REVIEW

Stoichiometric asymmetric processes

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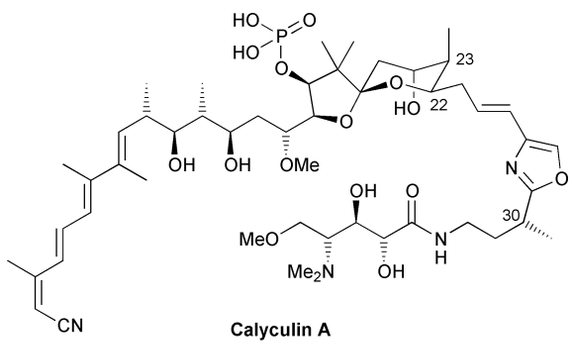
1 Introduction

This article covers the use and application of stoichiometric asymmetric processes for the whole of the 1999 calender year. The review focuses on the development of synthetic protocols involving the stoichiometric use of chiral reagents and auxiliaries. In particular, since the ultimate aim of any new piece of asymmetric methodology should be to use it in synthesis, I have tried to review the tried and trusted methods as well as identifying methods that have wider potential and application for the future. I have excluded stereoselective processes in which an existing chiral centre (often from the chiral pool) is incorporated in the final target structure and I have also chosen to ignore "chiral auxiliary" methods where the auxiliary is never removed at the end of the synthesis. Thus, the material contained herein is a personal selection of the offerings of 1999.

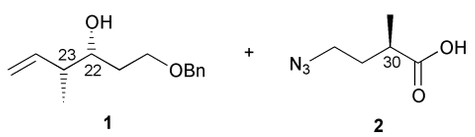
The review is split into three main sections. Using examples from 1999, Section 2 provides an overview of the surprisingly few chiral reagents and auxiliaries that are most widely used in total synthesis. It is intended that this selection will allow the reader to update his/her own teaching and research references on chiral auxiliaries and reagents as well as highlighting the most important methods. The new discoveries as well as the improvements to previously introduced methods in the areas of chiral auxiliaries and chiral reagents are reviewed in Sections 3 and 4 respectively. I have not tried to explain the sense of induction but have simply provided a representative example and have tried to identify where examples are of limited scope.

2 Frequently used chiral reagents and auxiliaries in synthesis

On reviewing the synthetic literature of 1999, it is strikingly obvious that two chiral auxiliary methods (Evans' oxazolidinones for α-alkylation and *syn*-aldol reactions) and one chiral reagent method (Brown's allylboration chemistry) dominate the stoichiometric asymmetric methods used in total synthesis. A typical example illustrating this is the total synthesis of calyculin A (Scheme 1) reported by the Smith group.[1,2] At the simplest level, the total synthesis evolved by construction



Calyculin A



1 **2**

Scheme 1

of some key chiral building blocks and further elaboration *via* a series of diastereoselective processes and coupling reactions. The elaboration and coupling steps formed most of the novel chemistry in the total synthesis but none of these investigations would have been possible without easy access to multi-gram quantities of two key chiral building blocks **1** and **2**.

The preparation of enantioenriched **1** and **2** is summarised in Scheme 2. Thus, reaction of *B*-(*Z*-crotyl)diisopinocampheylborane **3** with aldehyde **4** followed by alkaline hydrogen peroxide work-up furnished *syn*-homoallylic alcohol **1** of 90% ee.[1] α-Alkylation of Evans' oxazolidinone **5** using sodium hexamethyldisilazide and methyl iodide gave adduct **6** in 95% de which, after purification of the major diastereoisomer and hydrolysis, gave acid **2** in 98% ee.[2] Both these types of transformations are robust, reliable, easily scaleable and are successful on a wide range of substrates. In addition, they provide access to either enantiomer of products which contain a variety of functionality for further manipulation. These approaches are tried and tested over a number of years and, together with a number of catalytic asymmetric methods not covered in this review, form the cornerstone of modern asymmetric synthesis.

Brown's allylboration methodology is *the* most used stoichiometric chiral reagent procedure in total synthesis. Because of this, Brown and co-workers have continued to develop the reaction further and have recently reported the reaction of *B*-allyldiisopinocampheylborane with formyl esters as a route to chiral lactones of high enantiomeric excess.[3] As well as using Brown's methodology in total synthesis (of, for example, restrictinol[4]), the Barrett group recognised a limitation of

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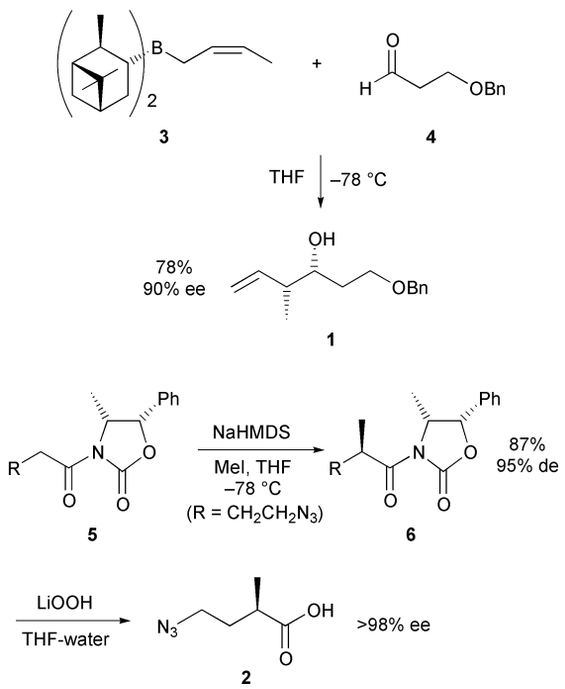
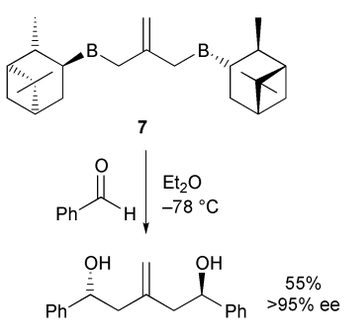


Scheme 2

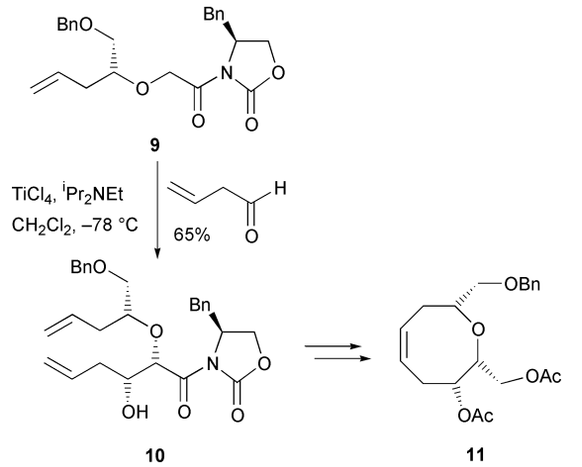
allylboration reactions: the resulting alkene is terminal. To address this, they developed a clever silicon-tethered metathesis route for the elaboration of terminal homoallylic alcohols to disubstituted alkenes.[5] In a further extension, the same group described the use of a double allylboration reagent **7** in the synthesis of C_2 symmetric diols.[6] As an example, reaction of **7** under salt-free conditions with benzaldehyde generated diol **8** in high (>95%) enantiomeric excess together with about 15% of the *meso* diastereoisomer (Scheme 3).



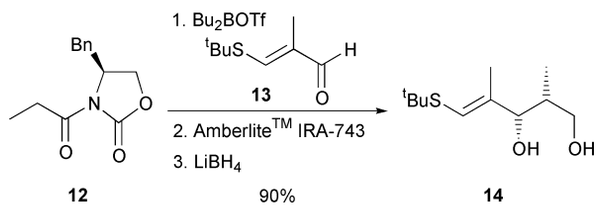
Scheme 3

Although useful for α-alkylation (see Scheme 2 for an example), Evans' oxazolidinones find most utilisation in *syn*-selective aldol reactions mediated by boron or titanium enolates. For example, Crimmins and Choy used a titanium enolate derived from **9** to produce *syn*-aldol **10** as a single diastereoisomer (Scheme 4).[7] Subsequent cleavage of the chiral auxiliary in **10** and transformations including ring closing metathesis generated an eight-membered cyclic ether **11** suitable for the synthesis of the marine natural product laurencin.

Heathcock, one of the pioneers of aldol reaction methodology, continues to improve on existing aldol technology within the framework of total synthesis. In a recent synthesis of myxalamide A, Heathcock and Mapp found that a 90% yield of enantiomerically pure *syn*-diol **14** could only be obtained if the aldol reaction between **12** and aldehyde **13** was worked up with an Amberlite™ exchange resin (to remove the dialkyl boronates) and then subjected to direct reduction with lithium borohydride (Scheme 5).[8] Heathcock has developed a reason-

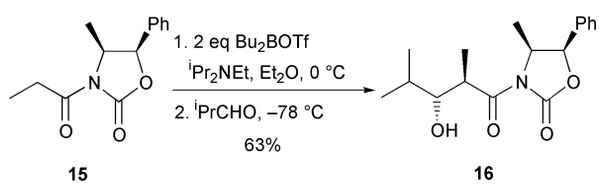


Scheme 4



Scheme 5

ably good route to enantiomerically pure *anti*-aldol products using Evans' oxazolidinones and Staunton and co-workers made use of such a reaction in their synthesis of prelactone B. Thus, use of *two* equivalents of dibutylboron triflate for the aldol reaction of **15** with isobutyraldehyde gave a 63% yield of *anti*-aldol **16** together with 28% of the undesired *syn*-aldol (Scheme 6).[9]



Scheme 6

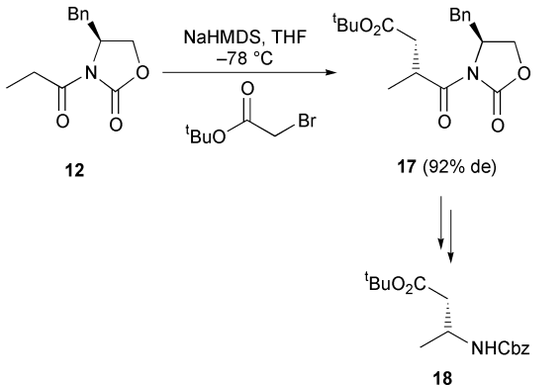
3 Chiral auxiliaries

3.1 α-Alkylation

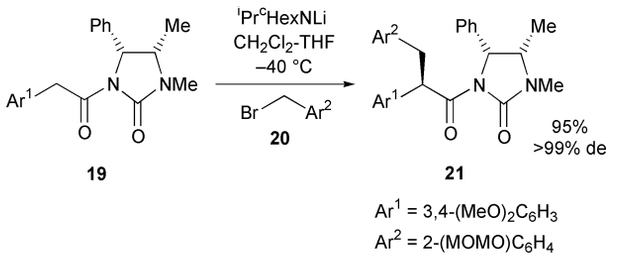
Evans *et al.* reported a useful extension of the oxazolidinone α-alkylation methodology to include a general route to β-substituted β-amino acids.[10] As a representative example, alkylation of oxazolidinone **12** with *tert*-butyl bromoacetate gave an 84% yield of **17** (92% de) and subsequent hydrolysis and Curtius rearrangement provided enantiomerically enriched β-amino acid **18** (Scheme 7).

Improved versions of Evans' oxazolidinones are now available and imidazolidinones (*e.g.* **19**) have proved a popular choice. During studies towards the total synthesis of amphinolide A it was found that imidazolidinones were much more amenable to scale-up than the corrresponding oxazolidinones.[11] In developing a general approach to isoflavans, Ferreira *et al.* showed that under appropriate conditions, imidazolidinones completely out-performed oxazolidinones.[12] Thus, deprotonation of imidazolidinone **19** with lithium isopropylcyclohexylamide and reaction with benzyl bromide **20** afforded **21** in excellent yield and diastereoselectivity (Scheme 8).

The Davies group has been actively developing modified oxazolidinones (the so-called "SuperQuats") to further improve Evans' original methodology for α-alkylation.[13] In a detailed

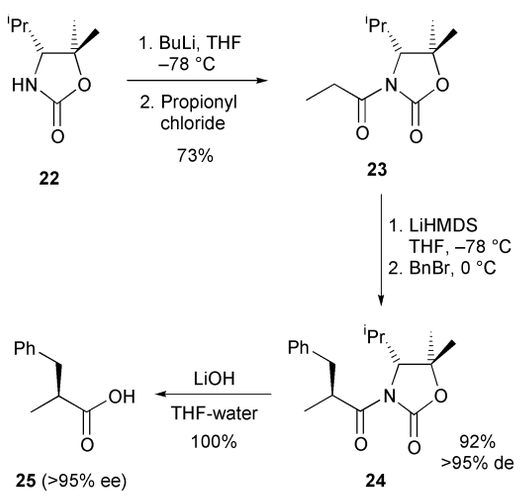


Scheme 7



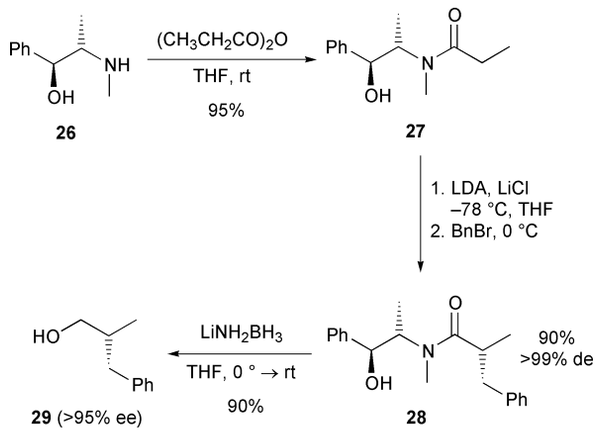
Scheme 8

full paper, Davies *et al.* identify 4-ispropyl-5,5-dimethyl SuperQuat **22** as the auxiliary of choice for asymmetric enolate alkylations. A typical sequence to illustrate this is depicted in Scheme 9. Alkylation of **23** using lithium hexamethyldisilazide and reaction with benzyl bromide at 0 °C furnished a 92% yield of **24** (>95% de) which could be hydrolysed in quantitative yield to give enantiomerically pure acid **25**.



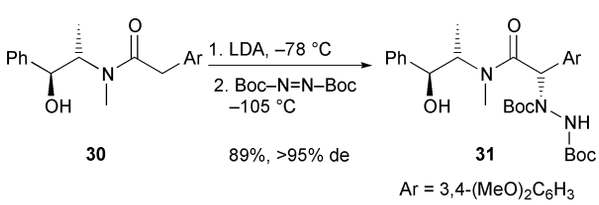
Scheme 9

Myers and co-workers have described the use of pseudoephedrine **26** for α-alkylation. This is one of the most significant developments in asymmetric α-alkylation technology and full experimental details have recently been reported.[14] Acylation of pseudoephedrine **26** with propionic anhydride gave a 95% yield of **27** which was alkylated with benzyl bromide using lithium diisopropylamide in the presence of lithium chloride. In this way, a 90% yield of alkylated amide **28** (>99% de) was obtained and the auxiliary could be removed by reduction using lithium amidotrihydroborate to give enantiomerically pure alcohol **29** (Scheme 10). Methods for removal of the chiral auxiliary to directly produce aldehydes and ketones have also been developed.[15]



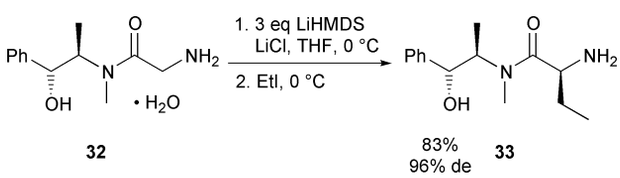
Scheme 10

The Myers methodology is especially attractive: pseudoephedrine is cheap and available in both enantiomeric forms; attaching the auxiliary *via* acylation is facile and high yielding; alkylation reactions are high yielding and almost completely stereoselective over a wide range of substrates and alkylating reagents; isolation of acylation and alkylation products can often be achieved by simple recrystallisation thus avoiding the need for chromatography; and very good protocols for removal of the chiral auxiliary to reveal a range of functionality have been established. Based on this, it seems reasonable to suggest that Myers' methodology could become a competitor to the well-established Evans methodology for α-alkylation. Others are already starting to use the methodology: research in my own group used the Myers approach to prepare a required chiral alcohol[16] and Badía and Domínguez have utilised the methodology in attractive routes to tetrahydroisoquinolines[17] and arylglycine amino acids.[18] As outlined in Scheme 11, the route to arylglycine amino acids involved amination of the enolate derived from amide **30** using di-*tert*-butyl azodicarboxylate to give an 89% yield of **31** (>95% de). Interestingly, in stark contrast to Myers' alkylations, lithium chloride was not required to mediate the amination reactions.



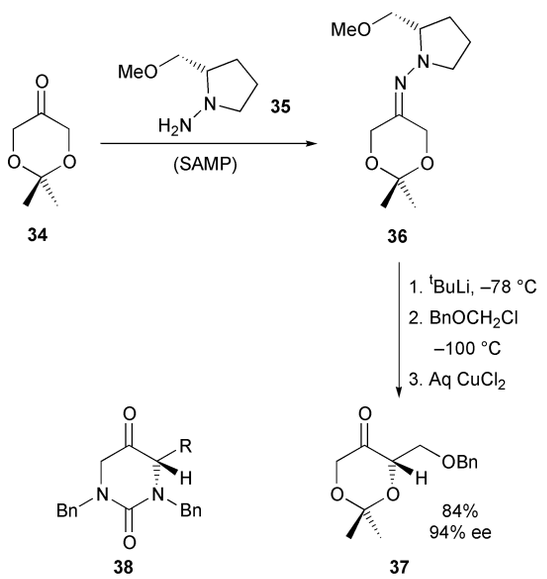
Scheme 11

An alternative route to α-amino acids, effectively *via* alkylation of glycine, has been developed by the Myers group. Significant pratical improvements to the methodology were reported which allowed the direct enolisation of pseudoephedrine glycinamide *hydrate* **32** using 3 equivalents of lithium hexamethyldisilazide. Subsequent alkylation with ethyl iodide, for example, afforded an 83% yield of adduct **33** (96% de) which could easily be converted into the required amino acid (Scheme 12).[19] This methodology is suitable for the preparation of fairly elaborate amino acids and Myers and Kung used it to prepare key building blocks in an elegant synthesis of the potent antitumour agent saframycin A.[20]

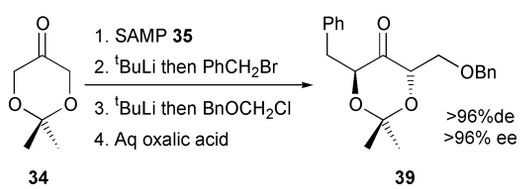


Scheme 12

Enders continues to develop asymmetric methodology mediated by (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) **35** including some new examples of α-alkylation.[21–23] Alkylation of hydrazone **36** (formed from ketone **34** and SAMP **35**) generated adduct **37** (94% ee) in 84% yield after removal of the auxiliary using the new conditions of aqueous copper(II) chloride (Scheme 13).[22] A similar route to a range of alkylated products **38**, precursors to potential HIV protease inhibitors, was also described.[23] In an extension of the process detailed in Scheme 13, Enders has provided a general route to 1,3-polyols with *anti*-relative stereochemistry.[24] Thus, double alkylation of **34** produced ketone **39** (>96% de and ee) (Scheme 14). Elaboration into an electrophile (*via* conversion of the ketone into a CH_2 group and transformation of the benzyloxy group into an iodide) for further alkylation reactions completed the iterative route to 1,3-polyols. Application of this methodology to the synthesis of the antitumour agent (+)-streptenol A has been described.[25]

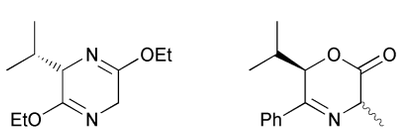


Scheme 13



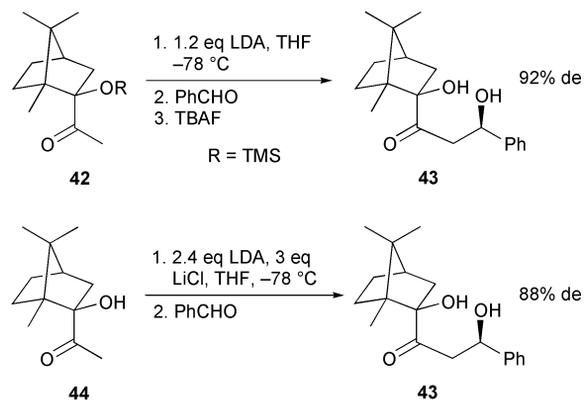
Scheme 14

Cook and co-workers have discovered that the diastereoselectivity of alkylation using the widely-used Schöllkopf template **40** is somewhat surprisingly dependent on the nature of the *leaving group* in the alkylating agent. Thus, the use of sterically demanding diphenylphosphate and tosylate leaving groups gave the highest levels of stereoselectivity.[26,27] Details of the use of a closely related auxiliary **41** for alanine alkylations have been described.[28]



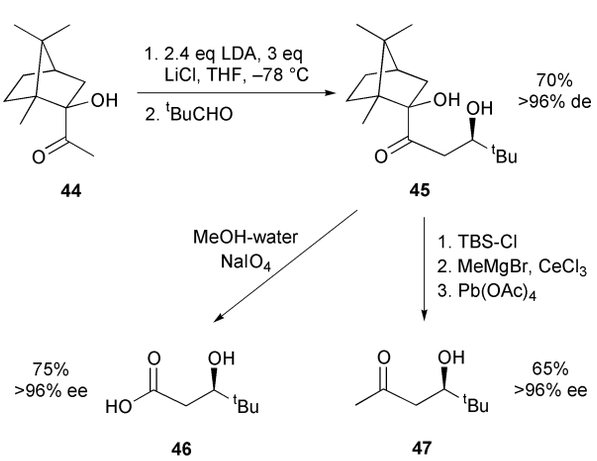
3.2 Aldol reactions and related processes

There is still a need to develop good, general methods for "acetate" aldol reactions and Palomo and co-workers have recently described full details of a camphor-based chiral auxiliary approach that appears to be very useful.[29] The "chiral acetate equivalent" is hydroxy ketone **44** which can be prepared from camphor in two steps (lithium acetylide addition followed by mercury(II)-mediated hydration to the methyl ketone). Initial studies were carried out on the TMS-protected version **42** (presumably to avoid complications due to multiply lithiated species in solution). Thus, deprotonation of chiral methyl ketone **42** followed by reaction with benzaldehyde and desilylation generated aldol **43** in 92% de (Scheme 15). To achieve such high stereoselectivity with chiral hydroxy ketone **44**, 3–6 equivalents of lithium chloride (and an extra equivalent of LDA) were employed and in this way, aldol **43** was obtained in 88% de (Scheme 15).



Scheme 15

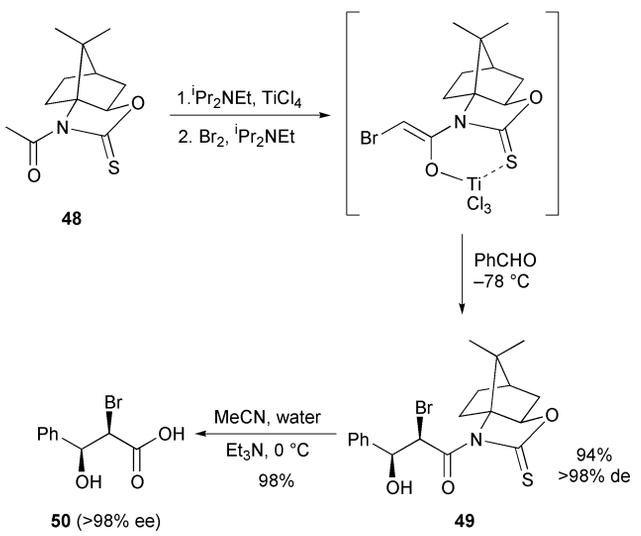
The use of hydroxy ketone **44** combined with excess lithium chloride was shown to be general and a wide range of aromatic and aliphatic aldehydes all gave highly stereoselective acetate aldol reactions. The highest stereoselectivity was obtained in the reaction of hydroxy ketone **44** with pivalaldehyde to give aldol **45** in >96% de (Scheme 16). Conditions for removal of the chiral auxiliary to generate β-hydroxy aldehydes, ketones and carboxylic acids were described. For example, treatment of **45** with sodium periodate gave β-hydroxy acid **46** whereas TBS protection of the secondary alcohol in **45** followed by Grignard addition (in the presence of cerium(III) chloride) and then reaction with lead tetraacetate produced β-hydroxy ketone **47** (Scheme 16). In both cases, the by-product of the oxidative cleavage reactions was camphor and this could be recovered enantiomerically pure and in good yield. The methodology developed by Palomo *et al.* is a very useful addition to asymmetric aldol reactions. The auxiliary is easy to prepare, gives high stereoselectivity, is easily removed to unmask a range of functionality and can be recovered for re-use. The



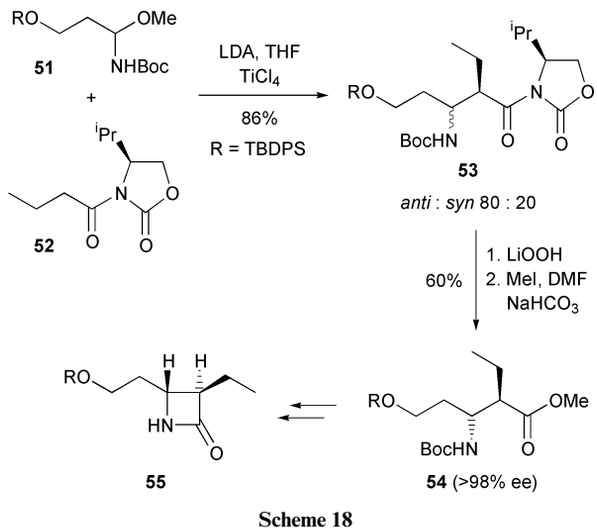
Scheme 16

only disadvantage is the higher cost of the unnatural isomer of camphor.

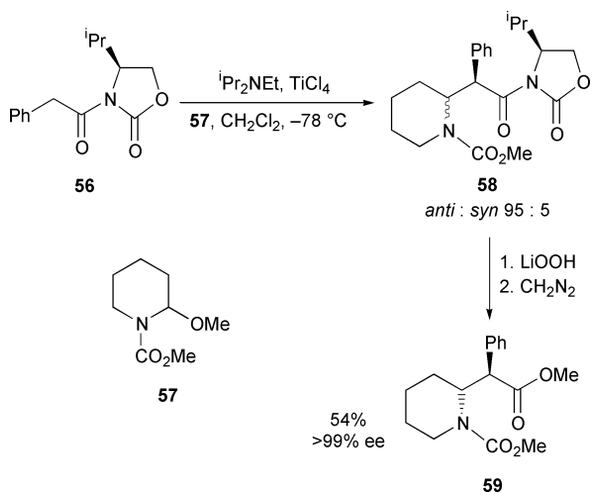
Yan and co-workers have described a highly stereoselective route to α-bromo-β-hydroxy carboxylic acids starting from acetate equivalent **48**.[30] Thus, treatment of thioimide **48** with titanium tetrachloride–Hünig's base, bromine–Hünig's base and benzaldehyde consecutively produced aldol **49** in an impressive 94% yield and >98% de (Scheme 17). Deprotection was achieved using triethylamine in water–acetonitrile to give enantiomerically pure **50**. The use of stronger bases such as lithium hydroxide for auxiliary removal led to the formation of significant amounts of the corresponding epoxide. Since α-bromo-β-hydroxy carboxylic acids such as **50** are precursors to epoxy acids[31] and β-hydroxy carboxylic acids (after reductive removal of the bromine), this methodology is effectively analogous to epoxidation of α,β-unsaturated acids and acetate aldol reactions respectively. In related work, Enders *et al.* have used a modified version of SAMP in an acetate-like aldol reaction.[32]



Scheme 17



Scheme 18



Scheme 19

The need to develop efficient methods for the construction of β-amino acid derivatives stimulated two independent studies on the addition of chiral enolates derived from Evans' oxazolidinones to *N*-acyl imines and iminium ions (both derived from α-methoxylated carbamates). Such reactions are essentially asymmetric Mannich reactions and could in principle have been contained in Section 3.4 of this review (additions to C=N). However, because of their aldol-like character I have chosen to include them in this section.

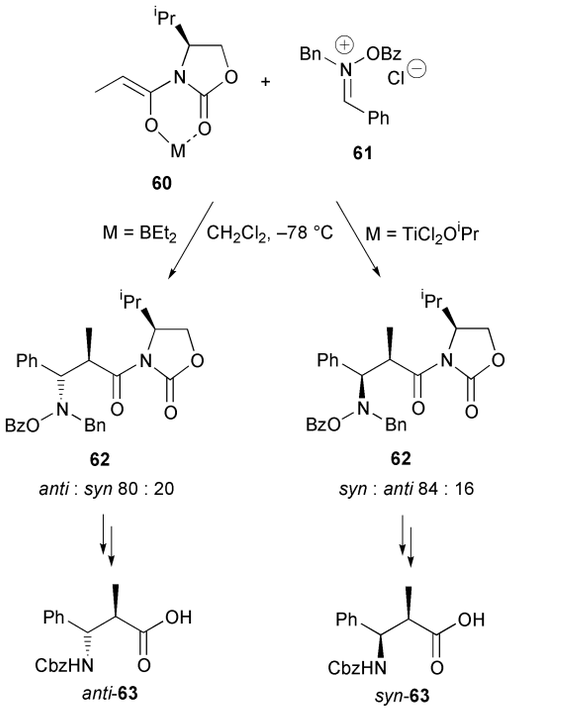
During research directed towards the synthesis of the carbapenem antibiotic PS-5, Kise and Ueda reacted the titanium enolate of oxazolidinone **52** with an open chain imine derived from α-methoxylated carbamate **51** to give a good yield of aldol-like adducts *anti*- and *syn*-**53** in moderate diastereoselectivity (Scheme 18).[33] Hydrolysis and methylation of the 80 : 20 mixture of *anti*- and *syn*-**53** followed by separation by chromatography afforded a 60% isolated yield of enantiomerically pure adduct *anti*-**54**. Synthetic manipulation of **54** gave β-lactam **55** which is a precursor to the required target antibiotic PS-5. A 15% yield of the deprotected *syn*-adduct (>98% ee) was also isolated from the hydrolysis–methylation protocol indicating that the chiral auxiliary performed excellently at controlling the α-stereocentre.

In very closely related work, Matsumura and co-workers reacted the titanium enolate of oxazolidinone **56** with cyclic *N*-acyl iminium ions (derived from α-methoxylated carbamates such as **57**).[34] As an example, combination of oxazolidinone **56** and carbamate **57** showed good *anti* stereoselectivity in generating adducts *anti*- and *syn*-**58** (Scheme 19). Subsequent auxiliary removal, methylation and chromatography generated a 54% yield of *anti*-**59** with 99% ee.

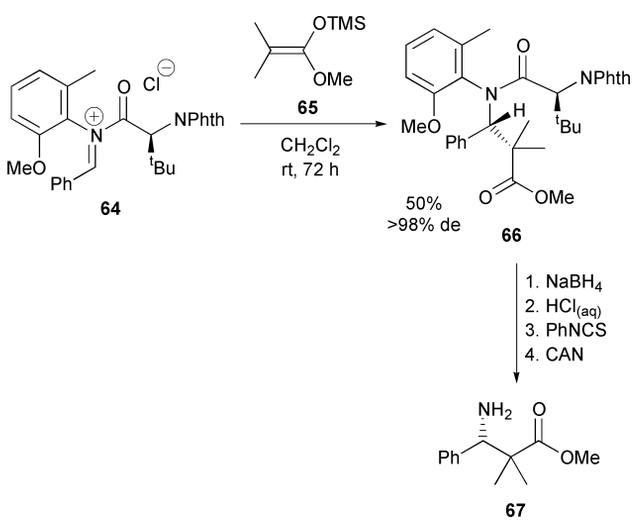
It is useful to compare the results depicted in Schemes 18 and 19. Although one example is an iminium ion and one an imine and although one example is acyclic and the other cyclic, the two reactions show significant similarity: they are both *anti* stereoselective; and in each case the two diastereoisomers are generated with essentially complete stereocontrol (>98% ee after removal of the chiral auxiliary).

In contrast, Murahashi *et al.* reacted metal enolate **60** with acyclic iminium salt **61** and found that *anti*- and *syn*-selective Mannich reactions could be achieved by varying the metal. Thus, with a boron enolate the reaction was *anti*-selective but with a titanium enolate *syn*-selectivity was obtained (Scheme 20).[35] In each case, it was possible to purify the major adducts **62** by chromatography and convert them into enantiomerically pure α-amino acid derivatives *anti*- and *syn*-**63**.

Finally, Waldmann and co-workers have reported that it is possible to carry out asymmetric Mannich reactions using a chiral auxiliary attached to the electrophile. Thus, reaction of silylketene acetal **65** with *tert*-leucine-derived iminium salt **64** generated a moderate yield of Mannich adduct **66** in 98% de (Scheme 21).[36] Unfortunately, quite a lengthy sequence of reactions was required to produce enantiomerically pure β-amino acid **67** from adduct **66**. In a similar way, Ellmann and Tang utilised a sulfoxide-based chiral auxiliary attached to the electrophile in an asymmetric Mannich reaction.[37]



Scheme 20

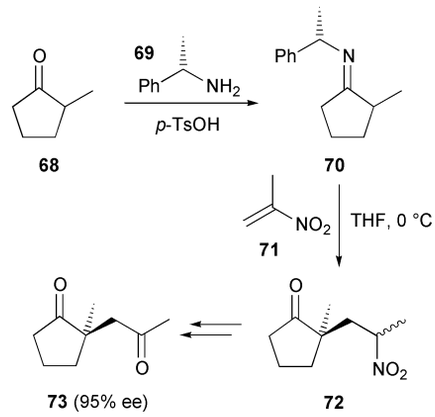


Scheme 21

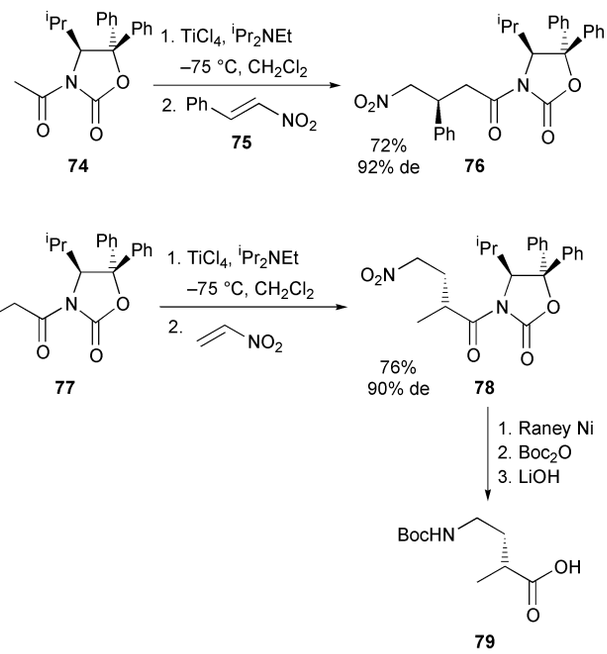
3.3 Michael additions

In asymmetric Michael additions of enolates and their equivalents, the chiral auxiliary can be attached to either the nucleophile or the electrophile. Both approaches can be successful and allow flexibility when designing synthetic approaches to target molecules. Desmaële, d'Angelo and co-workers used the addition of a chiral enamine to a nitro alkene as a key step in the asymmetric synthesis of chiral 1,4-diketones. For example, cyclic ketone **68** could be converted into 1,4-diketone **73** of 95% ee in just a few steps (Scheme 22).[38] The route involved combination of nitro alkene **71** and imine **70** formed from α-methylbenzylamine **69** (which presumably reacts *via* its enamine) to generate nitro ketone **72** in 77% yield. Unmasking of the second ketone functionality through a Nef reaction produced 1,4-diketone **73** of high enantiomeric excess.

Other chiral nucleophiles such as enolates derived from oxazolidinones **74** and **77** also add to nitroalkenes with high diastereoselectivity as Seebach and Brenner demonstrated whilst developing a new route to functionalised γ-amino acids (Scheme 23).[39] Addition of the enolate of **74** to nitro alkene **75** allowed good diastereocontrol over the β-chiral centre



Scheme 22

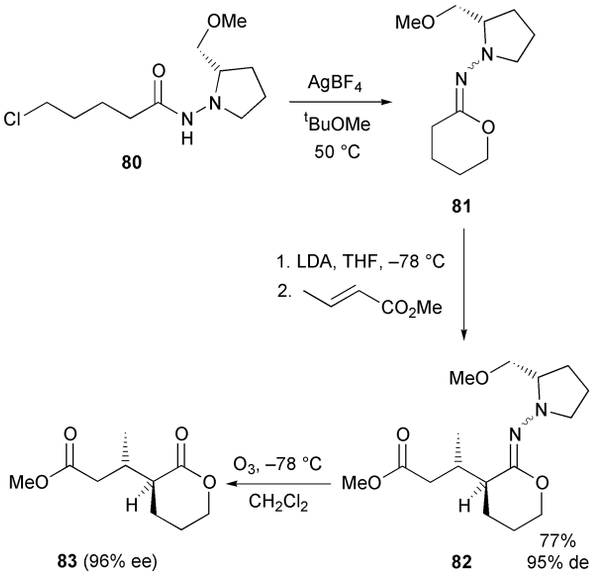


Scheme 23

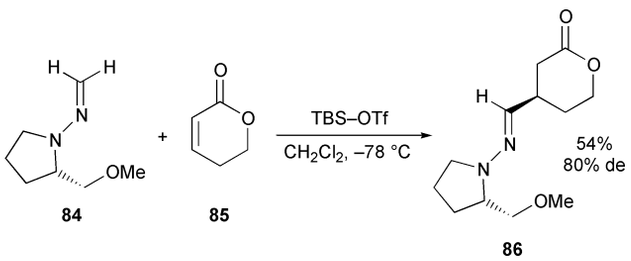
(72% isolated yield of the major diastereoisomer **76**). Similarly, addition of **77** to nitroethylene led to the formation of adduct **78** in 90% de and subsequent removal of the auxiliary gave γ-amino acid **79**. A number of examples were reported including the combination of oxazolidinone **77** with nitro alkene **75** which gave the expected *syn* adduct in high diastereomeric excess.

The use of SAMP **35** as a chiral auxiliary for Michael additions is also successful. A recent development reported by Enders *et al.* is the use of a lactone-derived SAMP hydrazone **81** (prepared from acyclic chloro hydrazide **80**).[40] Deprotonation of **81** and addition to *trans*-methyl crotonate gave Michael adduct **82** in 77% yield and 95% de (Scheme 24). Subsequent auxiliary cleavage using ozonolysis generated chiral 1,5-diester **83** in high enantiomeric excess.

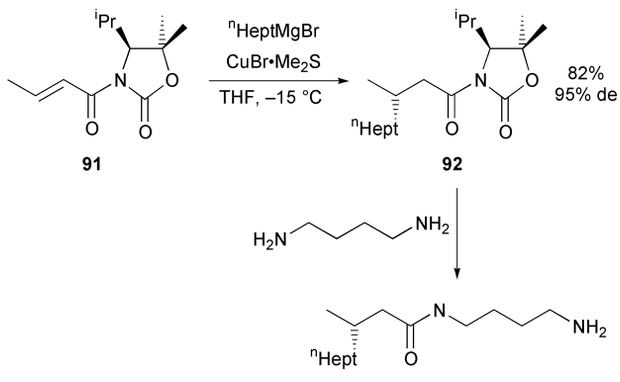
Another example of a chiral nucleophile Michael addition is the Lewis acid catalysed addition of formaldehyde SAMP hydrazone **84** to cyclic enoate **85**. This is formally a conjugate formylation process and generated hydrazone **86** in moderate yield and relatively good diastereoselectivity (Scheme 25).[41] Hydrazone **86** can be further modified (*e.g.* by α-alkylation) before auxiliary removal (to generate an aldehyde) and a range of functionalised building blocks have been synthesised from **86**.[41,42] Lassaletta *et al.* have developed an alternative way of removing the auxiliary to reveal a γ-cyano silyl enol ether.[43]



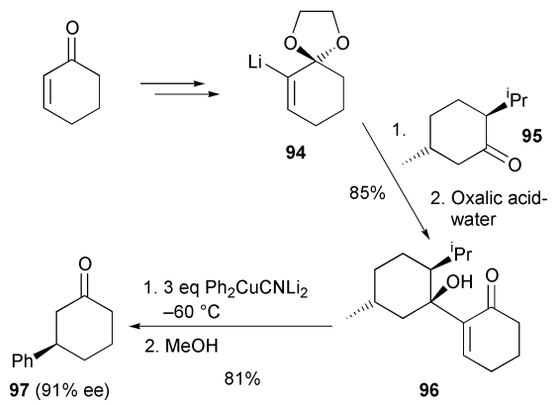
Scheme 24



Scheme 25



Scheme 27



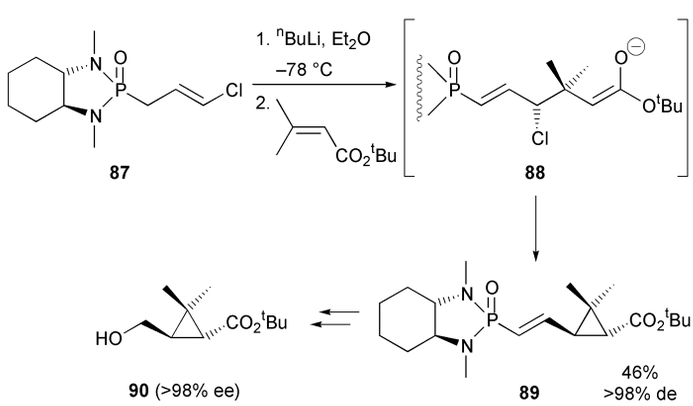
Scheme 28

Hanessian and co-workers have developed useful methodology for the asymmetric synthesis of functionalised cyclopropanes. In a recent synthesis of the antitumour agent anthoplalone, they prepared the key chiral cyclopropane building block **90** of >98% ee starting from chiral chloroallyl phosphonamide **87** (Scheme 26).[44] Lithiation of **87** followed by S_N2'–Michael addition generated an intermediate chloroenolate **88** which cyclised to a single diastereoisomer of cyclopropane **89** albeit in moderate yield.

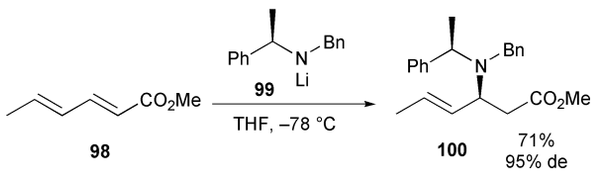
Michael additions with the auxiliary attached to the electrophile are less common. For example, Davies and co-workers carried out a highly diastereoselective addition of an organocuprate to a SuperQuat-derived Michael acceptor **91** (Scheme 27). Adduct **92** was generated in 82% yield and ≥95% de and the auxiliary was easily removed by treatment with a diamine to produce amide **93** which was used in the total synthesis of the antifungal and antibacterial agent aplysillamide B.[45]

There are few methods available for the highly enantioselective conjugate addition of organometallic reagents to *cyclic* α,β-unsaturated systems. This has been achieved by Funk and Yang using menthone as a chiral auxiliary as outlined in Scheme 28.[46] The auxiliary was attached by reacting vinyllithium **94** (derived from cyclohexenone) with menthone **95** and acetal hydrolysis. Then, highly diastereoselective addition of an organocuprate to enone **96** was accompanied by auxiliary removal *via* a retro-aldol process to generate the Michael adduct **97** in good yield and 91% ee. Although a few steps are required to attach the auxiliary to cyclohexenone, the self-removing nature of the chiral auxiliary is noteworthy.

Approaches for the synthesis of chiral β-amino acids were covered in Sections 3.2 and 3.3 (Schemes 7 and 18–20). An alternative method is the asymmetric Michael addition of a chiral ammonia equivalent and by far the most useful methodology in this area has been developed by the Davies group. A typical example illustrating the usefulness of the methodology is shown in Scheme 29. Thus, addition of lithiated α-methylbenzylamine derivative **99** to Michael acceptor **98** gave adduct **100** in 71% yield and 95% de.[47] Further synthetic manipulation of **100** enabled the total synthesis of



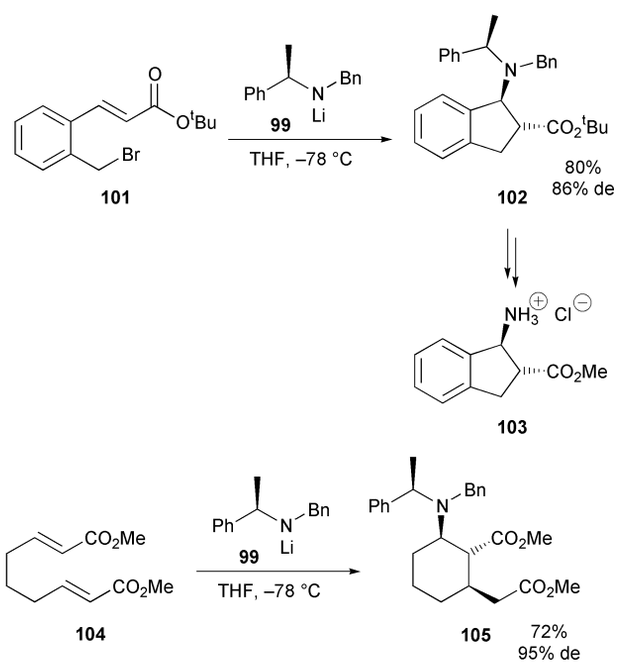
Scheme 26



Scheme 29

daunosamine to be completed. It is interesting to note that the lithium amide adds at the β-position even though there is an extended conjugated system. Davies' methodology is robust and gives high diastereoselectivity for a range of α,β-unsaturated esters: it has thus been widely exploited in synthesis.[48,49] Research within my own group has made use of the methodology and we have found it to be an extremely reliable reaction.[50]

Further developments of the Davies methodology have involved the introduction of tandem reaction sequences. Two examples are shown in Scheme 30. Thus, Price added **99** to a Michael acceptor (**101**) which contained a pendant benzyl bromide and was able to carry out Michael addition–intramolecular alkylation to produce adduct **102** in 86% de. Subsequent destruction of the auxiliary and recrystallisation yielded the required β-amino acid **103** derivative in enantiomerically pure form.[51] In related fashion, Garrido *et al.* synthesised cyclic β-amino acid **105** (95% de) from diester **104** *via* intermolecular lithium amide Michael addition followed by intramolecular enolate Michael addition.[52]



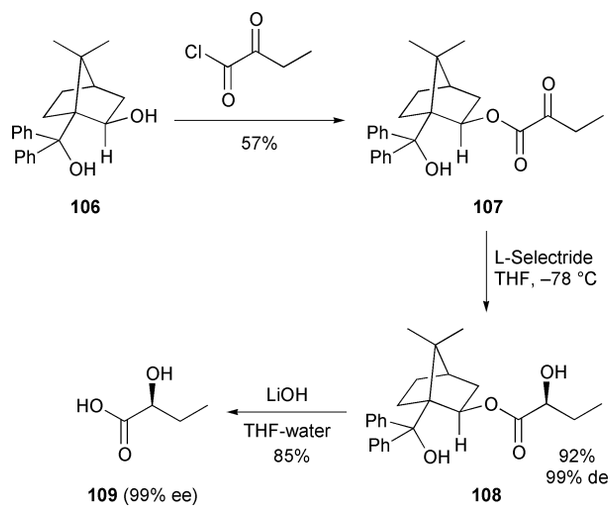
Scheme 30

Sato *et al.* utilised the Davies methodology in the asymmetric synthesis of a cyclic β-amino ketone that was then modified and the amino group eliminated to generate a chiral enone.[53] This is probably the first example where the amino group is introduced and then removed. Unfortunately, the route used by Sato is long-winded and not a general method as yet.

One of the limitations of the α-methylbenzylamine conjugate addition approach is that it only works for α,β-unsaturated esters. Other Michael acceptors cannot in general be used although Davies and co-workers have recently shown that α,β-unsaturated iron acyl complexes can be successfully employed.[54] One class of Michael acceptors that could very usefully be employed in Michael addition with chiral ammonia equivalents is alkenyl sulfones. The only example so far of this type of reaction was reported by Enders using SAMP **35**.[55] However, the addition reactions were low yielding and proceeded with only moderate diastereoselectivity.

3.4 Addition to C=O and C=N bonds

It is interesting to note that there are far more examples of asymmetric additions to imines than to aldehydes or ketones using chiral auxiliaries. A good route to α-hydroxy acids is to attach the chiral auxiliary to a keto acid and then carry out diastereoselective additions to the ketone group. For example, Chen *et al.* utilised diol **106**, derived from ketopinic acid methyl ester, as a chiral auxiliary. After attaching the auxiliary, L-Selectride®-mediated reduction of keto-ester **107** afforded a high yield of alcohol **108** (99% de) (Scheme 31).[56] The auxiliary was easily removed to give enantiomerically pure α-hydroxy acid **109**.

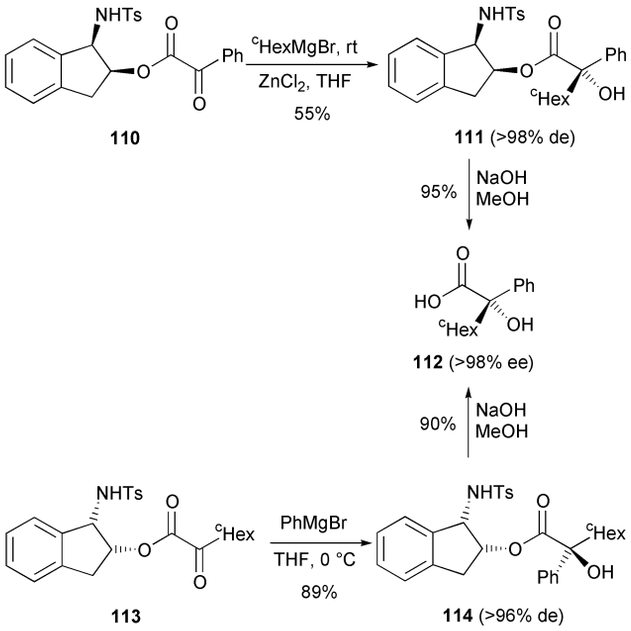


Scheme 31

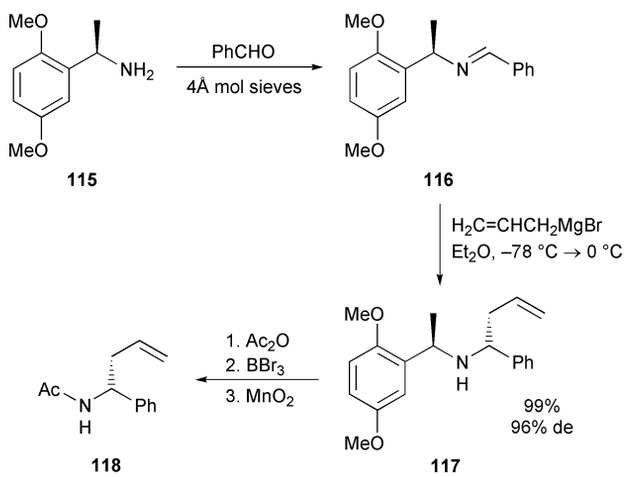
A similar approach was used by Senanayake, Fang and co-workers to prepare tertiary α-hydroxy acids.[57] In this case, additions of Grignard reagents to *cis*-aminoindanol-derived keto esters were explored. Reaction of phenyl ketone **110** with cyclohexylmagnesium bromide in the presence of zinc chloride gave an 84 : 16 mixture of diastereoisomeric adducts from which **111** could be obtained in 55% yield after recrystallisation (Scheme 32). Subsequent ester hydrolysis yielded alcohol **112** of >98% ee. The same tertiary alcohol enantiomer **112** could be produced more efficiently by reaction of phenylmagnesium bromide with cyclohexyl ketone **113**. In this way, and without the need for zinc chloride, an 89% yield of adduct **114** (>96% de) was obtained.

The diastereoselective addition of organometallics to imines derived from chiral amines continues to be a popular approach to more complex novel chiral amines.[58–62] For example, Hashimoto, Saigo and Kohara have introduced the readily resolved amine **115** as a useful chiral auxiliary.[58] Addition of allylmagnesium bromide to imine **116** gave a virtually quantitative yield of adduct **117** (96% de) (Scheme 33). A slightly elaborate auxiliary removal procedure was then employed to furnish chiral amine **118** of 96% ee. The full scope of this process was explored.

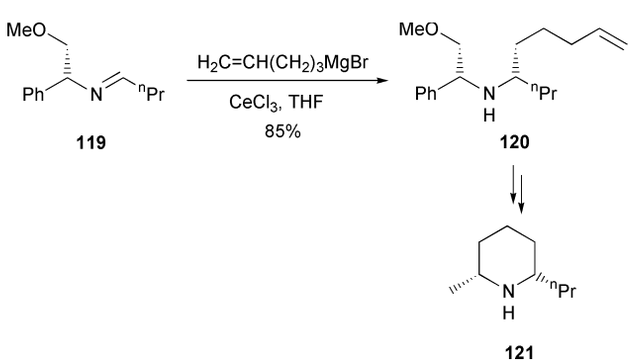
Imines obtained from phenylglycinol have also been successfully used. Thus, addition of a Grignard reagent in the presence of cerium(III) chloride to imine **119** gave an 85% yield of amine **120** as a single diastereoisomer which could be elaborated into naturally occurring dihydropinidine **121** (Scheme 34).[60] Similary, Steinig and and Spero prepared tertiary amine **123**,



Scheme 32

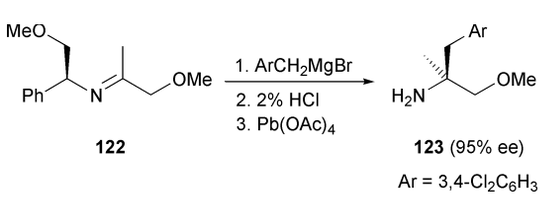


Scheme 33



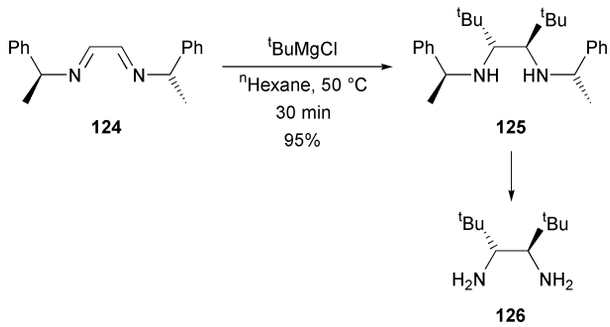
Scheme 34

a precursor to the antidepressant drug cericlamine, in 95% ee by reaction of imine **122** with a benzyl Grignard reagent and subsequent oxidative removal of the auxiliary (Scheme 35).[61]



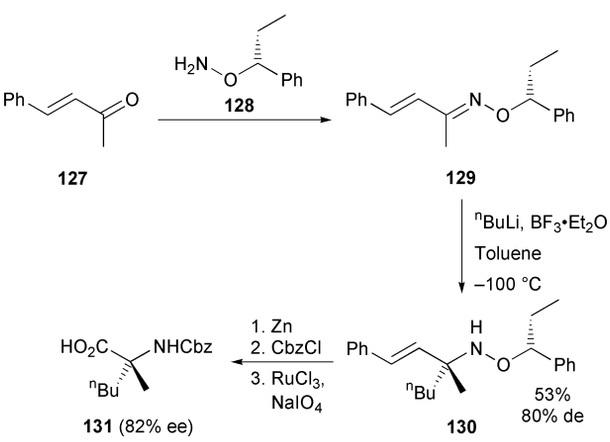
Scheme 35

A useful synthesis of C_2 symmetric diamines such as **126** *via* the bis addition of *tert*-butyl Grignard to bis-imine **124** has recently been reported.[63] Glyoxal-derived bis-imine **124** was prepared and reverse-addition of *tert*-butylmagnesium chloride at 50 °C generated a very high 95% yield of adduct **125** as a single diastereoisomer (Scheme 36). Hydrogenolysis then afforded enantiomerically pure diamine **126**, itself a useful chiral auxiliary.



Scheme 36

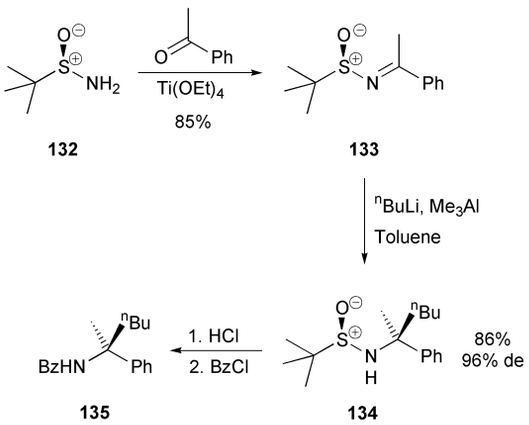
Moody and co-workers have continued to develop their methodology of stereoselective additions to oxime ethers and have extended it to include a useful route for α-amino acid synthesis.[64,65] A representative example is shown in Scheme 37. Condensation of hydroxylamine **128** (affectionately named ROPHy) with benzylideneactone **127** gave oxime ether (*E*)-**129** in moderate yield as it had to be separated from the (*Z*)-isomer. Then, addition of *n*-butyllithium at low temperature gave adduct **130** in 80% de. The amino acid functionality could then be revealed by reduction with zinc, Cbz-protection and oxidative cleavage of the pendant alkene. Unnatural amino acid **131** (82% ee) was thus obtained.



Scheme 37

The synthesis of chiral tertiary amines continues to present a challenge. One successful approach was depicted in Scheme 35 and Ellmann has made use of *tert*-butylsulfinamide† **132** as an auxiliary in developing a general route for tertiary amine synthesis.[66,67] Enantiomerically pure *tert*-butylsulfinamide **132** can be prepared in two steps *via* asymmetric catalysis and it appears to be a very promising chiral auxiliary. For example, reation of **132** with acetophenone generated sulfinyl imine **133** and subsequent addition of *n*-butyllithium in the presence of trimethylaluminium smoothly generated adduct **134** in good yield and high diastereoselectivity (Scheme 38). Unmasking of the tertiary amine to give amine **135** was achieved using dilute acid.

† The IUPAC name for *tert*-butylsulfinamide is dimethylethanesulfinamide.

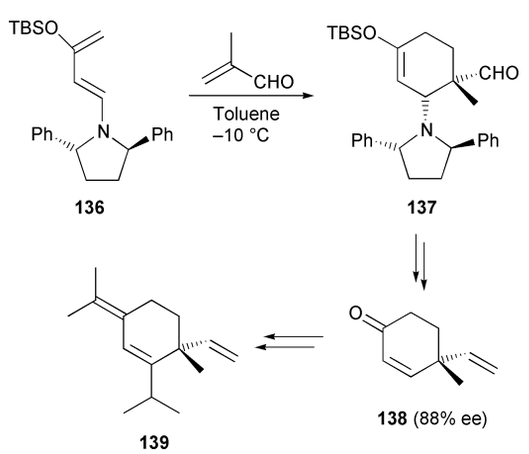


132 133 135 134

Scheme 38

3.5 Miscellaneous uses of chiral auxiliaries

In this section, I have collected together examples of a wide range of reactions in which a chiral auxiliary was successfully used to control the stereochemistry. They are in no particular order. Asymmetric Diels–Alder reactions using a chiral auxiliary are a useful way of constructing carbocyclic and heterocyclic rings with several chiral centres. In general, the auxiliary is attached to the dienophile (*e.g.* acrylate derivatives) and some recent results on the effect of varying the Lewis acid in these classic Diels–Alder reactions have been reported by Kim and co-workers.[68] Meanwhile, Rawal and Kozmin have described full details on the use of a chiral auxiliary attached to the diene.[69] Their methodology uses diene **136**, effectively a chiral version of Danishefsky's diene. Reaction of **136** with methacrolein gave Diels–Alder adduct **137** which could be further manipulated into enone **138** of 88% ee and thence into the natural product elemene **139** (Scheme 39).

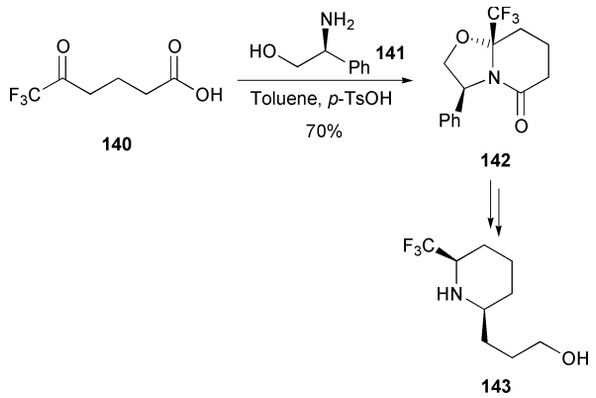


136 137 138 (88% ee) 139

Scheme 39

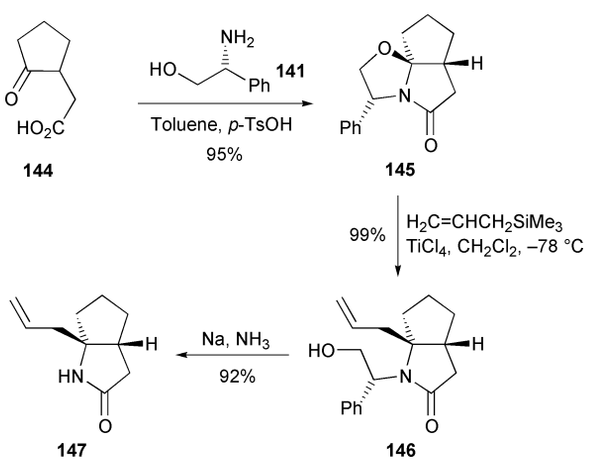
Over the last few years, Meyers and co-workers have been combining amino alcohols with keto acids to produce single diastereoisomers of bicyclic lactams which can be utilised in synthesis. Recent examples of use in synthesis reported by the Meyers group include studies towards viridenomycin,[70] the trisporic acids,[71] indolizomycin,[72] *cis*-3,4-disubstituted piperidines,[73] mastigophorene A[74] and polyhydroxylated alkaloids.[75] Most importantly of all, the methodology has now reached the stage where others are using it and, as its popularity grows, it is now established as a useful method in synthesis.[76–81]

A representative example of the Meyers bicyclic lactam methodology is shown in Scheme 40. Jiang *et al.* reacted keto acid **140** with phenylglycinol **141** to give a single diastereoisomer of lactam **142**.[76] Further manipulations and reductive removal of the auxiliary furnished trifluoro-substituted piperidine **143**. Condensations with cyclic keto acids are also possible. For example, during the total synthesis of halichlorine, Danishefsky and co-workers condensed phenylglycinol **141** with keto acid **144** to give lactam **145** in high yield (Scheme 41).[77,78] Subsequent Lewis acid-mediated reaction with allyltrimethylsilane gave adduct **146** (with retention of configuration) and the auxiliary was removed using sodium in liquid ammonia to give the key synthetic intermediate **147** in enantiomerically pure form.



140 142 143

Scheme 40



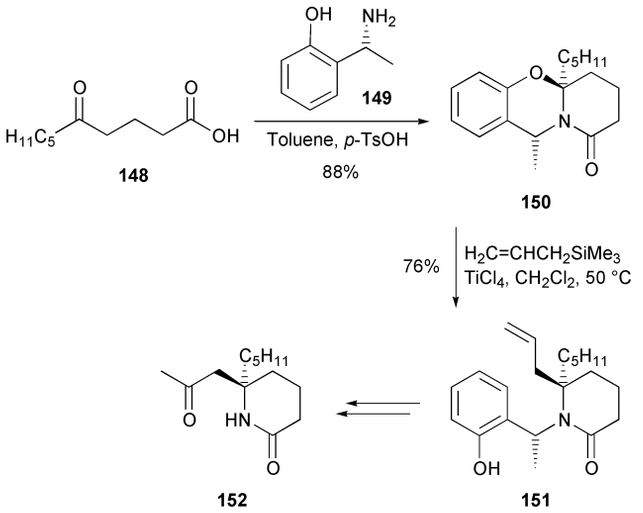
144 145 146 147

Scheme 41

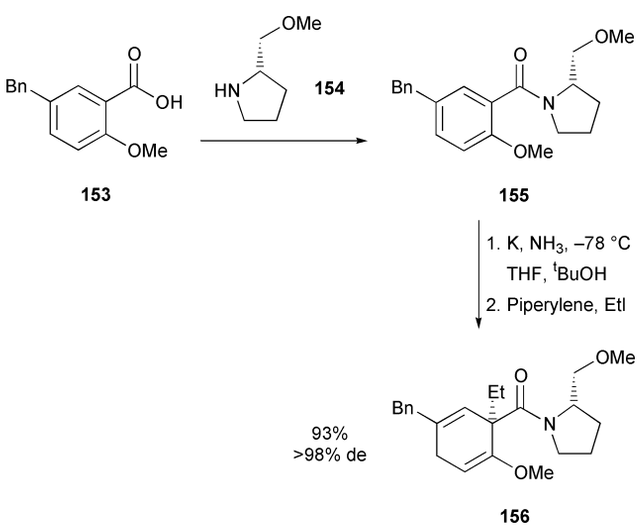
As a final example of Meyers' methodology, Kibayashi *et al.* have reported a concise total synthesis of the alkaloid adalinine **152** in which a variety of amino alcohols were investigated for the key condensation reaction. Reaction of keto acid **148** with amino alcohol **149** gave the highest diastereoselectivity.[79] Adduct **150** thus obtained was reacted with allyltrimethylsilane to give the allylated lactam **151** (Scheme 42) with retention of configuration in a similar way to reaction of lactam **145** (see Scheme 41).

Asymmetric Birch reductions using chiral auxiliaries have been pioneered by Schultz and co-workers.[82] A recent and representative example was provided during synthetic studies towards the melodinus alkaloids. Thus, reaction of aromatic amide **155** (obtained from **153** and prolinol derivative **154**) with potassium and liquid ammonia followed by alkylation gave diene **156** in 93% isolated yield and >98% de (Scheme 43).[83]

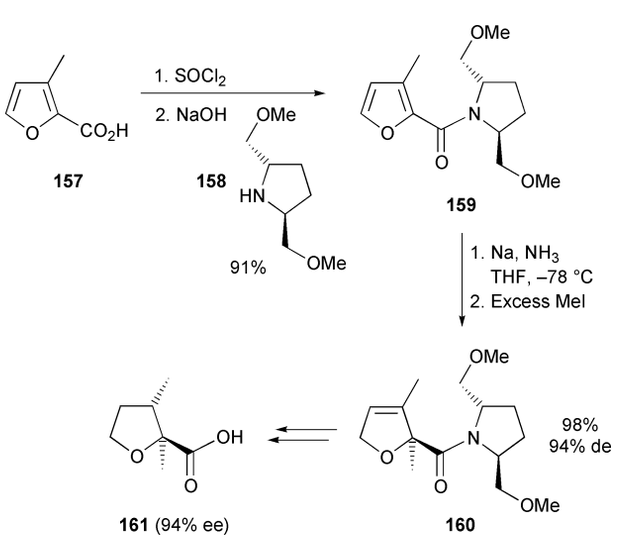
Donohoe and co-workers have successfully extended Schultz's general approach to include the asymmetric reduction–alkylation of furans (Scheme 44)[84] and pyrroles (Scheme 45).[85] In each case, different auxiliaries to the one used by Schultz turned out to be optimal. For example, conversion of furan **157** into *cis*-crobarbatic acid **161** of >94% ee utilised C_2 symmetric pyrrolidine **158** as a chiral auxiliary (Scheme 44). The key Birch reduction–alkylation reaction (**159→160**) proceeded in an impressive 98% yield with 94% diastereoselectivity.[84]



Scheme 42

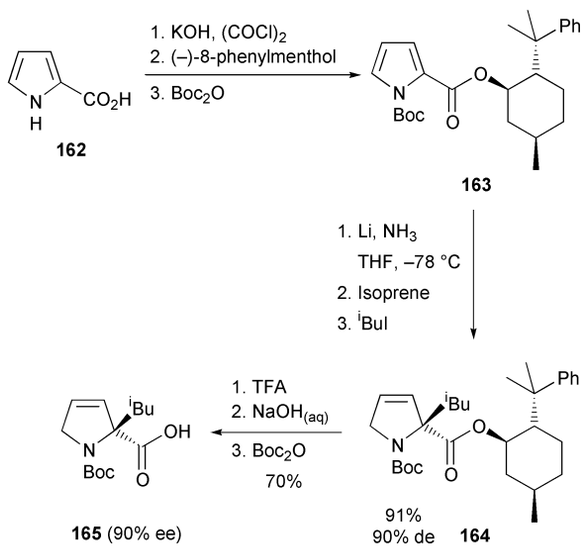


Scheme 43



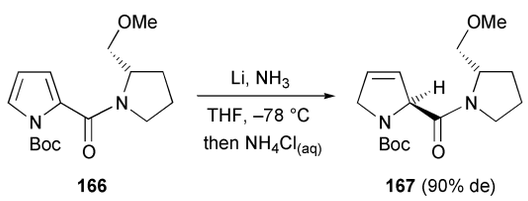
Scheme 44

In the pyrrole series, the most successful auxiliary was 8-phenylmenthol. After coupling of pyrrolecarboxylic acid **162** with the auxiliary to give **163**, reduction and alkylation (even with sterically hindered electrophiles such as isobutyl iodide) gave **164** in good yield and 90% de (Scheme 45). A slightly lengthy deprotection protocol afforded novel amino acid **165** in 90% ee.[85] Schäfer and Schäfer found that it was



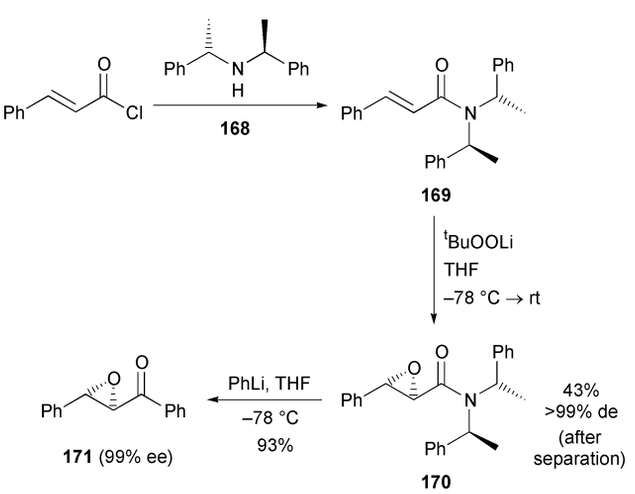
Scheme 45

possible to use the same auxiliary as Schultz for the reduction–protonation of a pyrrolecarboxylic acid derivative.[86] Thus, amide **166** was reduced with lithium–ammonia and then reacted with different electrophiles. Alkylation reactions were not very diastereoselective but reaction with aqueous ammonium chloride gave **167** in 90% de (Scheme 46).



Scheme 46

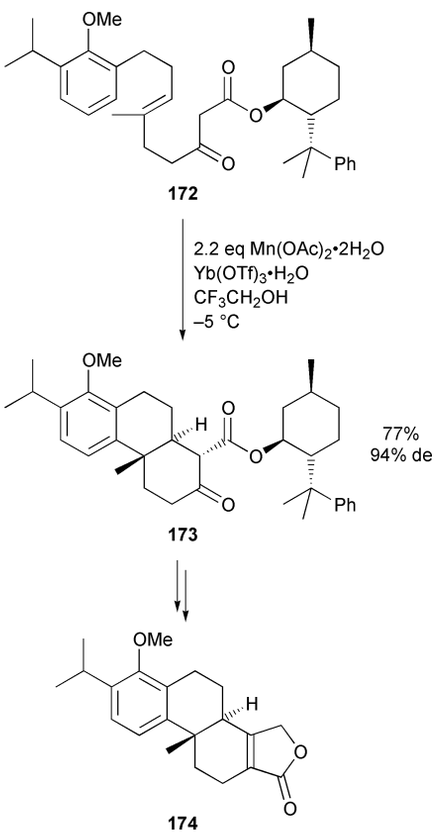
Even though there are now a range of chiral catalysts available for asymmetric epoxidation reactions, the fact that an auxiliary approach allows enantiomerically *pure* epoxides to be generated means that such an approach is still useful. Meth-Cohn and Chen have reported a simple method for the preparation of enantiopure α,β-epoxy ketones as outlined in Scheme 47.[87] Amine **168** was condensed with cinnamoyl chloride to give amide **169**. Subsequent epoxidation using *tert*-butyl hydroperoxide and *n*-butyllithium was not very diastereoselective but gave **170** in 43% isolated yield after chromatography (a 32% yield of the other diastereoisomer was also obtained after purification and gives access to the enantiomeric



Scheme 47

series). Subsequent reaction of epoxy amide **170** with phenyllithium gave epoxy ketone **171** of 99% ee. This is a simple procedure that could be very useful for compounds that give low enantioselectivity with chiral catalysts.

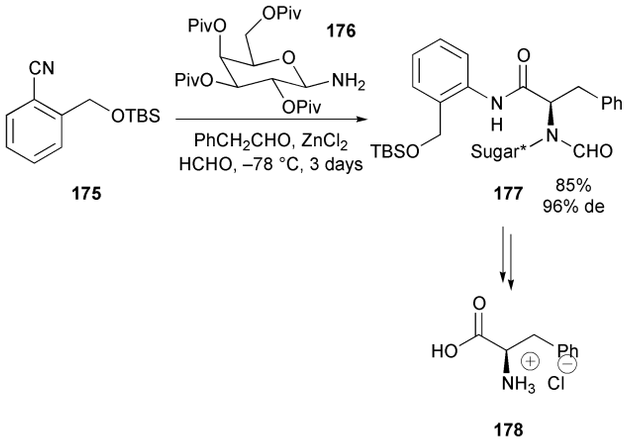
Highly diastereoselective radical reactions using chiral auxiliaries are not that common. One recent example which proceeded with a very high level of diastereocontrol was described by Yang and co-workers.[88] Using 8-phenylmenthol as a chiral auxiliary, $Mn(OAc)_3$-mediated oxidative cyclisation of ester **172** in the presence of ytterbium triflate gave a 77% yield of adduct **173** in 94% de (Scheme 48). Subsequent manipulations gave naturally occurring triptophenolide **174** in >99% ee.



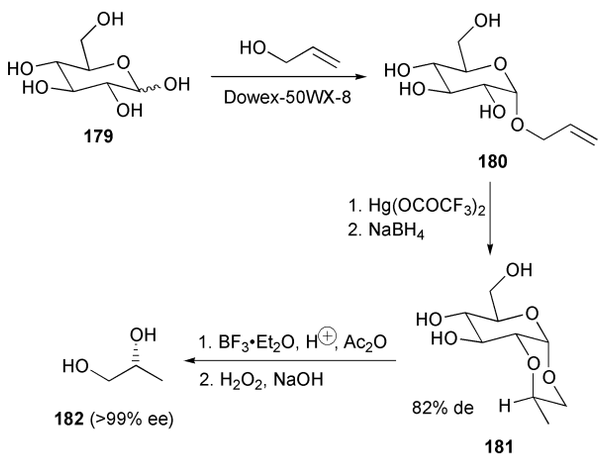
Scheme 48

Two potentially useful examples of carbohydrate-derived chiral auxiliaries are presented in Schemes 49 and 50. For example, Lindermann *et al.* have described a route to α-amino acids (*e.g.* **178**) using an asymmetric Ugi reaction between **175** and Kunz's auxiliary galactosylamine **176** (Scheme 49).[89] In this way, an 85% yield of adduct **177** (96% de) was obtained and this could easily be manipulated into α-amino acid **178**. Hollingsworth and Huang have used unprotected glucose **179** as an auxiliary for the asymmetric synthesis of 1,2-diols as outlined in Scheme 50.[90] The auxiliary is attached to allyl alcohol to give **180** and then mercury(II)-mediated cyclisation followed by reduction gave bicyclic adduct **181** in 82% de. After purification by chromatography and removal of the auxiliary, 1,2-diol **182** of 99% ee was produced.

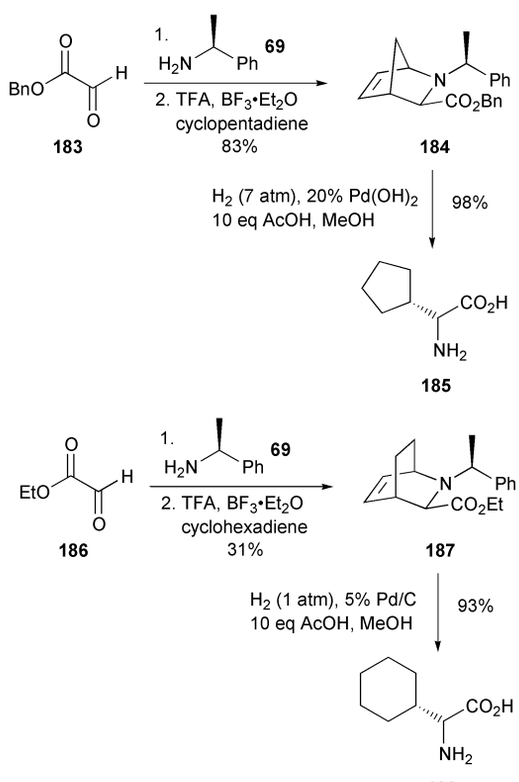
An interesting and unusual route to unnatural α-amino acids has been reported by Andersson and co-workers. Although limited in scope it is a very good way of preparing amino acids **185** and **188** (Scheme 51) and related derivatives.[91] For example, Diels–Alder reaction of the imine derived from **183** and **69** with cyclopentadiene gave a good yield of adduct **184**. Subsequent hydrogenolysis under optimised conditions led to cleavage of all of the activated C–N bonds to give amino acid **185**. The related sequence of **186** plus **69** and reaction with cyclohexadiene gave adduct **187** and thence amino acid **188**.



Scheme 49

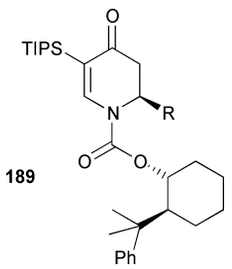


Scheme 50



Scheme 51

Finally, Comins and co-workers have continued to exploit the use of dihydropyridones **189** in synthesis.[92–97] Dihydropyridones **189** are derived from chiral 1-acylpyridinium salts.

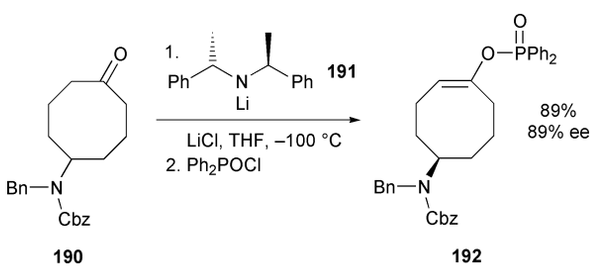


189

4 Chiral reagents

4.1 Chiral lithium amide bases

Enantioselective deprotonation of cyclic ketones using chiral versions of LDA can now be carried out routinely with ≥90% enantioselectivity and is therefore a well used method in total synthesis.[98–100] The use of chiral base **191**, made popular by Simpkins, is the benchmark for enantioselective deprotonation of cyclic ketones. For example, during work directed towards the total synthesis of anatoxin-a, Aggarwal *et al.* used chiral base **191** to deprotonate ketone **190** (Scheme 52).[98] The resulting enolate was trapped with diphenylphosphinoyl chloride to give enol phosphate **192** in 89% yield and 89% ee which was used to complete their synthesis. Aggarwal and co-workers have also tried to develop some new chiral bases for ketone deprotonations with limited success.[101]



190 192

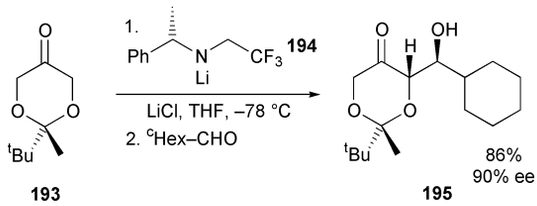
Scheme 52

The simple chiral base **194**, introduced by Koga, also performs very well in ketone deprotonations. Majewski and Nowak utilised it in an asymmetric deprotonation aldol reaction to convert ketone **193** into a single diastereoisomer of aldol **195** (90% ee) (Scheme 53).[102] In a further and very interesting development, Majewski has reported the first example of polymer supported chiral lithium amide bases. In the aldol reaction of tropinone **196**, aldol **197** was generated in around 75% ee using chiral base **99** or its polymer supported analogue **198** (Scheme 54).[103]

Simpkins and co-workers have described a novel desymmetrisation reaction mediated by dilithiated chiral base **200**.[104] Thus, deprotonation of *meso*-bis-ester **199** using chiral base **200** and subsequent trapping with methyl iodide afforded enantiomerically pure piperidine **201** (Scheme 55). In addition, this was the only diastereoisomer detected from this reaction.

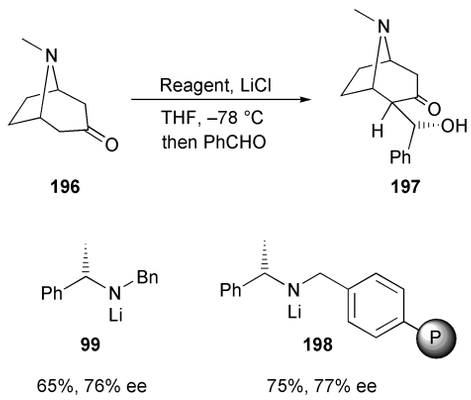
There is still scope for development of the epoxide to allylic alcohol rearrangement reaction that is mediated by chiral bases. One highly enantioselective example (**202**→**203**, Scheme 56) has been reported by two different research groups: Asami *et al.* used chiral base **204** to give allylic alcohol **203** in 90% ee[105] and results from my own laboratory revealed that it was possible to prepare **203** of 92% ee using the novel chiral base **205**.[106] We also found that chiral base **205** was suitable for other epoxide rearrangement reactions.[107,108] As well as synthetic aspects, theoretical[109,110] and mechanistic aspects[111] of the epoxide rearrangement reaction have been studied.

Organometallic substrates are also suitable for desymmetrisation using chiral bases and Kündig,[112] Gibson[113] and Simpkins[114] have all been active in this field. One notable



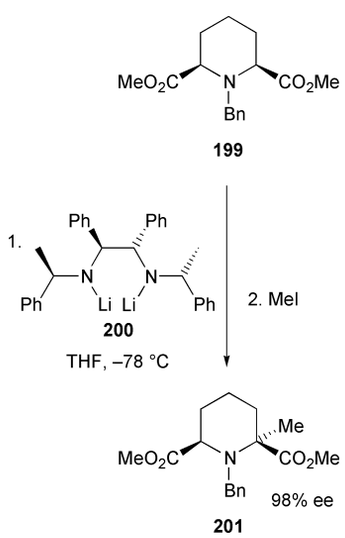
193 195

Scheme 53

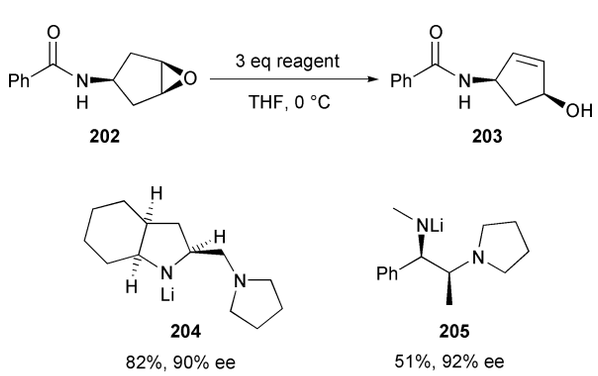


196 197 99 198

Scheme 54

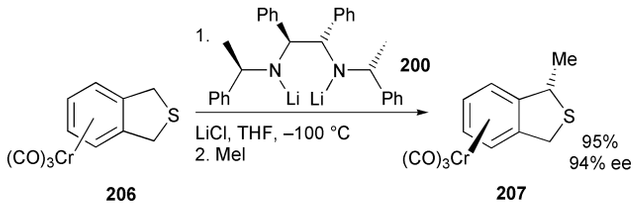


Scheme 55



Scheme 56

example is shown in Scheme 57. Thus, Simpkins and co-workers were able to transform chromium complex **206** into the methylated adduct **207** in high yield (95%) and high enantioselectivity (94% ee) *via* benzylic functionalisation using dilithiated chiral base **200**.[114] Quite a detailed study on the effect

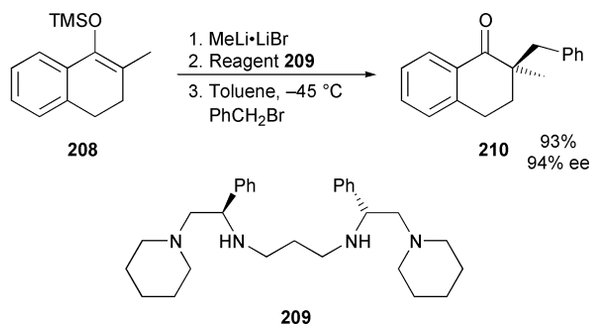


206 207

Scheme 57

of chiral base structure on the enantioselectivity of similar benzylic functionalisations has been carried out by Gibson *et al.*[113] These results indicate that dilithiated chiral base **200** is optimal for such reactions.

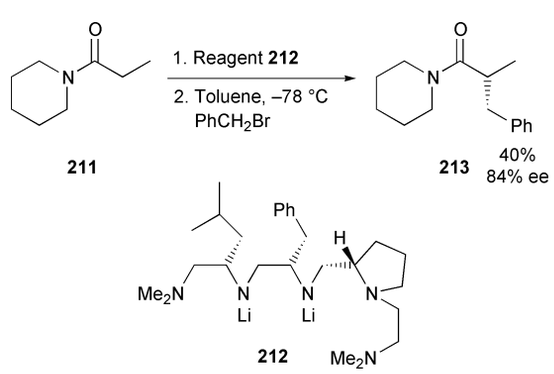
The direct asymmetric α-alkylation of enolates using chiral lithium amide bases is an area of research pioneered by Koga. Optimum conditions for the construction of quaternary chiral centres have now been developed. For example, generation of the lithium enolate from silyl enol ether **208** using methyllithium–lithium bromide and subsequent benzylation in the presence of chiral tetraamine **209** gave the alkylated adduct **210** in 93% yield and 94% ee (Scheme 58).[115]



208 210 209

Scheme 58

Enantioselective alkylation in acyclic carbonyl compounds has, in general, received much less attention presumably as a result of a lack of control over the enolate geometry. However, one of the best examples reported to date was described by Kobayashi and co-workers for the α-alkylation of amide **211**. In order to find the best chiral lithium amide base for the transformation of amide **211** into adduct **213** (Scheme 59),[116] 21 different chiral pentamine derivatives were constructed using classical solid phase peptide synthesis methods and then screened in terms of reactivity and enantioselectivity. In this way, dilithiated chiral base **212** was identified as the optimum one and using this base, amide **213** was generated in 40% yield and 84% ee. This solid phase synthesis approach for the preparation of a range of chiral amine ligands for screening in terms of enantioselectivity could prove the quickest way of finding the best chiral bases in the future.

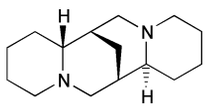


211 213 212

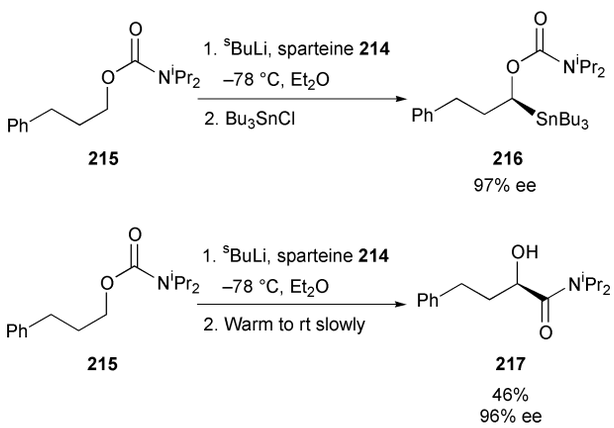
Scheme 59

4.2 Sparteine-mediated reactions and related processes

The naturally occurring diamine sparteine **214** continues to be a popular way of providing a chiral organolithium reagent for asymmetric reactions. The combination of *sec*-butyllithium and sparteine **214** in diethyl ether as solvent is an excellent reagent for asymmetric functionalisation α to oxygen and nitrogen. For example, Nakai and co-workers reported that deprotonation α to oxygen in carbamate **215** using *sec*-butyllithium–sparteine followed by trapping with tributyltin chloride afforded stannylated adduct **216** of 97% ee (Scheme 60).[117] However, it was also found that the intermediate organolithium species can be induced to carry out a 1,2 carbamoyl shift upon warming to room temperature. In this way, a moderate yield of hydroxy amide **217** of 96% ee was generated (Scheme 60).



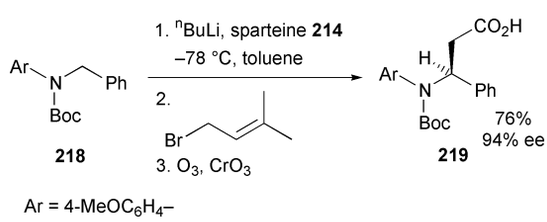
Sparteine **214**



Scheme 60

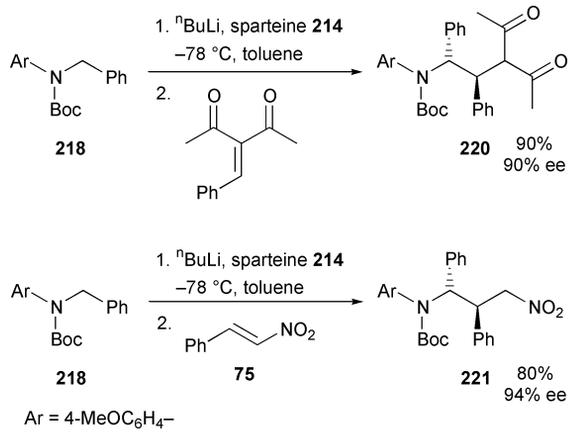
Asymmetric functionalisation α to nitrogen in carbamates using sparteine **214** was originally introduced by Beak and co-workers and the scope of this process has been extended still further. For example, asymmetric lithiation and subsequent intramolecular cyclisation provides an attractive route to some chiral pyrrolidines and piperidines.[118] A novel route to β-amino acids, which is as good as the chiral auxiliary approaches described in Section 3, has also been developed. Thus, diprotected benzylamine **218** was lithiated with *n*-butyllithium–sparteine **214** in toluene and reacted with prenyl bromide. Ozonolysis and oxidation then gave β-amino acid derivative **219** of 94% ee in 76% overall yield (Scheme 61).[119] Beak *et al.* have also reacted the same organolithium intermediate with a range of Michael acceptors. Two examples are shown in Scheme 62: Michael adducts **220** (90% ee) and **221** (94% ee) were generated in good yields and as essentially single diastereoisomers using sparteine **214** as the chiral mediator.[120]

Carbometallation of alkenes is another process that has been rendered asymmetric using sparteine **214**. Hoppe[121,122] and Normant[123] have both been particularly active in this area.



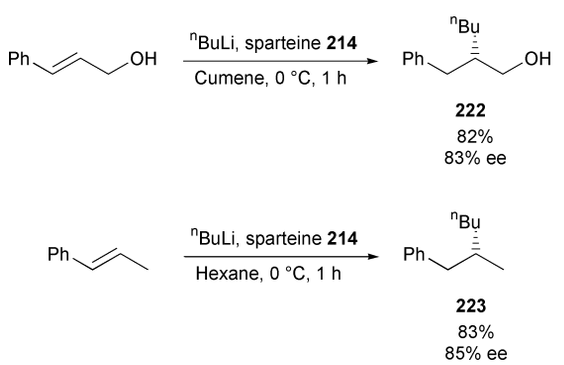
218 219

Scheme 61



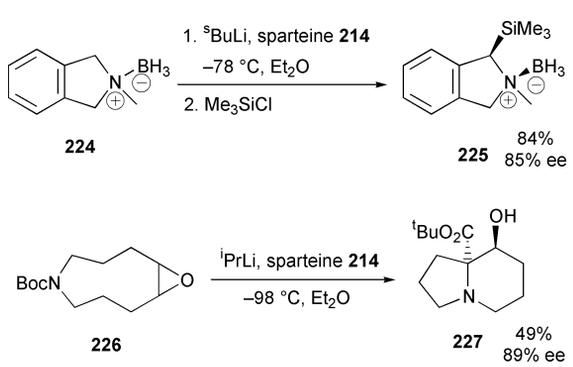
Scheme 62

Normant and co-workers have reported the asymmetric addition of *n*-butyllithium to cinnamyl alcohol to give alcohol **222** of 83% ee (Scheme 63). They subsequently found that the hydroxy group was not necessary for activation of the alkene since *trans*-β-methylstyrene underwent the same reaction with almost the same enantioselectivity (**223** of 85% ee was produced).[123] This appears to be a very simple one-step method for preparing alcohols such as **222** which would traditionally be constructed using some of the chiral auxiliaries discussed in Sections 2 and 3.1.



Scheme 63

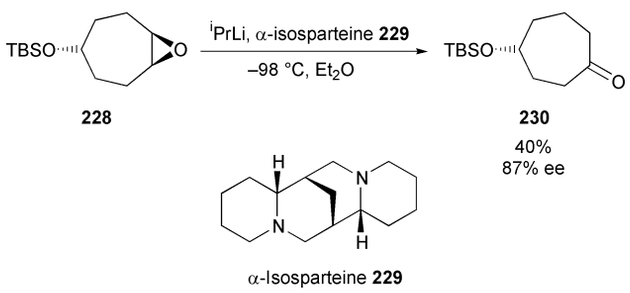
There is an ongoing search for new types of asymmetric transformations that can be mediated using the alkyllithium–sparteine **214** reagent. Two examples, both proceeding with a good level of enantioselectivity, are depicted in Scheme 64. Simpkins *et al.* have described the asymmetric functionalisation of amine–borane complex **224** using sparteine **214**. Thus, silylated adduct **225** was produced in 84% yield and 85% ee as a single diastereoisomer.[124] The conversion of amino epoxide **226** into indolizidine **227**, reported by Hodgson and Robinson,



Scheme 64

represents a new entry into this class of molecules.[125] Reaction of epoxide **226** with isopropyllithium–sparteine **214** leads first to asymmetric α-lithiation and then transannular insertion and 1,2-carbamoyl migration (reminiscent of the reaction reported in Scheme 60) gave indolizidine **227** in 89% ee.

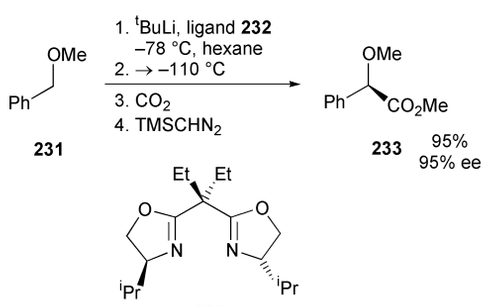
Sometimes, sparteine **214** itself is not the best chiral diamine for a particular reaction and the C_2 symmetric isomer, α-isosparteine **229** (actually synthesised from sparteine **214**) can give higher enantioselectivity. One recent example has been reported by Hodgson and co-workers. The conversion of epoxide **228** into ketone **230**, a key intermediate for the synthesis of the alkaloid physoperuvine, *via* α-lithiation was carried out with the highest enantioselectivity using α-isosparteine (Scheme 65).[126]



Scheme 65

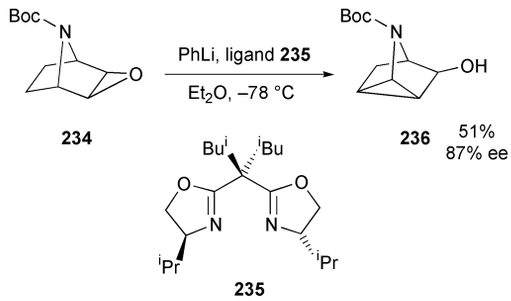
One of the limitations of using sparteine in synthesis is that only the naturally occurring enantiomer **214** is commercially available. To address this, Hoppe's[127] and our own group[128] have been searching fruitlessly for other diamines that will function as replacements for sparteine. However, more success has been achieved using chiral bis(oxazoline)s in place of sparteine in some organolithium reactions.[129–132]

Nakai and co-workers have reported the highly enantioselective carboxylation of methylated benzyl alcohol **231** (Scheme 66).[129] Lithiation of ether **231** was achieved using *tert*-butyllithium in combination with bis(oxazoline) **232** and as long as the reaction mixture was cooled to –110 °C before addition of carbon dioxide, methyl ester **233** was generated (after methylation with $TMSCHN_2$) in 95% ee. The methodology was subsequently extended to include reaction of the intermediate organolithium species with aldehydes.[130] Nakai and co-workers have also reported the use of bis(oxazoline) **232** in an enantioselective [1,2] Wittig rearrangement.[131]



Scheme 66

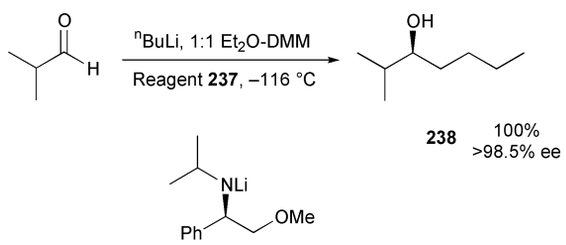
In a similar fashion, Hodgson *et al.* described the use of bis(oxazoline) **235** as an *ent*-sparteine analogue for the conversion of epoxide **234** into alcohol **236** *via* α-lithiation.[132] Thus, reaction of epoxide **234** with phenyllithium and bis(oxazoline) **235** gave alcohol **236** in 51% yield and 87% ee (Scheme 67). Interestingly, the enantiomer of alcohol **236** could be generated in 77% ee using sparteine **214** and 2-tolyllithium.



Scheme 67

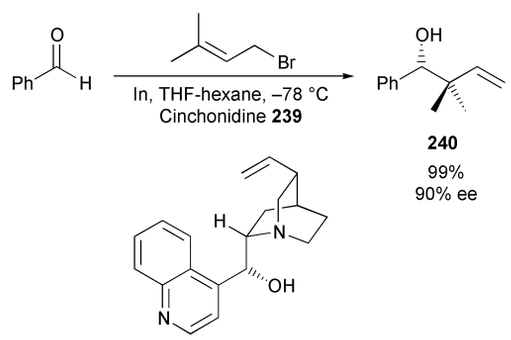
4.3 Addition to C=O and C=N bonds

The direct asymmetric addition of alkyllithiums to aldehydes and ketones is a reaction that is not in general easy to do with high enantioselectivity. However, Hilmersson and co-workers have reported that lithium amide **237** is a good chiral ligand for the addition of *n*-butyllithium to a range of aldehydes.[133] A representative example is shown in Scheme 68. Thus, addition of 2 equivalents of *n*-butyllithium to isobutyraldehyde in the presence of 4 equivalents of lithium amide **237** in 1:1 diethyl ether–dimethoxymethane generated alcohol **238** in >98.5% ee. These examples are particularly interesting as they work well for aliphatic *and* aromatic aldehydes.



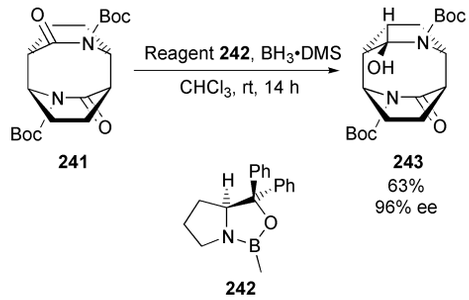
Scheme 68

Another example of a highly enantioselective addition to an aldehyde has been reported by Loh *et al.*[134] Treatment of benzaldehyde with prenyl bromide and indium in the presence of the chiral alkaloid cinchonidine **239** gave homoallylic alcohol **240** in 90% ee *via* an indium-mediated prenylation reaction (Scheme 69). The example in Scheme 69 was the best result and this reaction does not yet appear to have broad scope. For example, the pseudoenantiomer cinchonine did give the opposite enantiomer of alcohol **240** but with reduced enantioselectivity (76% ee).



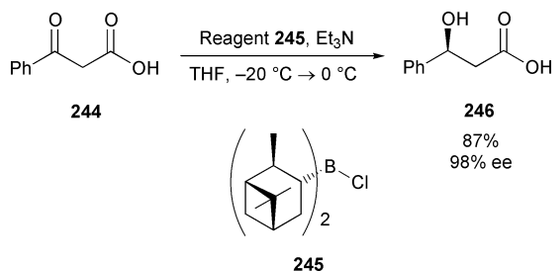
Scheme 69

There are a wide variety of chiral reagents available for asymmetric reduction but new applications of tried and tested methods are still sought. Spivey and co-workers used a stoichiometric amount of Corey's CBS (Corey–Bakshi–Shibata) reagent **242** to desymmetrise a centrosymmetric molecule.[135] Thus, reduction of bisamide **241** with **242** gave a 63% yield of aminal **243** of 96% ee (Scheme 70) and this represents the first ever desymmetrisation of a centrosymmetric molecule.



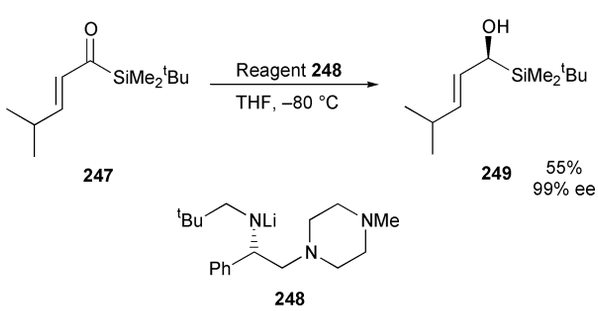
Scheme 70

Although there are good methods available for the asymmetric reduction of β-keto esters, there is still a need to develop a useful direct asymmetric reduction of β-keto acids. Wang and co-workers have reported a useful and general method for this using *B*-chlorodiisopinocampheylborane **245**.[136] A typical example is illustrated in Scheme 71: β-keto acid **244** was converted directly into hydroxy acid **246** of 98% ee.



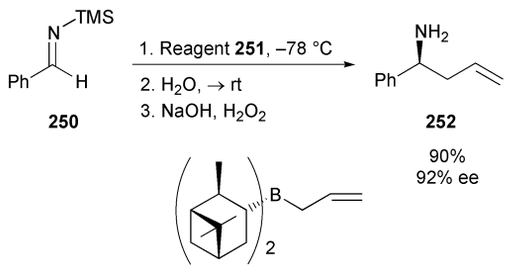
Scheme 71

One final and somewhat unexpected example of an asymmetric C=O reduction reaction is shown in Scheme 72. Takeda *et al.* found that chiral lithium amides such as **248** could deliver hydride to certain ketones in a Meerwein–Ponndorf–Verley type reduction reaction.[137] Reduction of α,β-unsaturated acylsilane **247** using chiral lithium amide **248** gave a respectable yield of alcohol **249** of 99% ee. Unfortunately, reduction of structurally simpler ketones proceeded with much lower enantioselectivity.



Scheme 72

There are few chiral reagents for asymmetric addition to imines. Allylboration of imines, a close relative of the highly successful allylboration of aldehydes (see Section 2), has received the most attention recently from the research groups of Brown[138] and Itsuno.[139,140] Amazingly, Brown and co-workers found that for the successful asymmetric allylboration of imines, 1 mole equivalent of water was required. Thus, they developed the protocol highlighted in Scheme 73 for such reactions: addition of *B*-allyldiisopinocampheylborane **251** to



250 252 251

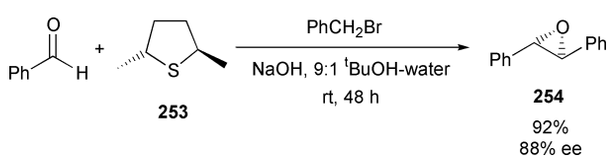
90%
92% ee

Scheme 73

imine **250** followed by water gave, after alkaline hydrogen peroxide work up, homoallylic amine **252** in 90% yield and with 92% ee.[138] This appears to be a reaction of good scope and should therefore prove to be a very useful addition to synthetic methodology.

4.4 Miscellaneous uses of chiral reagents

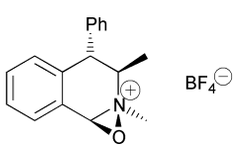
In this section, I have summarised a selection of unrelated examples of the use of chiral reagents. Although there are several excellent methods for catalytic asymmetric epoxidation, stoichiometric approaches can be useful if their protocols are easy to use. Such a process has been developed by Metzner and co-workers. Thus, reaction of benzaldehyde with the sulfur ylide generated from the *in situ* combination of 2,5-dimethylthiolane **253**, benzyl bromide and sodium hydroxide produced a 92% yield of predominantly *trans*-stilbene oxide **254** of 88% ee (Scheme 74).[141] The same epoxide **254** of 61% ee can be produced by oxidation of *trans*-stilbene with the novel oxaziridinium salt **255** as reported by Bohé and co-workers.[142]



253 254

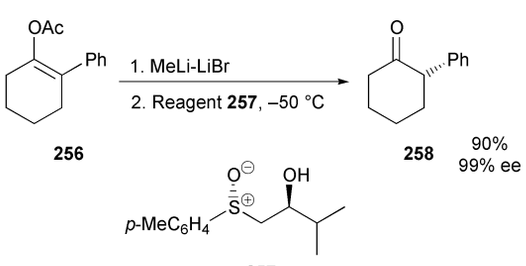
92%
88% ee

Scheme 74



255

Asymmetric protonation is still a popular area of research[143–146] but its main limitation is that there is no general method for protonation of enolates with reliably high enantiomeric excess for a range of substrates. One specific example that works very well indeed was reported by Asensio and co-workers.[143] Thus, treatment of enol acetate **256** with methyllithium in the presence of lithium bromide and subsequent protonation with chiral hydroxy sulfoxide **257** afforded ketone **258** in 90% yield and an outstanding 99% ee (Scheme 75). However, this method has not yet been generalised.



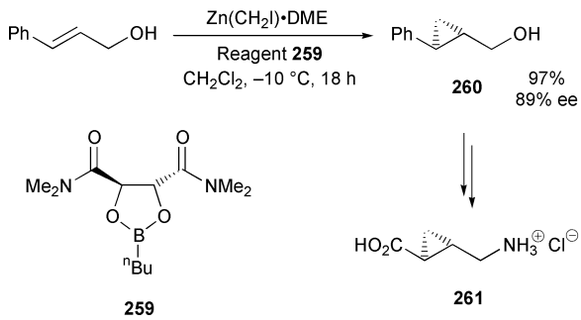
256 258

90%
99% ee

257

Scheme 75

The Charette asymmetric cyclopropanation of allylic alcohols is still one of the best ways for the direct synthesis of chiral cyclopropanes. A recent example was described by Mohapatra in which Simmons–Smith cyclopropanation of cinnamyl alcohol using chiral reagent **259** gave cyclopropyl alcohol **260** in 89% ee (Scheme 76).[147] Subsequent elaboration of **260** gave amino acid **261**, a cyclopropyl analogue of γ-aminobutyric acid.

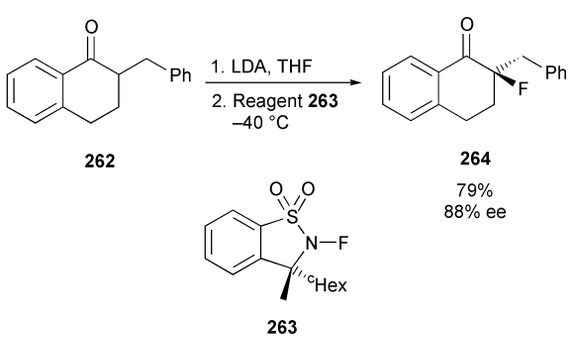


260 259 261

97%
89% ee

Scheme 76

There are virtually no methods available for the direct enantioselective fluorination of enolates. *N*-Fluorosulfonamide **263**, developed by Takeuchi and co-workers, is a useful asymmetric fluorinating reagent.[148] The reagent does not yet have broad scope but one example that works well is shown in Scheme 77. Reaction of the lithium enolate of ketone **262** with reagent **263** gave fluorinated ketone **264** of 88% ee.



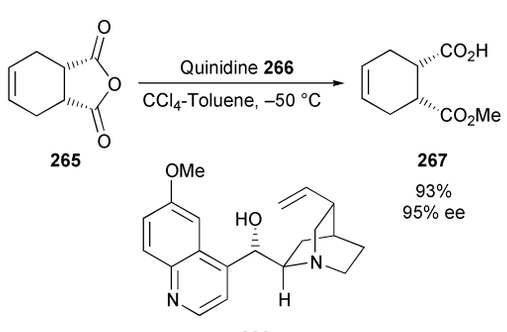
262 264

79%
88% ee

263

Scheme 77

The preparation of monoesters such as **267** is normally carried out using enzyme-mediated hydrolysis or esterification. However, Bolm and co-workers have developed a very successful non-enzymatic desymmetrisation approach to such compounds.[149] They found that methanolysis of *meso*-anhydride **265** in the presence of quinidine **266** proceeded to give a 93% yield of monoester **267** of 95% ee (Scheme 78). Other *meso*-anhydrides were desymmetrised with similar efficiency and the use of quinine allowed access into the opposite enantiomeric series with similarly high enantioselectivity.



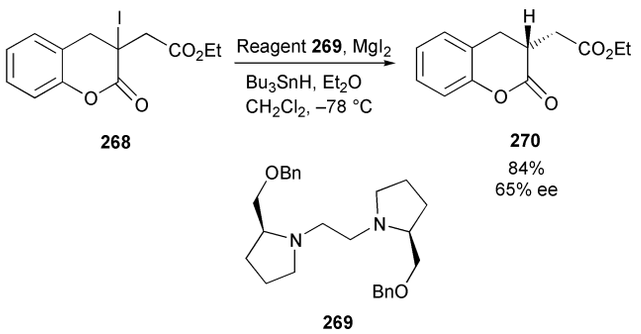
265 267

93%
95% ee

266

Scheme 78

As a final example, there are few reports on the use of chiral reagents in radical-mediated processes.[150,151] However, one example which illustrates the way ahead in this area is shown in Scheme 79. Radical cleavage of the C–I bond in lactone **268** generated a radical that could be enantioselectively reduced using tributyltin hydride in the presence of chiral diamine **269** to give lactone **270** of 65% ee.[150]



268 **270** 84% 65% ee

269

Scheme 79

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