cdot}OEt_2$, benzene, Δ, then H_2O–Pr^{i}OH

Using the side-chain of asparagine in a completely different way, Christie converted the amide of asparagine into a nitrile, and used this to construct the piperidine ring in an asymmetric synthesis of vincamine **31**, a known hypertensive agent.[12] Thus, L-asparagine was converted into the iodide **29**, which was cyclised in the presence of LDA and ethyl iodide to afford the piperidine derivative **30** equipped with two chiral centres at positions 2 and 3. Apovincamine, a known precursor to vincamine **31**, was synthesised from **30** in six further steps (Scheme 5).



Scheme 5 *Reagents and conditions*: i, $NaHCO_3$, CH_2Cl_2, 9-phenylfluoren-9-yl bromide, K_3PO_4, $Pb(NO_3)_2$, MeCN; ii, NaI, MeCN, Δ; iii, LDA (excess), EtI (excess), −78 °C

Other amino acids. The amino acids discussed above all utilise the functionalised side-chains to become part of the piperidine ring. It is also possible to use both the α-amino and α-carboxylic acid groups of amino acids to form piperidine rings, in which case the amino acid side-chain becomes a piperidino subsituent. In such cases, the amino acid must be chosen so that the side-chain matches the target molecule. For example, starting from L-alanine, Angle *et al.* completed a nine step synthesis of (+)-monomorine, with the key step in the synthesis involving a Claisen rearrangement.[14]

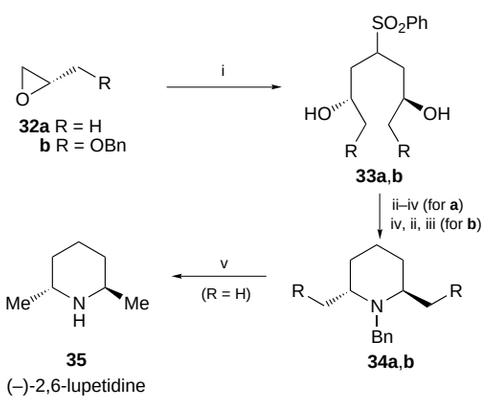
Sugars

Sugars have been used extensively to prepare polyhydroxylated piperidines; these aza-analogues of pyranose sugars often have potent enzyme inhibitory properties, and are thus of medicinal

importance. There is clearly a wide range of sugar building blocks available that might provide much of the functionalisation and stereochemistry, and the one selected depends on the specific target. The major challenge is to successfully differentiate the hydroxy groups so that one of them can be converted into an amino group, and a second one can be converted into a leaving group. This field has been dominated by Fleet's group, and he has developed a number of elegant tactics for achieving the necessary selectivity for the synthesis of polyhydroxylated targets.[15] Less oxygenated targets can also be accessed relatively quickly, as exemplified by the work of Tadano *et al.*[16]

Other chiral building blocks

As many alkaloids incorporate one or more 'isoprene' units within their structure, terpenes are sometimes attractive chiral building blocks. For example, Honda *et al.* developed an efficient stereoselective route to nuphar piperidine alkaloids starting from the readily available chiral monoterpenes, (−)- or (+)-carvone;[17] stereoselective construction of the piperidine ring was achieved *via* an intramolecular aza-Wittig cyclisation. Many other chiral building blocks are specific to the target in question, rather than providing general routes to substituted piperidines; for example, the chiral epoxide **32a** allows a short efficient synthesis of the C_2-symmetric target (−)-2,6-lupetidine **35** (Scheme 6)[18] and elaboration of the oxygenated analogue **34b** might provide access to other C_2-symmetric piperidine derivatives.



Scheme 6 *Reagents and conditions*: i, MesPh–BuLi; ii, TsCl, Py; iii, $PhNH_2$; iv, Na–Hg; v, Pd–C

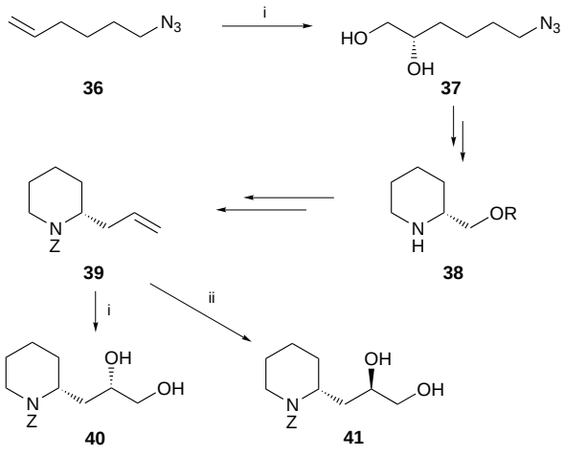
Use of chiral reagents

There are now many chiral reagents that induce asymmetry, and some of these have found widespread applicability in the synthesis of substituted piperidines. In most of the examples below, the reagent utilises a chiral catalyst, with obvious economic advantages.

Sharpless asymmetric dihydroxylation

This procedure has been used quite widely, as exemplified by the asymmetric syntheses of *trans*-2,6-disubstituted piperidines, (+)-epidihydropinidine and (+)-solenopsin A, reported by Takahata *et al.*[19] The asymmetric dihydroxylation (ADH) reaction was exploited even more effectively by Takahata *et al.*, using the ADH reaction to provide access to the piperidine ring, and then employing it again to generate the dihydroxylated targets **40** and **41**; the ADmix control of absolute stereochemistry was able to override any diastereocontrol for dihydroxylation in the penultimate step (Scheme 7).[20]

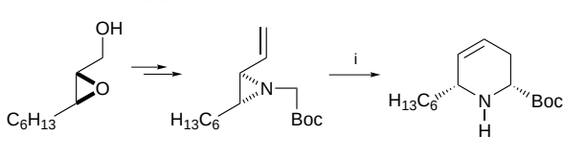
Sharpless's more recent asymmetric aminohydroxylation procedure is certain to be used extensively for the synthesis of piperidine targets.[21]



Scheme 7 *Reagents and conditions*: i, AD Mix-α; ii, AD Mix-β

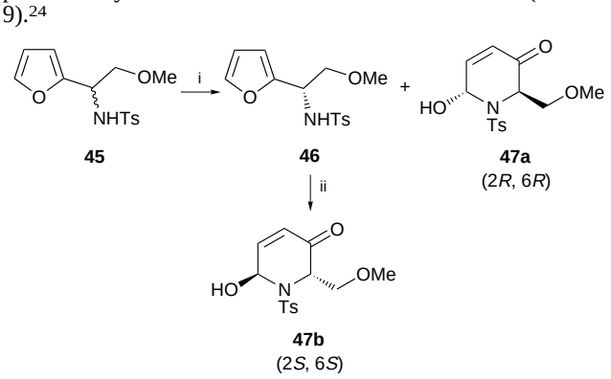
Sharpless asymmetric epoxidation

The Sharpless asymmetric epoxidation reaction is now a well-established and reliable procedure for the epoxidation of allylic alcohols, and there are many asymmetric syntheses of piperidine targets that exploit the reaction. One recent example nicely demonstrates how Sharpless asymmetric epoxidation (SAE) can be used to control (ultimately) the stereochemistry of three substituents on the piperidine ring.[22] A much more general approach is demonstrated by Ahman and Somfai, who prepared the chiral vinylaziridine **43** (> 95% ee) in a straightforward manner from the known epoxy alcohol **42**, itself produced *via* Sharpless asymmetric epoxidation. They showed that these types of vinylaziridines undergo an aza-[2,3]-Wittig rearrangement yielding the corresponding *cis*-2,6-disubstituted tetrahydropyridines **44** as single diastereoisomers (Scheme 8).[23] This methodology has been extended, allowing access to many indolizidine and piperidine alkaloids.



Scheme 8 *Reagents and conditions*: i, LDA, THF

Less conventional is the use of SAE conditions to effect kinetic resolution of the racemic furanyl sulfonamide **45**, which provided asymmetric routes to both enantiomers of **47** (Scheme 9).[24]

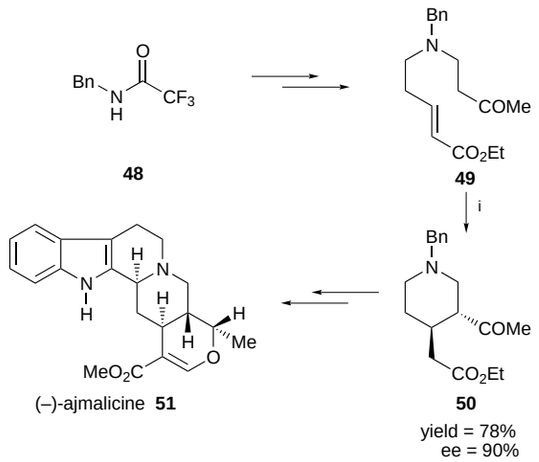


Scheme 9 *Reagents and conditions*: i, $Ti(OPr^i)_4$, L-(+)-DIPT, Bu^tOOH, SiO_2, CaH_2; ii, MCPBA

Chiral bases

Michael reactions using enolate nucleophiles can sometimes occur enantioselectively if triggered by a chiral base. For

example, the readily available achiral compound **49** has been shown to undergo an asymmetric intramolecular Michael reaction with the chiral base, (+)-1-phenylethylamine, to give the optically active cycloadduct **50** in good yield and 80% ee (Scheme 10).[25] This versatile chiral building block has been used in the synthesis of various alkaloids including kainic acid, (−)-tetrahydroalstonine and (−)-ajmalicine **51**.

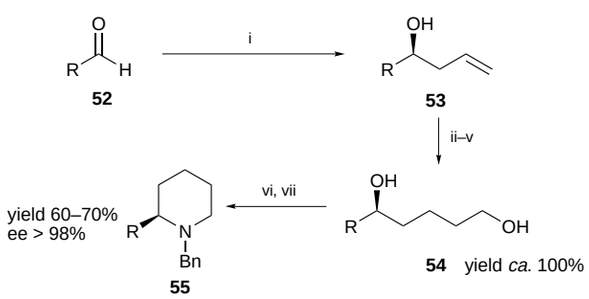


Scheme 10 *Reagents and conditions*: i, (+)-1-phenylethylamine, THF

Chiral boron reagents

The boron reagents developed by Brown are so efficient that their use in the asymmetric synthesis of substituted piperidines was inevitable. For example, the allylB(Ipc)$_2$ reagent can be reacted with a wide range of aldehydes, to provide homoallyl alcohols **53**; these can be elaborated to the diols **54**, from which the 2-substituted piperidines **55** are readily prepared. Not only does this provide a simple route to diverse 2-substituted piperidines, but either enantiomeric series is accessible by use of appropriate chiral boranes (Scheme 11).[26]

The use of chiral borane reagents as catalysts has been only moderately successful, but used in conjunction with a chiral auxiliary, the matched reagents can lead to very high asymmetric induction—see the section concerning Diels–Alder reactions of imines.



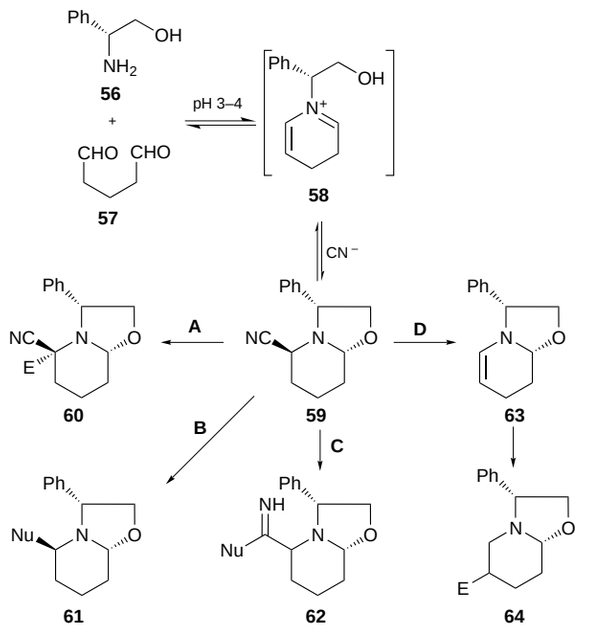
Scheme 11 *Reagents and conditions*: i, Ipc$_2$BAll, −100 °C; ii, BH_3·DMS; iii, MeOH; iv, $BrCH_2Cl$, −78 °C, then BuLi; v, H_2O_2–OH^-; vi, MsCl, NEt_3; vii, $BnNH_2$

Chiral auxiliaries

Chiral auxiliaries have been used with great success in the synthesis of piperidine ring systems. Perhaps the three most general and widely used methods are: the CN(*R,S*) method, the use of chiral lactams, and aza-Diels–Alder methodology.

The CN(R,S) *method*

The CN(*R,S*) method aptly derives its name from the Institut de Chemie des Substances Naturelles du C.N.R.S., where Husson *et al.* developed the use of chiral 2-cyano-6-oxazolopiperidine **59** for the asymmetric synthesis of functionalised piperidines; **59** can be readily obtained from a 'one-pot' condensation reaction between (−)-phenylglycinol, gluteraldehyde and KCN under acidic conditions (Scheme 12).



Scheme 12

The CN(*R,S*) method allows access to a wide range of 2,6-disubstituted piperidines of very high optical purity, exploiting the high functionality and facial selectivity in **59**. It possesses two non-equivalent reactive sites on the piperidine ring system; an α-amino nitrile at the C-2 position and an α-amino ether at the C-6 position. As summarised in Scheme 12, differential chemo- and stereo-selective reactions can be achieved at several positions, allowing access to a wide range of piperidine derivatives: (i) electrophilic attack at the C-2 position (route A); (ii) nucleophilic attack at the C-2 position (route B); (iii) attack at the cyano group (route C); and (iv) electrophilic attack at the C-3 position (route D).

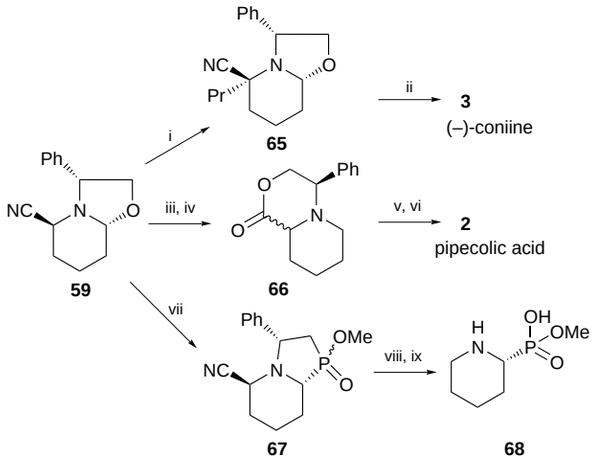
To demonstrate the versatility of the CN(*R,S*) method, Husson *et al.* have completed the syntheses of numerous enantiopure piperidine alkaloids which exhibit biological activity including monomorine, perhydrohistrionicotoxin, various analogues of podophyllotoxin and cephalotaxine.

For example the α-amino nitrile anion, generated by treatment of **59** with LDA, can be alkylated by reaction with alkyl halides. Elimination of the cyano group in the presence of NaH results in the formation of a single diastereoisomer; stereoelectronic effects are responsible for the addition of hydride to the *si* face, so that only *cis* diastereoisomers are formed. This has been illustrated in the synthesis of (−)-coniine[27] (Scheme 13).

Alternatively, the nitrile can itself be incorporated into the target molecule, as in a four step synthesis of (*S*)-(−)-pipecolic acid **2** from the synthon **59**.[28] The cyanide was first converted into the ethyl ester, and reduction with Zn(BH$_4$)$_2$ gave the lactone **66** as a mixture of diastereoisomers. A deprotonation and reprotonation procedure converted **66** into a single diastereoisomer, from which (*S*)-(−)-pipecolic acid was subsequently isolated in 47% overall yield by a simple hydrogenation under acidic conditions (Scheme 20). The phosphonic acid analogue of **2** can also be accessed using the CN(*R,S*) method, as indicated in Scheme 13.[29]

Chiral lactams

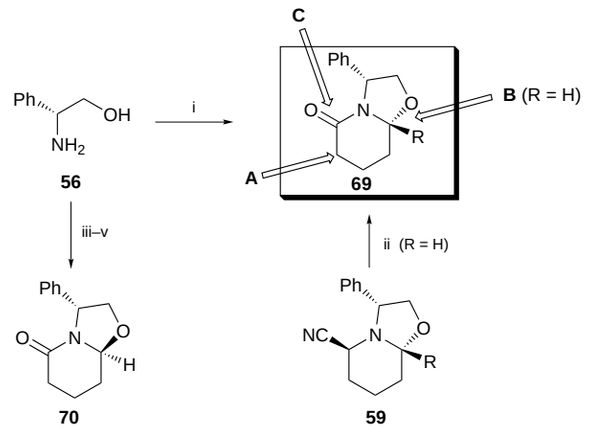
The use of chiral lactams has been developed most effectively by Meyer's group,[30] and this approach has wide applicability to



Scheme 13 *Reagents and conditions*: i, LDA, THF, −78 °C, then PrBr; ii, $NaBH_4$, then H_2SO_4; iii, HCl–EtOH, SiO_2, PhMe; iv, $Zn(BH_4)_2$, Et_2O; v, LDA, THF, AcOH; vi, H_2, Pd–C, HCl–MeOH; vii, $P(OMe)_3$–$SnCl_4$; viii, $NaBH_3CN$; ix, H_2, Pd–C

the synthesis of substituted piperidines, as indicated in Scheme 14. In particular: (i) the enolate of lactam **69** can be alkylated at the 3-position (A); (ii) the *N*-acyliminium intermediate allows introduction of C-6 substituents (B); and (iii) the amide carbonyl can be further functionalised (C). Overall, this provides access to 2,3,6-trisubstituted piperidines with excellent diastereo- and enantio-control.

In the course of their endeavours towards starting materials for the asymmetric synthesis of piperidine derivatives, Royer and Husson were also able to prepare **69** and epimeric **70** from **59**, as shown in Scheme 14.[31]

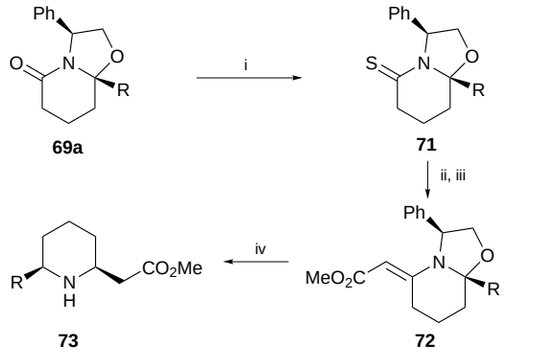


Scheme 14 *Reagents and conditions*: i, $RCO(CH_2)_3CO_2H$; ii, LDA, −78 °C, then O_2; iii, glutaric anhydride, AcCl; iv, $NaBH_4$; v, HCl–MeOH

Meyers has demonstrated the flexibility of his methodology in numerous syntheses.[30] For example, his approach readily allows access to 2,6-disubstituted piperidines (see Scheme 15),[32] whilst reduction of the (thio)lactam clearly provides a simple route to 2-substituted piperidines.

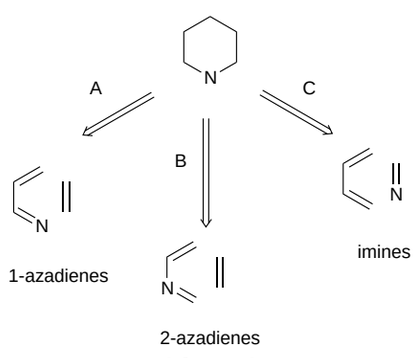
Aza-Diels–Alder reactions

The aza-Diels–Alder reaction has the potential to be a very effective method for the preparation of substituted piperidines.[33] The reaction potentially allows the rapid construction of quite complex piperidines, functionalised or derivatised at various positions, and there is the possibility of regio-, diastereo- and enantio-selectivity in the reaction. The aza-Diels–Alder reaction has therefore provided the key step in numerous syntheses of these compounds. Nevertheless, there



Scheme 15 *Reagents and conditions*: i, Belleau's reagent; ii, $BrCH_2CO_2Me$; iii, $P(OMe)_3$; iv, 3 atm. H_2, $Pd(OH)_2$–C

are problems associated with all of the possible aza-Diels–Alder routes to piperidines, and only recently has substantial progress been made concerning the general applicability of these reactions. The three basic variations of the aza-Diels–Alder reaction that can be used to form piperidine derivatives are shown in Scheme 16. An excellent recent review on 'Asymmetric Hetero-Diels–Alder Reactions' by Waldmann includes a valuable summary of asymmetric aza-Diels–Alder chemistry.[34]



Scheme 16

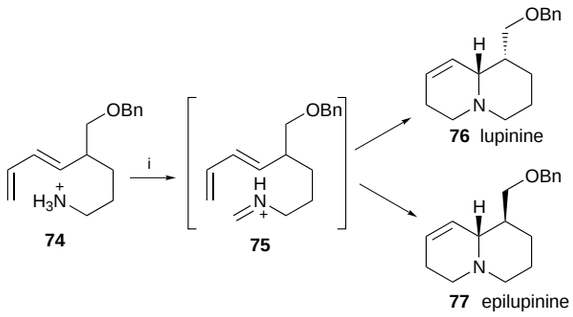
1-Azadienes (route A). 1-Azadienes have proved particularly capricious in (4 + 2)π cycloaddition reactions, with competing imine chemistry often thwarting the intended reaction, and although chiral auxiliaries can be attached to the nitrogen atom, this has not proved to be a major asymmetric route to substituted piperidines.

2-Azadienes (route B). 2-Azadienes have also been extensively studied as starting materials for the synthesis of piperidine-based compounds *via* the Diels–Alder reaction. Unfortunately, general asymmetric versions of these reactions have been elusive, as there is no simple way by which a removable chiral auxiliary can be attached.

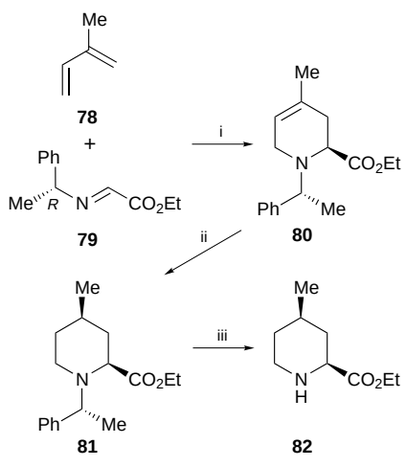
Imines as dienophiles (route C). The Diels–Alder reaction of imines or iminium salts with carbon dienes is probably the most efficient route to substituted piperidines reported to date. Intramolecular cycloadditions of *N*-acyl imines have been particularly useful in the synthesis of several natural products, including lupinine **76** and epilupinine **77** (Scheme 17).[35]

The chiral imine **79** can be readily produced by condensation of ethyl glyoxylate with 1-phenylethylamine, and the Diels–Alder reaction of **79** with a number of dienes has been investigated (Scheme 18).[36]

Bailey *et al.* have proposed a mechanism which explains why catalytic amounts of water are necessary to effect the cycloaddition under acidic conditions. It was suggested that intermolecular hydrogen-bonding between water and the imine formed a seven membered ring complex (Fig. 1) and that the diene approached this π-stabilised iminium intermediate from



Scheme 17 *Reagents and conditions*: i, HCHO



Scheme 18 *Reagents and conditions*: i, DMF, TFA (1 equiv.), H_2O (cat), 25 °C; ii, H_2, Pt–C, EtOAc; iii, H_2, $Pd(OH)_2$–C, EtOH

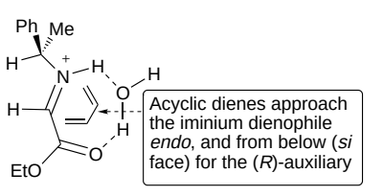
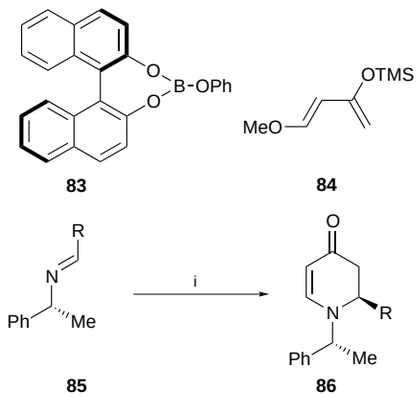


Fig. 1 Predictive model for the outcome of the aza-Diels–Alder reaction between acyclic dienes and **79**

the *si* face due to steric preferences induced by the chiral *N*-auxiliary.[37]

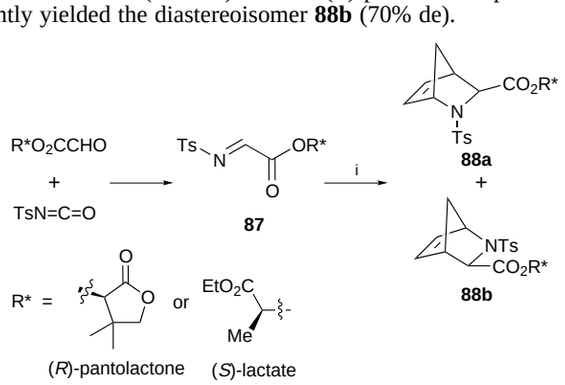
Stella and co-workers devised an alternative set of conditions in which the Diels–Alder reaction proceeded in the presence of TFA and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at low temperature. Application of these conditions in the cycloaddition of the chiral 1-phenylethylimine of methyl glyoxylate with cyclopentadiene led to total face selectivity and up to 98% *exo* selectivity in the cycloadduct, but extension to acyclic dienes was less successful.[38]

The Diels–Alder reaction of imines with *N*-chiral auxiliaries demonstrates that both high *endo*/*exo* selectivity and asymmetric induction can be achieved to allow access to a range of enantiopure piperidine derivatives. Moreover, the chiral Lewis acid **83**, derived from (*R*)-binaphthol and triphenyl borate, has been shown to catalyse the Diels–Alder reaction between chiral imines and Danishefsky's diene **84** with a very high degree of asymmetric induction (Scheme 19).[39] The use of lanthanide Lewis acid catalysts has been recently published in aza-Diels–Alder reactions of an imine derived from a chiral aldehyde,[40] and the addition of chiral ligands to these reactions has given very encouraging preliminary results—this may well turn out to be one of the most efficient and economical asymmetric routes to chiral piperidines.



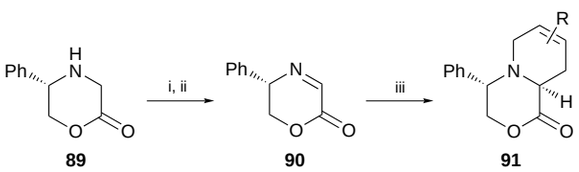
Scheme 19 *Reagents and conditiosn*: i, **83**, **84**, CH_2Cl_2, −78 °C

Holmes has investigated the participation of *N*-*p*-tolylsulfonyl imines **87**, carrying an chiral ester auxiliary, in the aza-Diels–Alder reaction with cyclopentadiene (Scheme 20).[41] The source of chirality on the ester moiety of the imines was from glyoxylate ester derivatives of (*R*)-pantolactone and ethyl (*S*)-lactate, which are known to coordinate Lewis acids in asymmetric cycloaddition reactions. The best results were obtained using Et_2AlCl in toluene at −78 °C. Use of the (*S*)-lactate auxiliary led to the formation of **88a** as the major diastereoisomer (76% de) whereas (*R*)-pantolactone predominantly yielded the diastereoisomer **88b** (70% de).



Scheme 20 *Reagents and conditions*: i, cyclopentadiene, Et_2AlCl, toluene, −78 °C

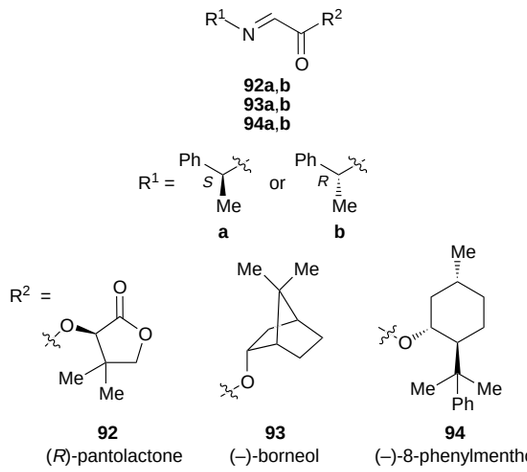
Several groups had sought to prepare the cyclic imines such as **90**, for which Diels–Alder reactions ought to proceed with excellent diastereo- (and hence enantio-)control. Routes in which the imine should have been generated by cyclisation of δ-amino aldehyde derivatives were singularly unsuccessful, but Harwood's group has successfully prepared **90** *via* an oxidative route, and the enantiocontrol in its aza-Diels–Alder reactions is (as expected) superb (Scheme 21).[42] The modest overall yield, and the cost of (unrecoverable) (*R*)- or (*S*)-phenylglycinol are limitations, but this method does provide the highest enantiocontrol from a single auxiliary, and (provided the reaction is sufficiently general) it offers to be a very attractive asymmetric route to a wide range of substituted piperidines.



Scheme 21 *Reagents and conditions*: i, NBS; ii, propylene oxide; iii, substituted butadienes, TFA or AcOH (*ca.* 1.5 equiv.), $BF_3{\cdot}OEt_2$, −78 °C (yield *ca.* 35% from **89**)

Returning to the readily accessed glyoxylate imines, the groups of Bailey and Holmes were able to combine their

auxiliaries and explore the effect of matched and mismatched auxiliaries on the nitrogen and the ester moieties of the imine in aza-Diels–Alder reactions.[43] The imines derived from alcohols (*R*)-pantolactone, (−)-borneol and (−)-8-phenylmenthol in combination with (*R*)- and (*S*)-1-phenylethyl *N*-auxiliaries were studied (imines **92**–**94**) using 2,3-dimethylbutadiene as the 4π partner.



Optimum results were recorded for the Diels–Alder reaction using the imine PhMeCHN=CHCO$_2$PhMen* **94a** bearing matched auxiliaries, and the reaction provided single stereoisomeric products with a range of dienes. The reactions also occurred with complete regiospecificity in all cases, and acyclic dienes added *via* an *endo* transition state, whilst cyclic dienes yielded the *exo* adducts. Detachment of the (recoverable) ester auxiliary was achieved by saponification, and removal of the (cheap) 1-phenylethyl auxiliary could be achieved by catalytic hydrogenation, allowing access to piperidines of known absolute stereochemistry.

Other chiral auxiliaries

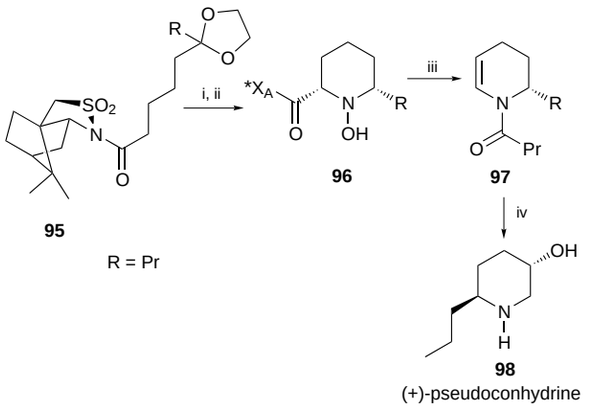
There are many other examples of syntheses involving chiral auxiliaries for the synthesis of piperidines, although most have yet to demonstrate that they are as reliable and versatile as the general methods outlined above. Nevertheless, the wide range of other approaches may provide the best method for a specific target. We have selected a dozen or so examples to illustrate the types of methodology available.

Oppolozer's group has led the way in the use of chiral sultams in asymmetric synthesis, and their methodology provides access to 2,6-*trans*-dialkylated piperidines.[44] Their approach can also be adapted to other substitution patterns, such as the 2,5-disubstituted piperidine (+)-pseudoconhydrine **98**, which has been prepared *via* a versatile deoxygenative decarboxylation–imine trapping route (Scheme 22). In most of the sultam work, the moderately high asymmetric induction can be improved by recrystallization, and the chiral sultam auxiliary can be efficiently recovered part way through the synthesis.

A similar camphor-like auxiliary has been developed by Wanner's group, providing access to 2-substituted piperidines.[45] The key step involves the conversion of an *N*-acyl 2,3-didehydropiperidine into an acyliminium derivative, which is susceptible to nucleophilic attack with high stereocontrol.

Alkylation of acyliminium intermediates has also been achieved, using a C_2-symmetric chiral hydrazone derivative as the source of asymmetry.[46] Hydrazones have also been used by Enders and Jegelka in a further development of RAMP/SAMP methodology, although the approach perhaps lacks generality.[47]

A rather unusual variation of the SAMP/RAMP auxiliary uses a cyclic hydrazine, and involves C–O bond cleavage that is reminiscent of Meyer's chiral lactam work.[48]



Scheme 22 *Reagents and conditions*: i, NaN(SiMe$_3$)$_2$, 1-chloro-1-nitrocyclohexane, H_3O^+; ii, $NaCNBH_3$; iii, NaH, 110 °C, PrC(O)X, base; iv, $BH_3.SMe_2$, THF, then H_2O_2, NaOH, then Pd(OH)$_2$–C, MeOH

The enantiospecific reduction of imines can be used to gain access to piperidines, as demonstrated by Moody's group.[49] The approach should be quite flexible, as a variety of alkyl derivatives could be introduced during the synthesis to yield a range of 2,6-disubstituted piperidines.

Using well-established auxiliaries, several groups have developed quite general asymmetric routes to substituted piperidines. For example, Agami *et al.* utilised an intramolecular ene-iminium cyclisation in which stereoselective control was exerted *via* a morpholinone auxiliary;[50] this gave access to *cis*-2,4-disubstituted piperidines, in which the solvent provided the nucleophile stereospecifically. Using the ephedrine auxiliary, hetero-Diels–Alder chemistry has also been used to gain rapid access to a linear piperidine precursor; although the stereocontrol was modest, the minor diastereoisomer was readily removed, and the second (and final) step provided 5-hydroxy-2-methylpiperidine as a single enantiomer, with full recovery of the auxiliary.[51] The aza-annulation of enamines is another general approach,[52] and asymmetric versions have been developed. In contrast, Jones' imidazoline chiral auxiliary effects complete stereocontrol, and provides access to a wide range of 2-substituted piperidines, but the auxiliary is lost upon final deprotection.[53] Finally, Meyer's formamidine chiral auxiliary, which labilises the proton α to nitrogen, can be used in the synthesis of piperidines.[54]

Conclusions

The huge amount of work on the synthesis of piperidines testifies to their importance. However, there are only a few really concise approaches that provide access to a wide range of substitution patterns. If 2-substituted piperidines are required, then there are many possible synthetic strategies. But for more complex targets, three main options dominate the literature: (i) a tailor-made synthesis using a chiral pool precursor (*e.g.* an amino acid or a sugar); (ii) the construction of a linear precursor using the best asymmetric reagents available (*e.g.* chiral AD-Mix or borane reagents), although such syntheses are often long; and (iii) the use of a chiral auxiliary to control the construction or derivatisation of a piperidine derivative. The last approach offers the potential of short, flexible, highly stereospecific syntheses, despite some limitations. The top methods are the CN(*RS*) approach, the use of Meyers' bicyclic lactam chemistry, and aza-Diels–Alder reactions.

Despite much success, the apparently simple piperidine ring system remains a demanding challenge for synthetic chemists, and there is still enormous scope for improvement. It seems certain the the biological properties of substituted piperidines will ensure that synthetic work on them continues apace.

Acknowledgements

We thank Quintiles for financial support towards an MPhil studentship (for P. A. M.) and a PhD studentship (to P. D. S.).

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