REVIEW
PERKIN 1

Stoichiometric asymmetric processes

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1 Introduction

This article covers the literature from April 1996 to March 1997, and continues the coverage of the previous review. Since the field of asymmetric processes is such a large one, this review covers stoichiometric processes only, and asymmetric catalytic processes are now the subject of a separate review.

2 Chiral auxiliaries

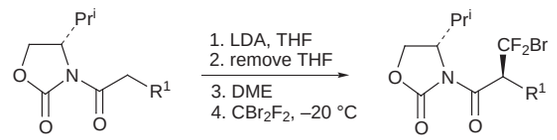
2.1 Reactions of chiral enolates

2.1.1 Alkylation

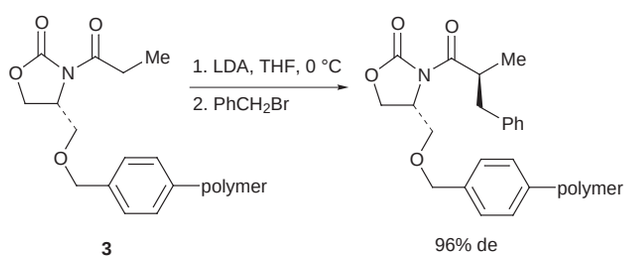
One of the most well-established and widely used types of auxiliary for asymmetric reactions of enolates is the oxazolidinone class developed by Evans. A new procedure for the *N*-acylation of the parent oxazolidinones with either acid chlorides, or symmetrical or mixed anhydrides, uses catalytic 4-(*N,N*-dimethylamino)pyridine (DMAP) in the presence of triethylamine at room temperature, rather than deprotonation of the oxazolidinone with strong bases such as butyllithium.[1] Alkylation of the lithium enolates of the *N*-acyl oxazolidinones **1** with dibromodifluoromethane gives the α-(bromodifluoromethyl) products **2** in 68% de for the *N*-propionyl case (R^1=Me), improving to 92% de when $R^1 = Bu^t$ (Scheme 1).[2] An ionic chain mechanism is proposed, involving formation of difluorocarbene, and similar results are obtained using bromodifluoromethane.

An Evans-type oxazolidinone has been attached to a Merrifield polystyrene resin, as in **3**, and the lithium enolate alkylated with benzyl bromide (Scheme 2).[3] After hydrolysis, the polymer bound auxiliary can be reisolated by simple filtration, and the α-benzylated acid is formed in 96% ee.

The tricyclic oxazolidinone **4** is prepared from a chiral

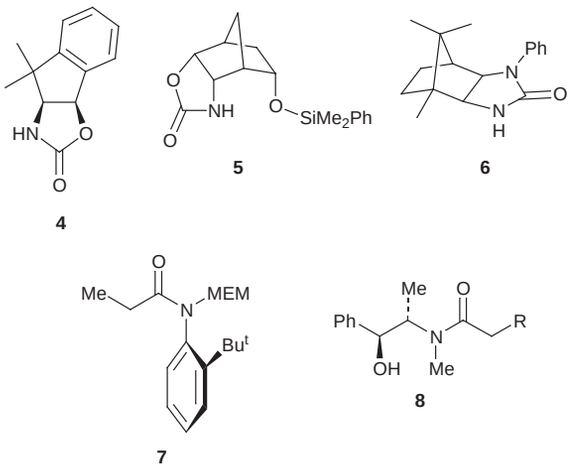


Scheme 1

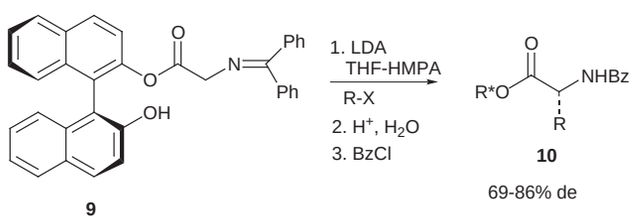


Scheme 2

aminoindanol which is fully synthetic, and resolved using mandelic acid, rather than being derived from natural amino acids.[4] Enolates of *N*-acyl-**4** undergo alkylation, acylation, bromination, and hydroxylation, all with high diastereoselectivities. Another tricyclic oxazolidinone **5** has a rigid bridged ring system, where the bulky silyl-protected alcohol is essential in order to obtain very high diastereoselectivities in alkylation reactions of enolates of the corresponding *N*-acyl compounds (dr = 300:1 to >500:1).[5] The corresponding *N*-alkenoyl oxazolidinones have also been used both as dienophiles in Diels–Alder reactions, and as Michael acceptors for conjugate additions of cuprates. The *N*-acylcamphor-derived auxiliary **6** also has a rigid bridged ring system, but has a cyclic urea ring in the *exo*-orientation, as compared with the *endo*-oxazolidinone in **5**.[6] Alkylation reactions of the sodium enolate of the *N*-propionyl derivative of **6** give uniformly high diastereoselectivities of >99:1, even with the small electrophile methyl iodide. The *N*-propionylanilide **7** possesses axial chirality, with enantiomeric atropisomers.[7] Diastereoselective alkylation of the lithium enolate of **7** occurs with good selectivity (15:1 to >25:1) for a range of alkyl halides. Aldol reactions of the lithium enolate are also highly stereoselective for one of the *syn*-isomers. The *N*-MEM group in **7** appears to enhance the stereoselectivity of reactions of the enolate, since the corresponding *N*-methyl analogue gives rather low selectivities. Only racemic **7** has so far been used, but some progress has been made towards its kinetic resolution using a chiral lithium amide base. Pseudoephedrine has been developed as an effective practical chiral auxiliary by Myers for the alkylation of its amides **8**, and an extension of this is the use of epoxides as the electrophiles.[8] Ethylene oxide gives moderate diastereoselectivities (49–59% de), however the use of the "matched" enantiomer of a monosubstituted epoxide gives double-diastereoselective reactions of 93 to ≥99% de. Hydrolysis of the γ-hydroxyacyl products also results in cyclisation to γ-lactones.

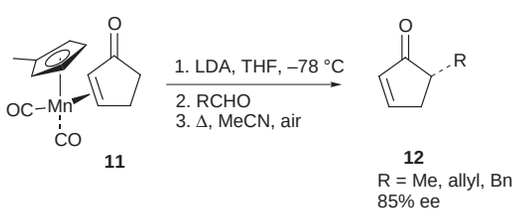


The binaphthol mono-ester **9** has been used as a chiral glycine equivalent:[9] alkylation of the lithium enolate followed by hydrolysis of the imine and benzoylation gives the protected α-aminoesters **10** in 69–86% de (Scheme 3).



Scheme 3

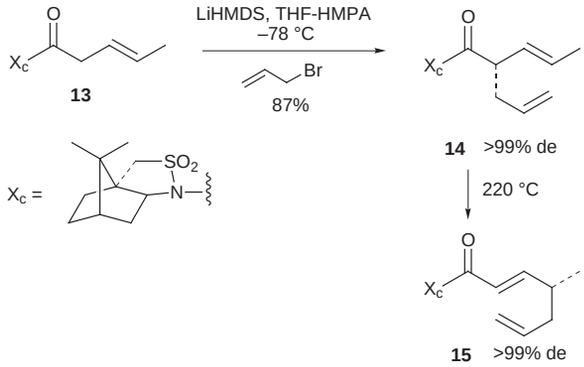
The planar-chiral η^2-manganese complex **11** has previously been used for diastereoselective alkylation and aldol reactions, but only in a racemic form. By forming the complex from optically active cyclopentenol, followed by oxidation of the alcohol to give **11**, alkylation and aldol reactions of the optically active lithium enolate give products (*e.g.* **12**) in 85–88% ee after oxidative removal of the manganese (Scheme 4).[10]



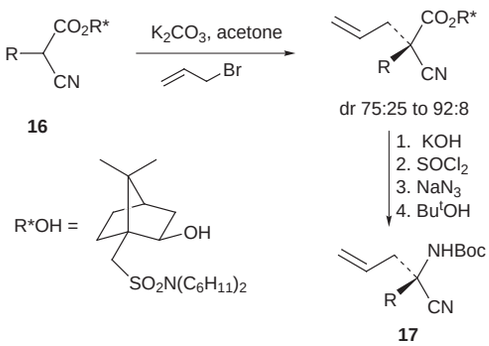
Scheme 4

An asymmetric allylation–Cope rearrangement sequence has been developed by Nakai and co-workers[11] using the enolate of the β,γ-unsaturated acyl Oppolzer auxiliary **13** (Scheme 5). Good diastereoselectivity in the allylation reaction to give **14** is observed (>99%), together with complete retention of the (*E*)-stereochemistry of the alkene. Interestingly, the corresponding α,β-unsaturated isomer of **13** gives mostly the (*Z*)-isomer of **14**, and use of the Evans' auxiliary gives much lower selectivity in the allylation (48% de). The Cope rearrangement of **14** at 220 °C is highly stereoselective, giving **15** as the sole product, whereas the (*Z*)-isomer of **14** rearranges with lower selectivity (85 : 15 dr) to give the epimer of **15**. A similar sequence involving an aldol reaction followed by Cope rearrangement is also possible,[12] by initial aldol reaction of the enolate of **13** with crotonaldehyde in the first step, rather than alkylation with allyl bromide.

α-Cyanoesters **16** of Helmchen's chiral auxiliary can be alkylated under mild conditions with allyl bromide (Scheme 6).[13] Hydrolytic removal of the auxiliary followed by Curtius



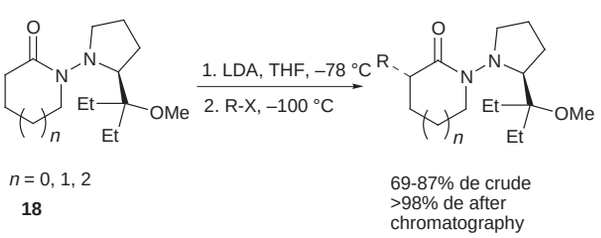
Scheme 5



Scheme 6

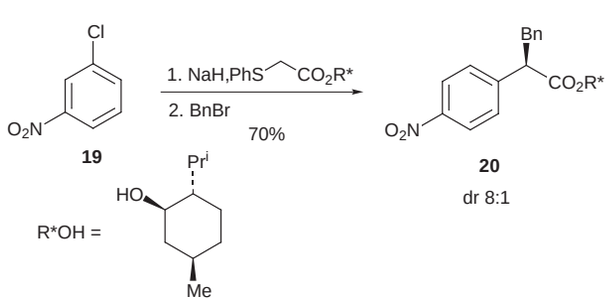
rearrangement gives optically active protected α-aminonitriles **17** which can be converted into α-aminoacid derivatives.

Chiral *N*-dialkylaminolactams **18** are alkylated in fairly good diastereoselectivity, which can be improved to >96% after chromatography (Scheme 7).[14] Reductive removal of the auxiliary provides a route to optically active 2-substituted lactams containing 5- to 7-membered rings.



Scheme 7

Enolates of menthyl arylacetates can be formed by vicarious nucleophilic substitution of hydrogen in 1-chloro-3-nitrobenzene **19** (Scheme 8); alkylation in the same reaction vessel gives the products **20** in up to 8 : 1 dr.[15]

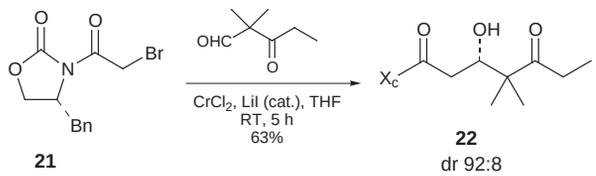


Scheme 8

2.1.2 Aldol reactions

One of the problems in the area of asymmetric aldol reactions has been to find effective methods for acetate enolates, since

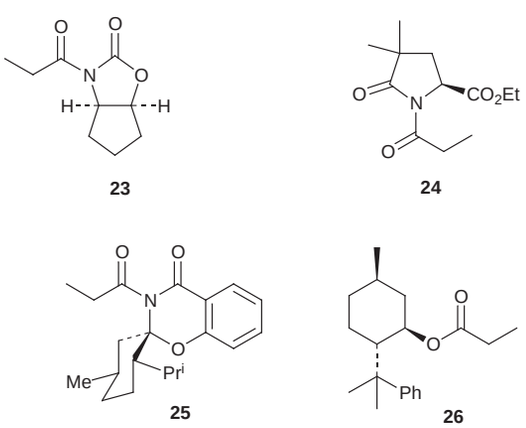
these often react relatively unselectively compared to the corresponding propionate enolates. One solution to this problem is to use a chromium–Reformatsky species prepared from an (α-bromoacetyl) Evans' auxiliary **21** (Scheme 9).[16] The aldol product **22** is formed with good diasteroselectivity (92 : 8) in the opposite sense to more usual methods. The *N*-acetyl analogue of the cyclic urea **6** has also been used for lithium and titanium aldol reactions with useful diastereoselectivities for aromatic aldehydes. Aliphatic aldehydes react rather less selectively, and the titanium and lithium mediated reactions give selectivities in the opposite sense to each other. Asymmetric aldol reactions of acetate enolate equivalents have also been achieved using chiral reagents (see below).



21 **22** dr 92:8

Scheme 9

New designs of chiral auxiliary for the aldol reaction continue to appear. The *N*-propionyloxazolidinone **23** is prepared from 2-aminocyclopentanol, which is itself formed by bakers' yeast reduction of ethyl 2-oxocyclopentanecarboxylate, followed by Curtius rearrangement.[17] Boron aldol reactions of **23** under the usual conditions give uniformly high diastereoselectivities (>99%) for one of the *syn*-aldol products. The *N*-propionyl "quat"-type lactam **24** gives similarly high selectivities for the same *syn*-aldol isomer.[18] The 1,3-benzoxazinone **25** is derived from menthone, and aldol reactions of its sodium and titanium enolates with benzaldehyde give the two alternative *syn*-diastereoisomers, in 91 : 2 and 2 : 96 dr respectively.[19]

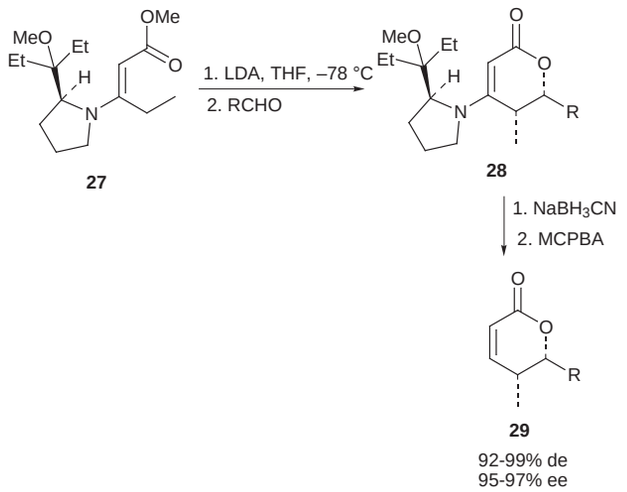


23 **24** **25** **26**

The standard combination of a dialkylboron triflate and a tertiary amine base, widely used for aldol reactions of ketones, thioesters, and *N*-acyl chiral imides, has also been shown to be effective for esters,[20] contrary to widespread assumption. As well as simple achiral esters, 8-phenylmenthyl propionate **26** is converted into its enol borinate with dicyclohexylboron triflate, and following equilibration of the geometical isomers, aldol reaction with isobutyraldehyde gives a 98 : 2 ratio for the two possible *syn*-isomers. Aldol reaction of the kinetic enol borinate is very selective for the two *anti*-aldol products, but both are formed in almost equal amounts (48 : 52).

The vinylogous urethane **27** contains a pyrrolidine auxiliary which has been reported as a more accessible replacement for 2,5-dimethylpyrrolidine (Scheme 10).[21] Aldol reactions of the extended lithium enolate of **27** give *syn*-lactones **28**, followed by a two-step removal of the auxiliary to give the unsaturated lactones **29**.

Some interesting new applications of established asymmetric

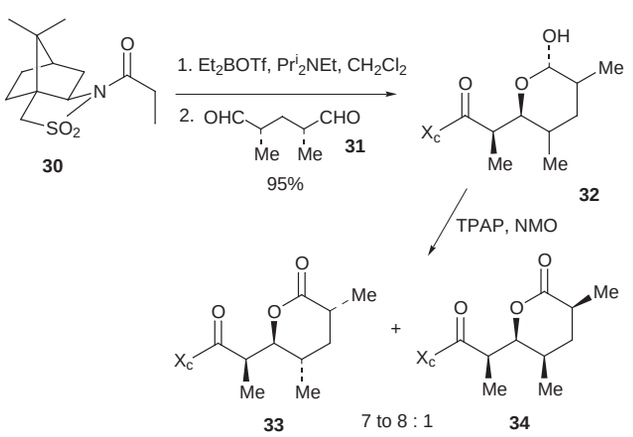


27 **28** **29**

92-99% de
95-97% ee

Scheme 10

aldol reactions include Oppolzer's use of his *N*-propionyl sultam auxiliary **30** for the desymmetrisation of the *meso*-dialdehyde **31** (Scheme 11).[22] Oxidation of the lactol product **32** gives the lactones **33** and **34** in a dr of 7 to 8 : 1, and hydrolytic removal of the auxiliary results in a short synthesis of the Prelog–Djerassi lactonic acid. An approach to the iterative construction of polyketide chains involves aldol reaction of an acylated Evans' oxazolidinone auxiliary with a polymer supported aldehyde.[23] Removal of the auxiliary and transformation of the imide into an aldehyde group *via* a Weinreb amide allows the asymmetric aldol reaction to be repeated, building up the chain on the polymer support. Evans' auxiliaries have also been used in aldol reactions with the ketone group of pyruvates, resulting in the construction of tertiary alcohol centres during the aldol step.[24] Complete control over the stereochemistry at the α-carbon is achieved, but the control over the new tertiary alcohol centre is less selective, resulting in a *syn : anti* mixture of diastereoisomers in up to 83 : 17 dr.



30 **31** **32** **33** 7 to 8 : 1 **34**

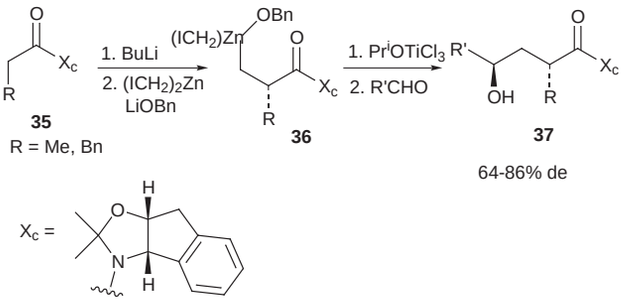
TPAP = tetra-*n*-propylammonium perruthenate
NMO = 4-methylmorpholine *N*-oxide

Scheme 11

The lithium enolate of the chiral amide **35** can be homologated to the zinc homoenolate **36**, and combined with a titanium homoaldol reaction to give α-alkyl-γ-hydroxyamides **37** in 64–86% de (Scheme 12).[25] The auxiliary can be removed with tosic acid, causing cyclisation of the products to α,γ-disubstituted γ-lactones.

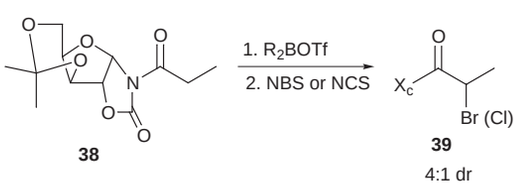
2.1.3 Miscellaneous reactions of chiral enolates

Halogenation of chiral enol borinates using *N*-halosuccinimides has been applied to the xylose-derived *N*-acyloxazolidin-

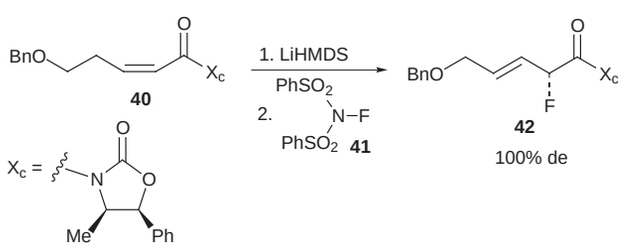


Scheme 12

one **38** to give α-bromo and α-chloro products **39** in up to 4:1 dr (Scheme 13).[26] Acylation of the lithium enolate of **38** is more selective, giving the β-ketoacyl oxazolidinones in up to 12:1 dr. Bromination (with NBS) of an Evans' acyloxazolidinone containing an *o*-carborane cage has been followed by azide displacement and reduction of the azide to the amine, affording a route to both enantiomers of carboranylalanine, a compound useful in boron neutron capture therapy.[27] The α,β-unsaturated acyloxazolidinone **40** has been converted into the lithium and sodium extended enolates, which are fluorinated with *N*-fluoro-(*N*-phenylsulfonyl)benzenesulfonamide **41** at the α-position to give **42** as a single diastereoisomer (Scheme 14).[28] The product **42** was then used as an intermediate in the preparation of 2-deoxy-2-fluoro sugars.

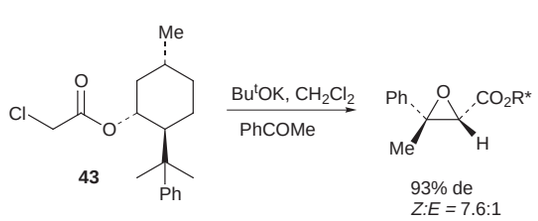


Scheme 13



Scheme 14

The asymmetric Darzens reaction of 8-phenylmenthyl chloroacetate **43** with ketones gives glycidic esters in 77–94% de (Scheme 15).[29] With unsymmetrical ketones there is also good selectivity in favour of the (*Z*)-epoxide (4.5:1 to 7.6:1). Asymmetric aza-Darzens reactions have also been achieved using the lithium enolate of a bromoacetyl Oppolzer sultam and *N*-(diphenylphosphinyl)imines, giving *cis*-disubstituted aziridines with >95% face selectivity.[30]

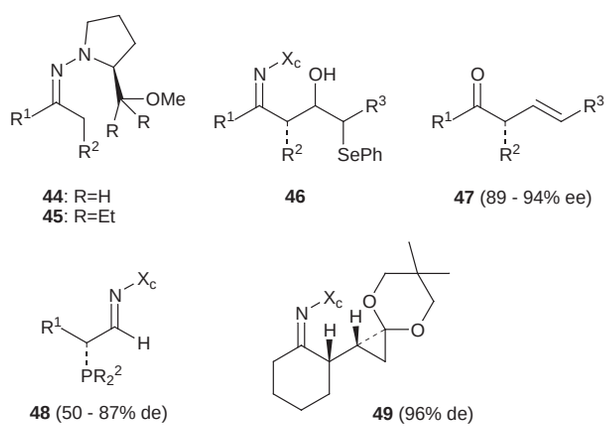


Scheme 15

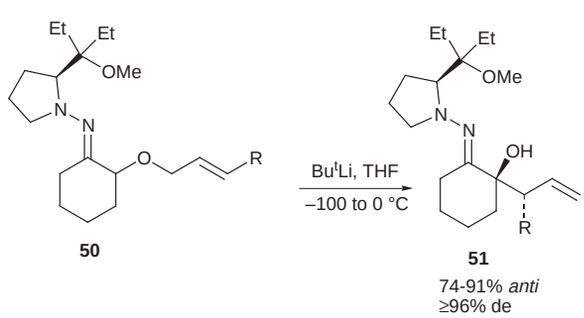
2.2 Reactions of carbanions

2.2.1 SAMP hydrazones

Enders and Klatt have reviewed the uses of 1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazones of aldehydes and ketones **44** in asymmetric synthesis.[31] In general, these involve creation of a new stereogenic centre α to the hydrazone group by deprotonation followed by reaction with an electrophile. The diethyl (SAEP) analogues **45** often give improved diastereoselection. New examples include the use of α-(phenylselanyl)aldehydes as electrophiles, which give hydroxyselenides **46**.[32] After removal of the auxiliary and elimination of the hydroxyselenide, chiral β,γ-unsaturated aldehydes and ketones **47** are formed with very little racemisation at the α-centre. Chiral 2-phosphinoalcohols can be prepared by reaction of SAMP or SAEP hydrazone anions with chlorodialkylphosphines to give **48**, followed by removal of the auxiliary and reduction of the aldehyde.[33] The lithiated SAMP hydrazone of cyclohexanone can be transmetallated to an organozinc reagent, which then adds to the alkene double bond of a cyclopropenone acetal, giving the cyclopropane **49** in 96% de.[34]

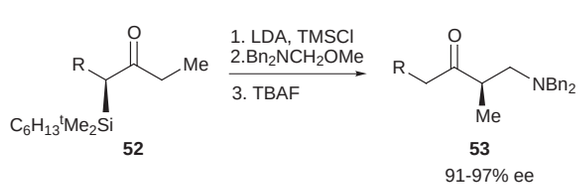


The SAEP hydrazone **50** undergoes regioselective lithiation and [2,3]-Wittig rearrangement to give the α-hydroxycyclohexanone derivatives **51** containing adjacent quaternary and tertiary stereogenic centres (Scheme 16).[35]



Scheme 16

Enantioselective Mannich reactions can be performed in an indirect way starting from SAMP hydrazones, which are used to prepare α-silylketones **52**. This is followed by formation of the α′-silylenol ether, and reaction with an iminium salt. The second stereogenic centre is controlled by the α-silyl group, which is then finally removed to give the chiral β-(dialkylamino)ketones **53** (Scheme 17).[36]

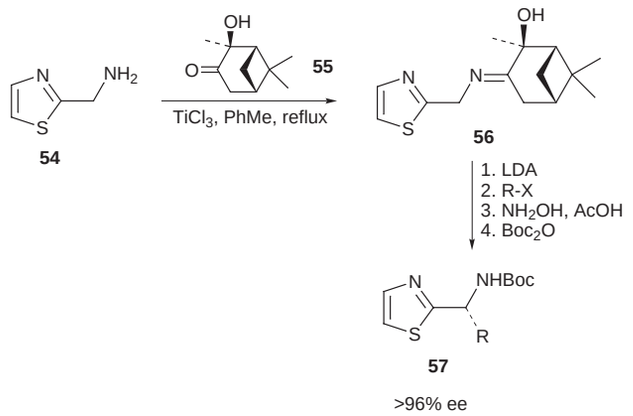


Scheme 17

2.2.2 Other carbanions

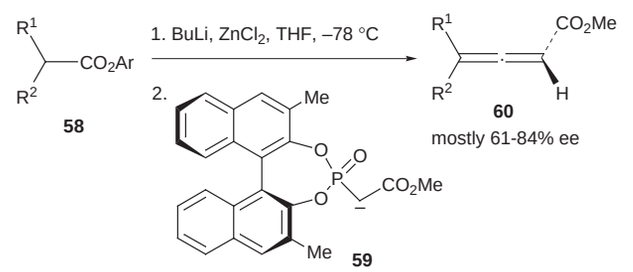
2-(Aminomethyl)thiazole **54** can be converted into imines (*e.g.*

56) by reaction with camphor or a hydroxypinanone **55** (Scheme 18).[37] Alkylation of the carbanion formed by deprotonation of **56**, followed by cleavage of the imine and protection affords the *N*-Boc-protected aminoalkylthiazoles **57**, which can serve as precursors to chiral α-aminoaldehydes. The hydroxypinanone imines show better selectivities (mostly >98 : 2 dr) in the alkylations than do those derived from camphor.



Scheme 18

An enantioselective preparaton of allenecarboxylate esters **60** relies upon an asymmetric Wadsworth–Emmons reaction of the phosphonoacetate **59**, containing a substituted binaphthol auxiliary, with ketenes which are generated *in situ* by treatment of the aryl esters **58** with BuLi and $ZnCl_2$ (Scheme 19).[38] The allenes **60** are mostly formed in 61–84% ee, and the unsubstituted binaphthol analogue of **59** shows much lower enantioselectivity.

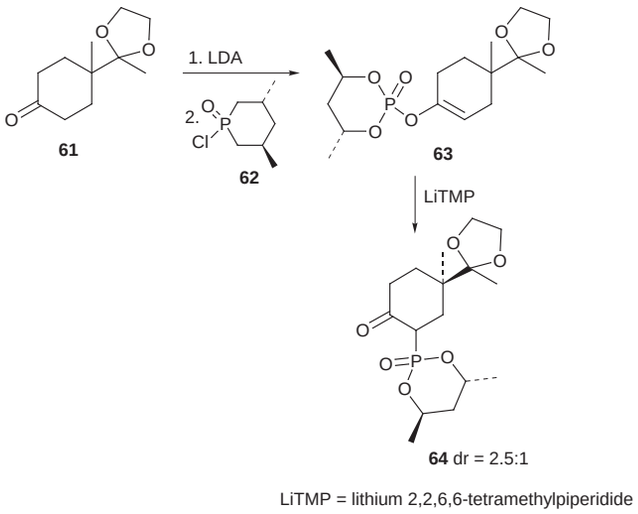


Scheme 19

An asymmetric synthesis of the β-ketophosphonate **64** starts with treatment of the achiral cyclohexanone **61** with LDA to give a racemic chiral enolate, which reacts with an optically pure phosphorochloridate **62** to give the vinyl phosphates **63** as a mixture of diastereoisomers (Scheme 20).[39] Deprotonation of **63** with LiTMP gives a delocalised allyl anion which is now a single stereoisomer, and which rearranges stereoselectively to **64** with a dr of 2.5 : 1 at the 5-position.

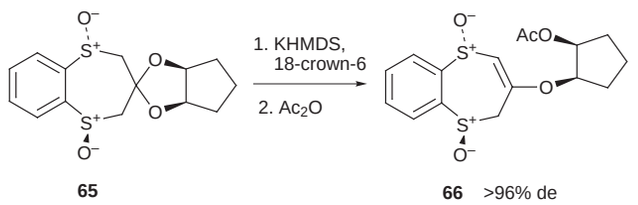
The C_2-symmetric cyclic bis-sulfoxide **65** has been used to desymmetrise *meso*-1,2-diols (Scheme 21).[40] Formation of the acetal **65** from the *meso*-diol, followed by asymmetric deprotonation, elimination and acetylation gives the desymmetrised product **66** in >96% de. The selectivity is very dependent on the metal counter-ion, since only 8% de is obtained using LiHMDS and 12-crown-4.

The reactions of chiral allyl organometallic species with aldehydes has been a very active area for some years. The metallated sulfoximines **67** and **68** containing 5- and 6-membered rings show very high levels of stereocontrol, even when combined with a chiral aldehyde in a mismatched sense (Scheme 22).[41] Analogous acyclic sulfoximines show good stereocontrol with achiral aldehydes and also with chiral aldehydes in matched pairs, but less control using mismatched pairs.

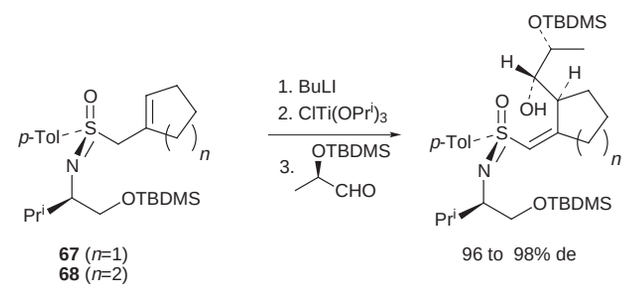


LiTMP = lithium 2,2,6,6-tetramethylpiperidide

Scheme 20



Scheme 21



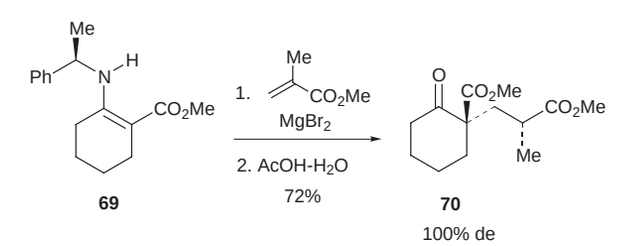
Scheme 22

2.3 Michael addition reactions

2.3.1 Michael addition reactions of chiral nucleophiles

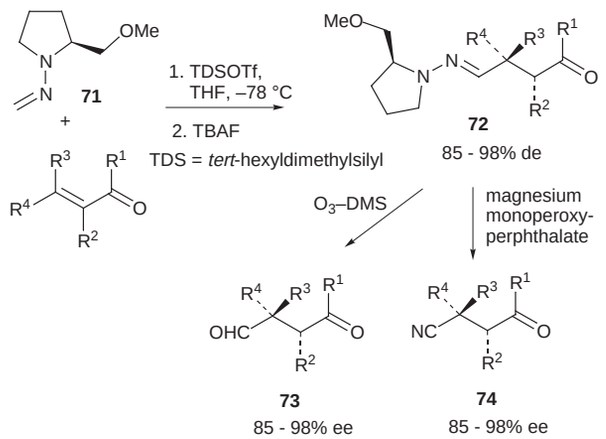
Conjugate additions of chiral enamines, *e.g.* **69**, formed from a cyclic ketone and 1-phenylethylamine have been extended to the study of the formation of a second stereogenic centre, by using α- or β-substituted Michael acceptors (Scheme 23).[42] Use of methyl methacrylate gives **70** as a single diastereoisomer, and although there is no reaction with methyl crotonate, some other more reactive β-substituted acceptors react successfully. A model is proposed for the transition state, and the face selectivity of this type of reaction has been interpreted as the chiral amine causing one cyclohexene chair conformation to be preferred over the other in the enamine intermediate.[43]

The SAMP-hydrazone of formaldehyde **71** undergoes Michael addition to enones as a *neutral* nucleophile (in contrast



Scheme 23

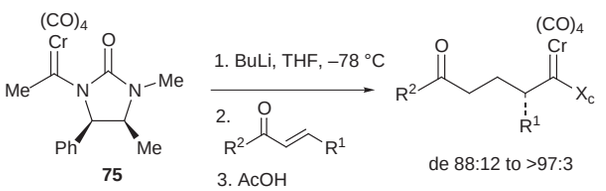
to the more usual carbanions discussed in section 2.2.1) in 85 to ≥98% de to give adducts **72**, which can be transformed into either 4-ketoaldehydes **73** or 4-ketonitriles **74** (Scheme 24).[44] The same hydrazone **71** also reacts with 1-nitroalkenes derived from sugars without any base or additive, in diastereoselectivities which are >96% for matched pairs of reagents, but 38–68% for mismatched pairs.[45]



Scheme 24

Conjugate addition of chiral lithium amides to α,β-unsaturated esters has been discussed in previous reports in this series, and Davies has extended this work by incorporating a subsequent stereoselective aldol reaction at the α-carbon atom, as a key step in the synthesis of a thienamycin intermediate.[46] Stereoselective reaction of the enolate with trisyl azide followed by reduction of the azide gives *anti*-2,3-diaminobutanoic acid.[47] The *syn*-diastereoisomer can also be prepared by an inversion at the α-carbon atom.

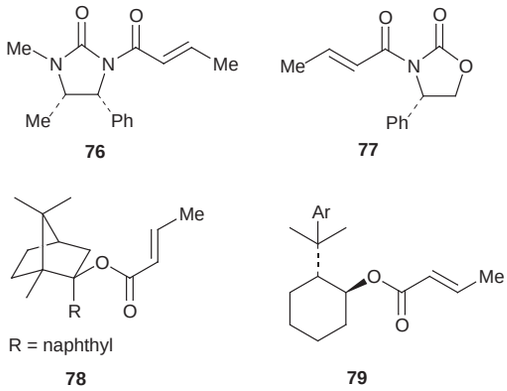
The anion of chromium carbene complex **75**, containing an imidazolidinone chiral auxiliary, acts as an acetate equivalent in the conjugate addition to α,β-unsaturated ketones, and generally shows a selectivity of at least 96 : 4 dr, with one exception. (Scheme 25).[48] Interestingly, the stereoselectivity reaches a maximum at −20 °C, and is reduced at both higher and lower temperatures. Oxidation of the carbene and removal of the auxiliary gives chiral β-alkyl-δ-oxoesters.



Scheme 25

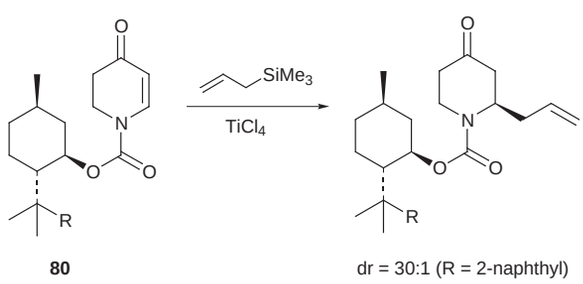
2.3.2 Michael addition reactions to chiral electrophiles

The conjugate addition of organometallic reagents to crotonyl derivatives of a variety of chiral auxiliaries has been a theme for some years now. New examples include the conjugate addition of Grignard reagents to the imidazolidinone **76** (using the same auxiliary as in **75**), where the presence of Me_2AlCl as a Lewis acid improves diastereoselectivity to 90 : 10 *via* a proposed chelated intermediate.[49] Copper(I)-catalysed asymmetric additions of organozirconocenes to the crotonyl Evans-type auxilary **77** have been reported for the first time.[50] The intermediate zirconium enolate formed during the conjugate addition can also be trapped with benzaldehyde in an aldol step to give a product with three new stereogenic centres in >97% de. Use of the more common benzyl or isopropyl-substituted oxazolidinones is less selective, as is the Oppolzer sultam auxiliary. The iodotrimethylsilane promoted addition of monocopper



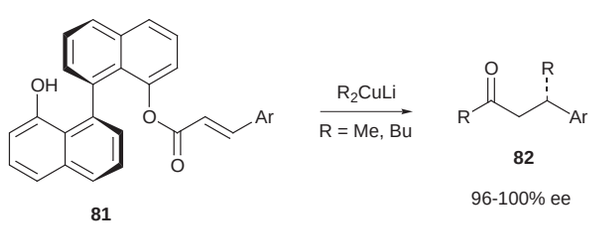
reagents to the bornyl crotonate **78** has been extended to the use of a farnesyl-derived homoallylic copper reagent, in the synthesis of geranylcitronellol† in 99% ee.[51] Replacement of the naphthyl group in **78** with a phenyl group reduces the stereoselectivity in the conjugate addition step to 73% de. The high pressure induced conjugate addition of amines to a variety of "arylmenthyl" crotonates **79** has been studied, together with crotonates of some chiral cyclohexanols.[52] Very high selectivities are obtained in additions to **79** where Ar = 2-methoxyphenyl, 4-phenoxyphenyl or 2-naphthyl, whereas only moderate selectivities are observed for *trans*-2-arylcyclohexanol esters. This difference is interpreted in terms of improved π-stacking in **79**.

8-Arylmenthols have also been studied as auxiliaries in the conjugate addition of allyltrimethylsilane to the dihydropyridones **80** (Scheme 26).[53] Again Ar = 2-naphthyl is particularly effective (30 : 1 dr), and the use of menthol itself (Ar = H) results in an almost completely unselective reaction.



Scheme 26

The monoesters **81** of 1,1′-binaphthalene-8,8′-diol undergo conjugate addition reactions of lithium dialkylcuprates, followed by 1,2-addition of the same reagent at the ester and elimination of the chiral auxiliary all in one process, to give ketones **82** in 96–100% ee (Scheme 27).[54] Previously, the corresponding esters of the widely used 1,1′-binaphthalene-2,2′-diol auxiliary had shown rather less stereoselectivity.

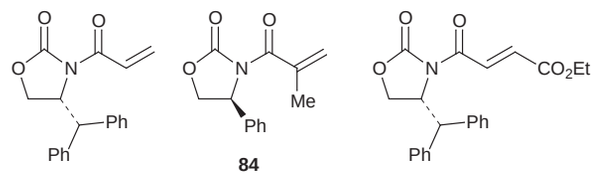


Scheme 27

Asymmetric conjugate addition reactions of radicals to chiral α,β-unsaturated acyloxazolidinones have been previously reported, but new examples include conjugate addition of an

† IUPAC name: 8-geranyl-3,7-dimethyloct-6-en-1-ol.

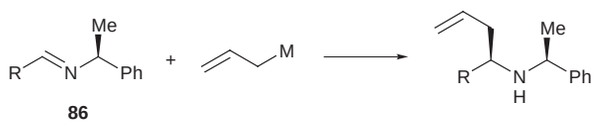
ethyl radical to **83**, followed by trapping of the intermediate radical with an allyl stannane, generating the new stereocentre during the trapping step only.[55] Related to this is the radical addition of tributyltin hydride to the α-methyl substituted acceptor **84**; here the stereogenic α-centre is created during hydrogen atom transfer in 92 : 18 dr.[56] Addition of an isopropyl radical to the fumaryl oxazolidinone **85** is both highly regio- and stereoselective in the presence of the correct choice of lanthanide triflate as a Lewis acid;[57] the saturated acyl oxazolidinone products can then be used in standard asymmetric aldol reactions, resulting in the creation of three contiguous stereogenic centres.



83 **84** **85**

2.4 Additions to C=N double bonds

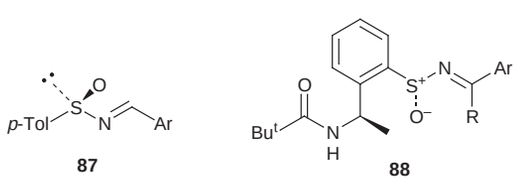
A contribution to the well-studied field of addition of nucleophiles to imines derived from 1-phenylethylamine is the investigation of the addition of allyl organometallic compounds, looking at the dependence of diasteroselectivity upon the allyl reagent used, and also the structure of the imine **86** (Scheme 28).[58] Allyl-BBN and diallylcuprate give the best results with both aliphatic and aromatic imines (up to 98% de), although with imines derived from pyridine-2-carbaldehyde, allylzinc bromide and allyl(dichloro)iodotin are better.



86

Scheme 28

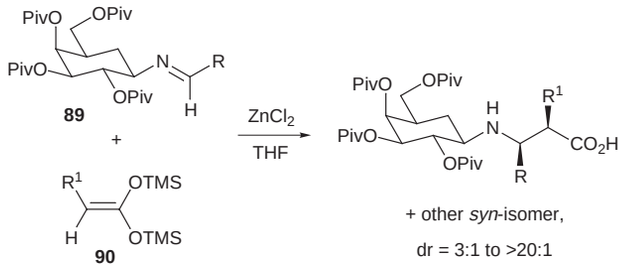
Additions to imines derived from chiral sulfinamides are represented by the addition of Grignard reagents to toluenesulfinamides **87** in 60–74% de,[59] and hydride reduction of imines **88** in up to 86% de using DIBALH.[60] Addition of $ZnBr_2$ to the DIBALH reduction gives the opposite sense of diastereoselectivity in up to 92% de. Addition of methyl and ethyl Grignard reagents to the analogous aldehyde imines is also stereoselective, in 79–85% de, and the sense of the stereoselectivity is as expected from the results using DIBALH without $ZnBr_2$.



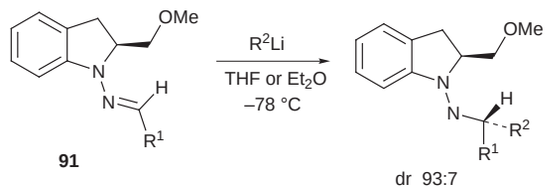
87 **88**

Asymmetric synthesis of β-amino acids has been achieved by additions to *N*-galactosylimines **89** (Scheme 29).[61] Addition of bis-silyl ketene acetals **90** gives only the two possible *erythro (syn)* isomers, and usually in >20 : 1 dr, whereas addition of the lithium enolate of *tert*-butyl phenylacetate gives exclusively the two *threo* isomers, but in a lower 3 : 1 ratio.

The addition of organolithium reagents to the C=N double bond of SAMP-hydrazones has been extended to the indoline-2-carboxylic acid derived hydrazones **91** (Scheme 30).[62] Uniformly high diastereoselectivities are observed (>93 : 7), even with imines which could be deprotonated at the α-position by the basic organolithium reagents. The same types of chiral



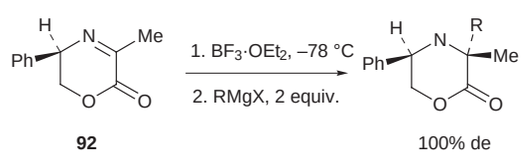
Scheme 29



Scheme 30

imines also undergo addition of trimethylsilyl cyanide in the presence of Et_2AlCl in up to 96% de.[63]

Dehydromorpholines **92**, prepared from *(R)*-phenylglycinol and α-ketoesters, undergo addition of Grignard reagents to the C=N bond in the presence of a Lewis acid with complete diastereoselectivity (Scheme 31).[64] Destructive removal of the chiral auxiliary by catalytic hydrogenation then results in optically pure α-methyl-α-amino acids.



Scheme 31

Enantiomerically pure 1,2-diamines have been prepared by a symmetrical pinacol-type coupling of optically pure chromium tricarbonyl complexes of benzaldehyde imines.[65] The reaction is promoted by SmI_2, and is an example of the formation of both stereogenic centres in a 1,2-difunctionalised compound, as well as the C–C bond connecting them, in a single step.

Hanessian has reported that the addition of allylzinc reagents to oximes of glyoxylic acid attached to Oppolzer's camphor-derived sultam gives α-allylglycines.[66] However a more direct approach from the same group uses an external chiral ligand for the same type of reaction (see Section 3.2).

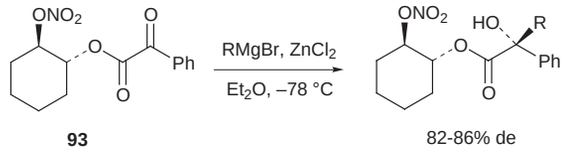
An unusual asymmetric addition to C=N bonds involves the addition of Grignard reagents to the 2-position of pyridinium salts, with *N*-alkoxycarbonyl groups formed from chiral alcohols as the chiral auxiliaries.[67] 8-Phenylmenthol and closely related derivatives were found to be the best auxiliaries, with diastereoselectivities of up to 95%.

2.5 Addition to C=O double bonds

This section covers additions of nucleophilic species to carbonyl groups which have not already been covered in section 2.1.1. Scheme 32 shows the addition of Grignard reagents to a ketone **93** bearing a chiral auxiliary which is of the now standard *trans*-2-substituted cyclohexyl ester type, but is novel in that the 2-substituent is a nitroxy group.[68]

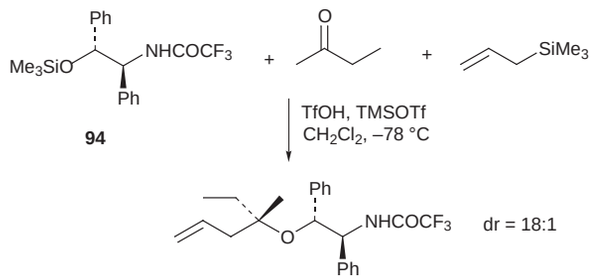
The aminoalcohol derived auxiliary **94** is not initially attached to the ketone substrate, but becomes covalently bonded during the reaction with the allylsilane (Scheme 33).[69] The auxiliary can be reductively cleaved using sodium in liquid ammonia, and gives improved selectivity over an earlier reagent.

Some of the most effective neutral chiral nucleophiles for



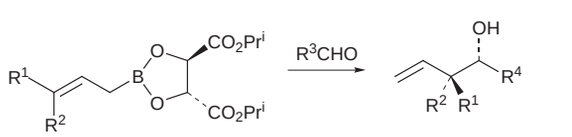
93 82-86% de

Scheme 32



Scheme 33

asymmetric addition to carbonyl groups are allyl boronates. The γ,γ-disubstituted allyl boronates **95** can be formed *in situ* from tartrate esters of either enantiomer, and add to aldehydes to give homoallylic alcohols with a quaternary stereogenic centre (Scheme 34).[70] Allyltrichlorosilane also reacts with tartrate esters to give a pentacoordinate allyl silicate which undergoes similar asymmetric addition of the allyl group to aldehydes in up to 71% ee.[71] Very similar work has also been reported by Kira and co-workers.[72] Tartrate esters are also used in the *in situ* formation of a pentacoordinate chiral allyltin species, which transfers the allyl group to aromatic aldehydes in the presence of catalytic amounts of copper salts in 89–94% ee.[73] Diisopinocampheylallylboranes have also been extensively investigated for asymmetric addition of allyl groups to aldehydes; incorporation of a γ-aminoallyl group results in the formation of unsaturated 1,2-aminoalcohols, and use of an imine as the protecting group on nitrogen is important to allow easy deprotection.[74]



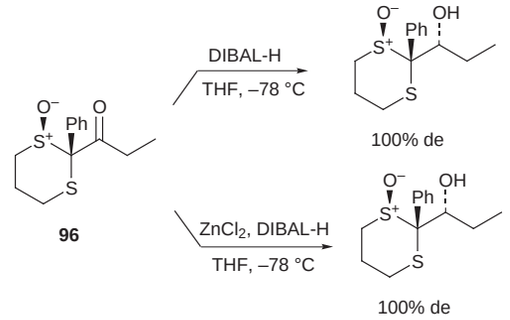
95 dr 96:4

major isomer: 62-85% ee

Scheme 34

Masked α-hydroxyketones are formed by reduction of a 2-acyldithiane-1-oxide **96** (Scheme 35), where the chiral auxiliary is formed by Kagan oxidation of the corresponding dithiane after incorporation into the substrate. Other examples related to **96** can also be prepared by acylation and methylation of the parent chiral 1,3-dithiane-1-oxide.[75] Reduction of ketone groups which are remote from the chiral auxiliary has been achieved using 4- and 5-oxoesters of anhydroglucose derivatives.[76] Use of $ZnCl_2$ in the reduction with sodium borohydride is essential for high selectivity, and chiral lactones are formed in up to 93% ee after removal of the auxiliary. β-Ketophosphine oxides containing a chiral oxazolidine auxiliary adjacent to the ketone have been reduced to the corresponding β-hydroxyphosphine oxides in 95:5 dr, and the auxiliary can be removed using ethane-1,2-dithiol.[77]

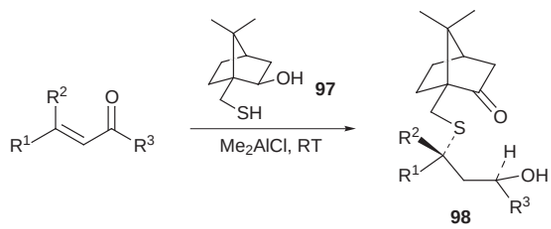
An intramolecular Meerwein–Ponndorf–Verley reduction is shown in Scheme 36, where the auxiliary **97** first undergoes Michael addition to the α,β-unsaturated ketones, followed by highly diastereoselective 1,7-hydride transfer to give **98**.[78] Destructive removal of the auxiliary by reductive cleavage with Raney nickel then gives secondary alchohols in 96–98% ee, with overall reduction of both alkene and ketone groups.



100% de

100% de

Scheme 35



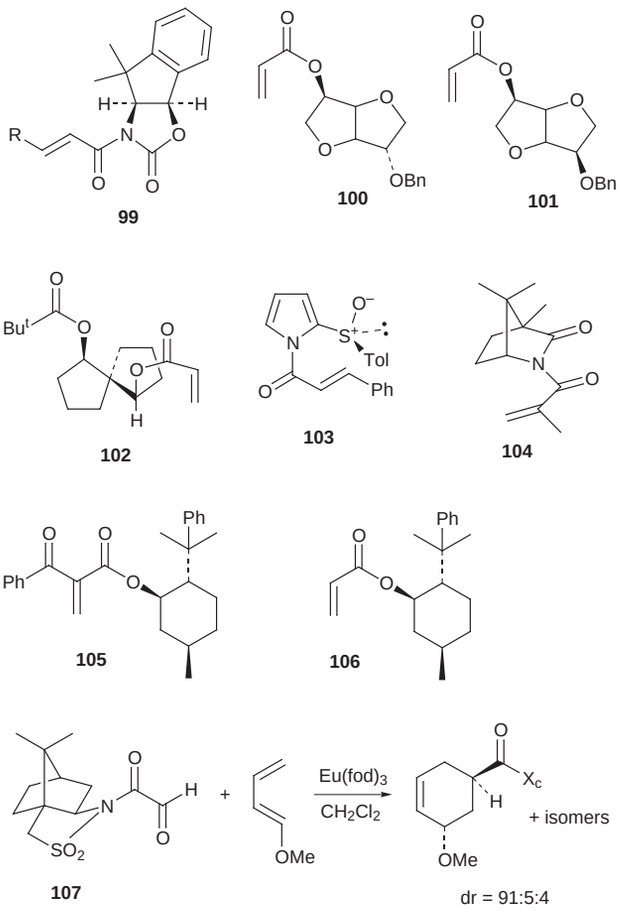
98

Scheme 36

2.6 Cycloaddition reactions

The majority of asymmetric Diels–Alder reactions employing chiral auxiliaries have the auxiliary attached to the dienophile, and there are several new examples of these. The aminoindanol-derived oxazolidinones **99** have a *gem*-dimethyl group to increase steric shielding on one face of the alkene, and give selectivities of 96:4 to >99:1 in reactions with both cyclic and acyclic dienes, using Et_2AlCl as a Lewis acid.[79] The acrylate ester **100** has been investigated because the parent chiral diol, isosorbide, is readily available in large quantities at low cost.[80] Using $SnCl_4$ as the Lewis Acid, Diels–Alder reaction of **100** with cyclopentadiene gives the *(S)-endo* product in 96:4 dr. However, the closely related epimeric isomannide acrylate **101** gives the *(R)-endo* adduct in 95:5 dr, using $EtAlCl_2$ as the Lewis acid. The dienophile **102** is the monoacrylate monopivalate diester of a chiral spiro-fused diol, and reacts, also with cyclopentadiene, to give the *endo*-adduct in >97% de using BCl_3 as the Lewis acid.[81] A chiral sulfoxide is the auxiliary in the *N*-acylated pyrrole **103**,[82] which gives >99% de in the *endo* adduct with cyclopentadiene, with $AlCl_3$ as the Lewis acid, and is one of the few examples of a dienophile with a sulfoxide auxiliary which is recoverable. The *N*-methacryloyl bicyclic lactam **104** shows complete diastereofacial selectivity in addition to an acyclic silyloxy-activated triene, and this was used as a key step in the synthesis of (−)-cassioside.[83] In the Diels–Alder addition of the α-methylene-β-ketoester of 8-phenylmenthol **105** with cyclopentadiene, either the ketone or the ester group of the dienophile could become the *endo*-substituent.[84] Using $FeCl_2I$ as the Lewis acid results in an *endo:exo* ratio of >99:1 for the ester group, and also complete diastereoselectivity. Asymmetric Diels–Alder reactions using furan as the dienophile are usually difficult, because furan is sensitive to many Lewis acids, chiral acrylate esters often react slowly with furan, and the adducts often readily undergo the reverse reaction, precluding kinetic control of the diastereoselectivity. However, 8-phenylmenthyl acrylate **106** has been found to react with furan using titanium or zinc halides supported on silica gel as Lewis acids, giving mixtures of *endo* and *exo* adducts with reasonable diastereoselecitivities (up to 70% de).[85]

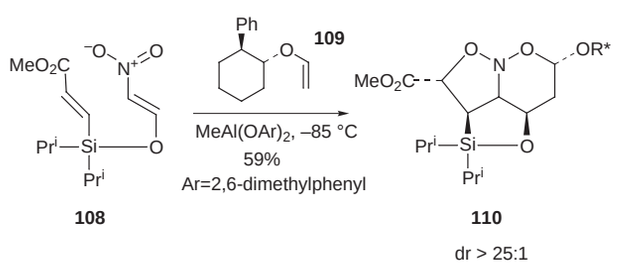
Hetero-Diels–Alder reactions between the *N*-glyoxyloyl Oppolzer sultam **107** and either 1-methoxybutadiene or Danishefsky-type 1-methoxy-3-silyloxydienes have been found to be highly diastereoselective when promoted by catalytic $Eu(fod)_3$ (Scheme 37).[86,87] However, when the diene is changed to 2-(trimethylsilyloxy)furan, a Diels–Alder reaction does not



Scheme 37

occur; instead there is addition of the furan to the aldehyde to give a γ-substituted butenolide in 90% de.[88]

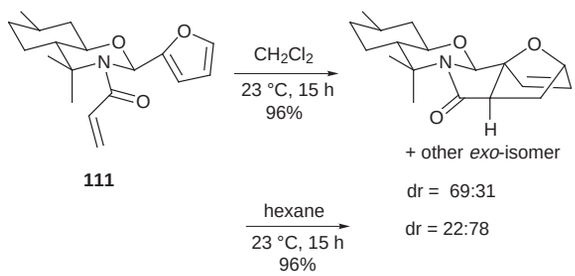
In the tandem reaction shown in Scheme 38 the vinyl ether of 2-phenylcyclohexanol **109** first acts as a dienophile in an intermolecular hetero-Diels–Alder reaction with the unsaturated nitroalkene **108**, and this is followed by an intramolecular [3+2] cycloaddition of the adduct with the unsaturated ester portion, which is held by a temporary silicon tether.[89] The product **110**, formed in >25:1 dr, is the key intermediate in a synthesis of (−)-detoxinine, and the same strategy has also been used for a synthesis of (−)-mesembrine.[90]



Scheme 38

Chiral auxiliaries attached to the diene component in Diels–Alder reactions are rather less common. A tartrate-derived dienyl boronate adds to methyl crotonate to give a cyclohexenyl boronate, which is then employed in a tandem addition to an aldehyde in 70% ee.[91] Dienes with a camphor-derived sulfinyl group at the 2-position give excellent selectivity (>99:1) in addition to *N*-phenylmaleimide as the dienophile, provided that $LiClO_4$ is used as a catalyst, however the auxiliary has not been removed from the products.[92]

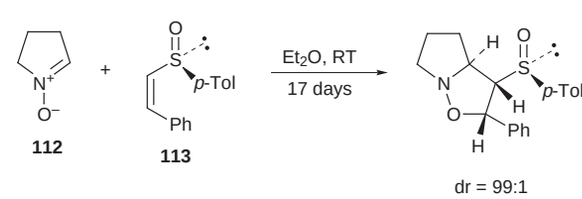
An interesting intramolecular Diels–Alder reaction of **111** allows reaction between a furan as the diene and acrylic acid as the dienophile, tethered together using 8-aminomenthol as the auxiliary (Scheme 39).[93] The reaction proceeds under very mild conditions, and by changing the solvent, either of the two *exo*-isomers can be produced selectively. These can be separated, and give enantiomeric products after cleavage of the auxiliary.



Scheme 39

The SAMP auxiliary, which has already been discussed in Section 2.2.1, has also been used as a chiral auxiliary attached to C-2 of a diene in a hetero-Diels–Alder reaction with *N*-silylimines, giving piperidine-4-ones after hydrolytic workup in moderate to very high enantiomeric excesses.[94]

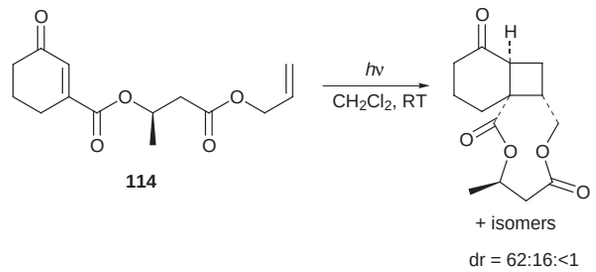
α,β-Unsaturated *N*-acyloxazolidinones, which have previously been used as dienophiles, can also serve as dipolarophiles in [3+2] cycloaddition reactions with azomethine ylides.[95] The products are chiral disubstituted pyrrolidines, and are formed in 56:44 to 80:20 dr. Vinyl sulfoxides are also effective chiral dipolarophiles in [3+2] cycloadditions to cyclic nitrones **112** (Scheme 40),[96] with the best selectivity being achieved using the (*Z*)-vinyl sulfoxide **113**. The six-membered ring homologue of **112** is also effective, giving products which can be transformed into piperidine alkaloids. The cyclic nitrone **112** also reacts with acrylates of chiral 9-anthrylalcohols as the dipolarophiles,[97] but this gives all four possible isomers (two regioisomers, each formed as two diastereoisomers), with the best ratio being 70:11:15:4.



Scheme 40

The [2+2] cycloaddition of ketenes to imines (the Staudinger reaction) is an important method for the construction of β-lactams, and use of either the ketene or the imine as a chiral component has already been extensively investigated. Recent developments include a study of double diastereodifferentiating reactions, where both components are chiral.[98] Use of an Evans' oxazolidinone auxiliary in the ketene component usually dominates the effect of a stereogenic centre in the imine, even when mismatched, but its influence can be overcome by using two stereogenic centres in the imine. Use of an *N*-[bis-(trimethylsilyl)methyl] protecting group on the imine component of this type of reaction has proved beneficial in supressing deprotonation at the α-position.[99]

Intramolecular [2+2]-photocycloadditions have been investigated using a chiral auxiliary to form a removable tether between the two components.[100] For example, the 3-hydroxybutyrate-derived diester **114** undergoes only one regioisomeric mode of cycloaddition (Scheme 41), and the tether can subsequently be removed with sodium methoxide. Intramolecular [2+2]-photocycloadditions using chiral trimethylsilylallenes as one component result in chirality transfer from the allene to the newly formed cyclobutane in a "self-immolative" fashion,[101]

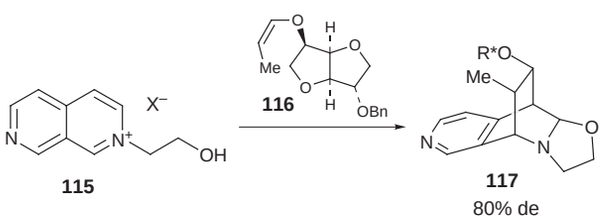


Scheme 41

where the silyl group is designed to be easily removed afterwards.

The Pauson–Khand reaction is one of the most widely used transition metal mediated cycloaddition reactions, and asymmetric versions have been developed using chiral alkoxy groups on either the alkene or alkyne component. By using a cleavable sulfide tether, the resulting cyclopentenones can undergo conjugate addition and reductive cleavage to generate quaternary stereogenic centres, exemplified by a synthesis of (+)-β-cuparenone.[102]

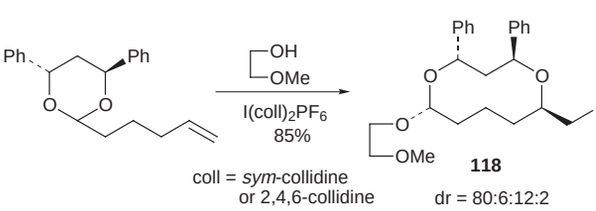
(*Z*)-Enol ethers, *e.g.* **116** have been formed using a wide variety of different chiral alcohols as possible auxiliaries, and then used in Bradsher cycloaddition reactions to the naphthyridinium salt **115** (Scheme 42).[103] Best results are obtained using isosorbide and isomannide enol ethers, which give the bridged isoquinoline derivatives **117** in 80% de.



Scheme 42

2.7 Other addition reactions

The reaction shown in Scheme 43 is interesting in that the acetal chiral auxiliary first directs the formation of one stereogenic centre during the haloetherification step, and then the resulting oxonium ion undergoes stereoselective addition of an alcohol to give **118**.[104] The iodide in **118** can be replaced by a nucleophile, and this can then be followed by Grignard reaction at the acetal carbon with retention of stereochemistry, giving chiral 1,4- and 1,5-diols after reductive cleavage of the auxiliary.

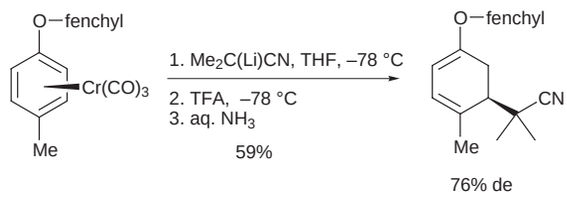


Scheme 43

Electrophile-induced cyclisation of alkenes can also be achieved by the reaction with chiral selenyl chlorides in up to 93:7 dr.[105] Chiral 1,4-diols have also been prepared with complete stereoselectivity by hydrogenation of *exo*-alkylidenebutyrolactones containing a menthyl auxiliary, followed by hydride reduction.[106] Hydrogenation of glucose-derived enol ethers conjugated to a carbonyl group shows diastereoselectivities ranging from 85:15 to 67:33, but the ratios can be improved by fractional crystallisation.[107]

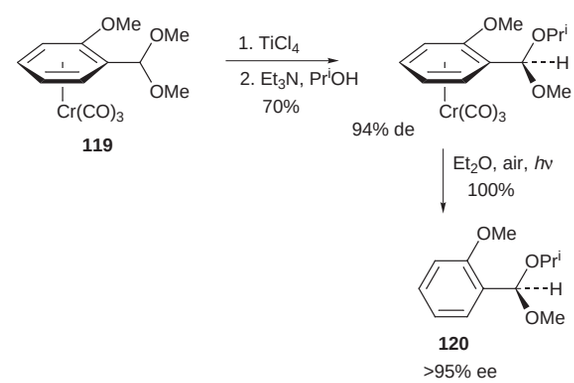
Chiral acetals of cyclic α,β-unsaturated ketones undergo Simmons–Smith cyclopropanation with a stereoselectivity which can be tuned up to >98% de by varying the size of alkoxy substituents on the acetal.[108]

Two groups have reported the asymmetric addition of lithiated 2-methylpropionitrile to chiral alkoxyarene–chromium tricarbonyl complexes in up to 76% de (Scheme 44).[109,110] The chiral ether is rather remote for control of the new stereogenic centre, but the reactions appear to be under thermodynamic control, and so simply reflect the relative stability of the two diasteroisomeric products.



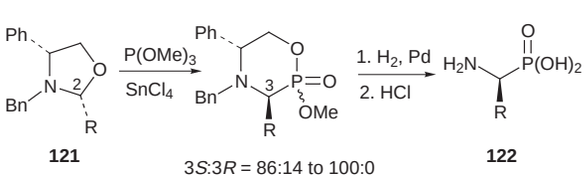
Scheme 44

Enantiopure arene chromium tricarbonyl complexes are also used in the first synthesis of chiral acetals, *e.g.* **120**, in which the acetal carbon is the only stereogenic centre (Scheme 45).[111] The chromium tricarbonyl unit in **119** effectively shields one face of an intermediate oxocarbenium ion during nucleophilic addition of the alcohol. Chiral acetals of unsubstituted benzaldehyde can also be prepared by using a trimethylsilyl group in place of the *o*-methoxy group, and removing it with TBAF as the final step. A more complex example, also containing an acetal carbon as the stereogenic centre, involves reaction of an alcohol with an α-bromoether attached to Boeckman's camphor-derived lactam auxiliary, and gives the acetal in 96:4 dr.[112]



Scheme 45

A novel synthesis of biologically important chiral α-aminophosphonates **122** involves the insertion of trimethyl phosphite into the C–O bond of oxazolidines **121** (Scheme 46).[113] Inversion of configuration at C-2 suggests that the reaction proceeds *via* ring opening, formation of a mixed phosphite ester, followed by addition of the phosphorus atom to an iminium species.

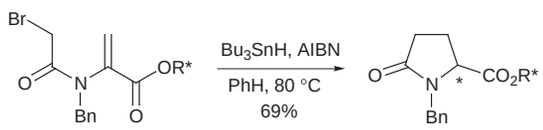


Scheme 46

2.8 Radical reactions

Radical cyclisation of the dehydroalanine derivatives **123** uses ester-based chiral auxiliaries to control the stereoselectivity

(Scheme 47).[114] The best diastereoselectivity of 4:1 is obtained using 8-phenylmenthyl esters, with the menthyl esters being less effective (1.75:1). An alternative approach to the synthesis of similar chiral 2-pyrrolidinones is an intermolecular allylation of a pyrrolidinone radical containing a substituted 1-phenylethyl group on the nitrogen atom as the chiral auxiliary; however the selectivities obtained so far are rather low.[115]

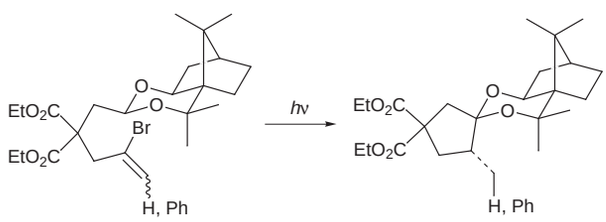


123
R* = 8-phenylmenthyl

dr = 4:1

Scheme 47

Radical cyclisation of acyl radical equivalents has been achieved using the vinyl bromides **124** shown in Scheme 48, where hydrogen atom transfer to the initially formed vinyl radical creates an acetal-carbon-centred radical, which subsequently undergoes cyclisation onto the alkene.[116,117] Rigid dioxanyl radicals (*e.g.* from **124**) which are constrained to a chair conformation give high diastereoselectivities, whereas simple chiral dioxanes formed from C_2-symmetric diols are ineffective.



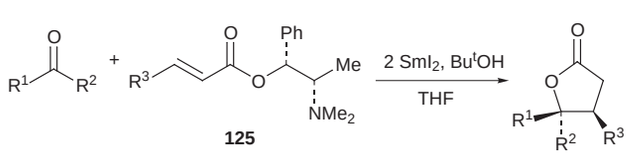
124

100% de

Scheme 48

Aldol-type products can be formed by the intermolecular addition of an alkoxy-centred radical (in a Barton-type procedure) bearing a glucal-derived chiral auxiliary to 2-nitropropene, followed by hydrolysis of the resulting nitro thioether group.[118]

A particularly simple synthesis of chiral γ-butyrolactones **126** involves reaction of acrylate or crotonate esters of *N*-methylephedrine **125** with ketones mediated by SmI_2 (Scheme 49).[119] Initial formation of a ketyl radical by one-electron transfer to the ketone is followed by coupling with the ester **125** and cleavage of the auxiliary, to give the chiral products **126** in one step and in high enantioselectivities (mostly 93–99% ee).



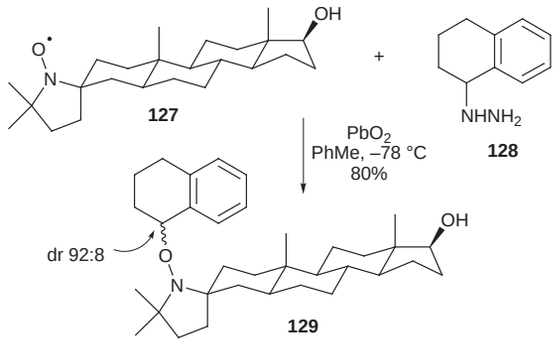
125

126

mostly 93-99% ee

Scheme 49

An unusual approach to asymmetric synthesis involves the intermolecular reaction of a long-lived chiral radical with another radical (Scheme 50).[120] Here the conformationally rigid nitroxyl radical **127** reacts with the benzylic radical generated from the hydrazine **128** to give **129** in 92:8 dr. Nitroxyl radicals with greater conformational mobility were initially studied, but they are much less selective.



127

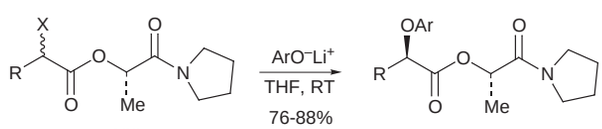
128

129

Scheme 50

2.9 Miscellaneous uses of chiral auxiliaries

The use of amino acids and their derivatives as chiral auxiliaries in a wide variety of asymmetric reactions has been reviewed.[121] Synthesis of α-amino acids using reaction of a chiral electrophilic glycine equivalent with Grignard reagents has been reported, with moderate diastereoselectivities ranging from 2.8:1 to 5.5:1.[122] α-Aryloxyesters **131** can be prepared by substitution reaction of esters **130** formed from *racemic* α-haloacids and a lactate-derived auxiliary (Scheme 51).[123] The two diastereoisomers of **130** (or a corresponding intermediate) react with the aryloxide at very different rates, with epimerisation of the slower reacting isomer.



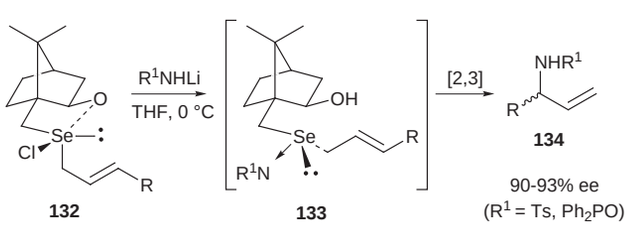
130

131

dr 95:5 to 99:1

Scheme 51

The allyl selenenimides **133**, prepared by nucleophilic substitution of the chloroselenuranes **132** with protected lithium amides, undergo a highly selective [2,3]sigmatropic rearrangement, with chirality transfer from the stereogenic selenium atom to give the chiral protected allylic amines **134** *via* an *endo* transition state (Scheme 52).[124] Enantiomerically pure allyl sulfoximines do not undergo significant rearrangement at room temperature, however S_N2' reaction with butylcopper gives alkenes in high enantioselectivity from the (*Z*)-sulfoximines, where the stereoselectivity is controlled by a chiral leaving group.[125] The corresponding (*E*)-isomers react much less selectively.



132

133

134

90-93% ee
(R^1 = Ts, Ph_2PO)

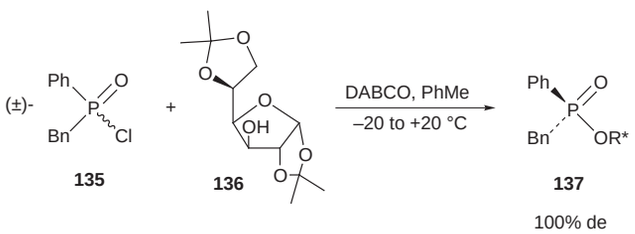
Scheme 52

Other rearrangements controlled by chiral auxiliaries include a vinyl epoxide attached to an Evans' acyl oxazolidinone, which rearranges to the dihydrofuran on heating to 180 °C.[126] The stereoselectivity is modest (*e.g.* 57:33:6:4), but the diastereoisomers can be separated by flash chromatography. Enolate Claisen rearrangements can be controlled by an η^4-diene iron(tricarbonyl) unit as the chiral auxiliary, with the newly formed C–C bond developing *anti* to the $Fe(CO)_3$ substituent.[127]

Formation of enantiomerically pure 1,3-dithiane 1-oxide by

direct asymmetric oxidation of 1,3-dithiane itself occurs with low selectivity, however attachment of a chiral auxiliary derived from camphor or diacetone glucose at the 2-position allows highly diastereoselective oxidations.[128] Interestingly, the best selectivities are observed using Sharpless oxidation conditions, but the same isomer is obtained irrespective of which enantiomer of diethyl tartrate is used. The auxiliary is then removed by base-catalysed hydrolysis.

Preparation of the chiral phosphinate ester **137**, which has a stereogenic phosphorus atom, can be achieved with complete diastereoselectivity by reaction of diacetone glucose **136** with the *racemic* chloride **135** (Scheme 53).[129] Chiral phosphinous esters can be formed similarly, and phosphines and phosphine oxides can be formed from the products with inversion of configuration, by displacement of the auxiliary with organolithium reagents.



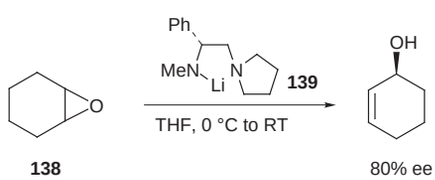
Scheme 53

3 Chiral reagents

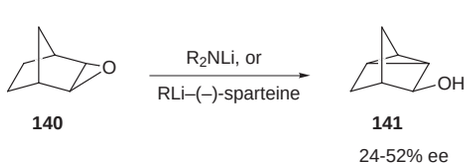
3.1 Chiral bases

The asymmetric deprotonation of cyclohexene oxide **138** was one of the first examples of the use of chiral lithium amide bases, and Singh and co-workers have revisited this reaction comparing a variety of bases derived from phenylglycine (*e.g.* **139**), which is available as both enantiomers at similar cost (Scheme 54).[130] This work has also been extended to the enantioselective deprotonation of 4-substituted cyclopentene oxides in order to prepare prostaglandin intermediates. O'Brien and Poumellec have also used the base **139** for the deprotonation of dioxygenated cyclohexene oxides in up to 92% ee.[131] *exo*-Norbornene oxide **140** undergoes deprotonation–rearrangement to give **141** in up to 52% ee using chiral lithium amide bases or an organolithium in the presence of (−)-sparteine (Scheme 55).[132] If the two *endo*-protons are replaced by methyl groups, then rearrangement of the epoxide to a ketone occurs instead in 35% ee.[133] Enantioselective deprotonation of medium ring *meso*-epoxides using organolithium reagents and (−)-sparteine results in bicyclic alcohols rather than simple ring opening of the epoxide, in up to 83% ee for the nine-membered ring.[134]

The asymmetric deprotonation of 4-substituted cyclohexanones has been previously studied by several groups, and by



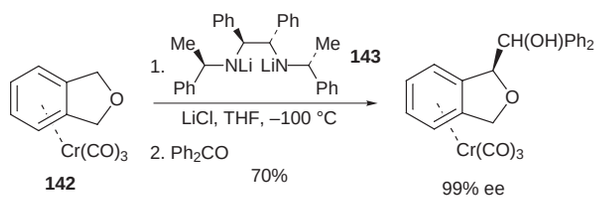
Scheme 54



Scheme 55

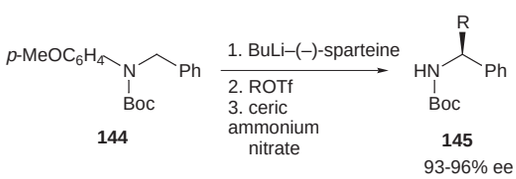
examining the NMR spectra of several analogues of a phenylalanine derived lithium amide base, together with a comparison of their enantioselectivities, Koga and co-workers have proposed an eight-membered cyclic transition state for this reaction.[135]

Several groups have reported on the asymmetric deprotonations of various arene chromium tricarbonyl complexes. Deprotonation at the benzylic position of the isobenzofuran complex **142** using the lithium amide **143** followed by reaction with benzophenone occurs in 99% ee (Scheme 56),[136] and in 75–80% ee using a simpler base and several different electrophiles.[137] Chromium tricarbonyl complexes of benzyl ethers are also deprotonated using **143** with very high enantioselectivities.[138] Benzaldehyde acetal complexes can be deprotonated at the *ortho*-position using either a chiral lithium amide[136] or a chiral organolithium reagent prepared from 8-phenylmenthyl chloride.[139]



Scheme 56

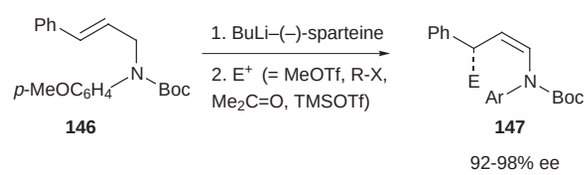
Beak and co-workers have extended their work on the enantioselective deprotonation of *N*-Boc-benzylamines using organolithium reagents in the presence of (−)-sparteine to the *p*-methoxyphenyl-protected example **144**, shown in Scheme 57.[140] Alkyl triflates give higher enantioselectivities than alkyl halides, and the *p*-methoxyphenyl group can then be removed oxidatively to give the *N*-Boc-protected primary amines **145**. By reacting with Me_3SnCl as the electrophile, followed by transmetallation of the product with BuLi, products with the opposite configuration can also be accessed. Carboxylation of deprotonated benzylamine **144** with carbon dioxide gives an α-amino acid derivative in 96 : 4 er, whereas changing the electrophile to methyl chloroformate gives the corresponding methyl ester of the opposite enantiomer.[141] Alternative electrophiles can also be used to give β- and γ-amino acid derivatives.



Scheme 57

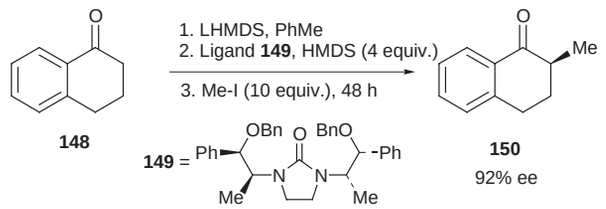
The cinnamylamine derivative **146** undergoes a similar enantioselective deprotonation, and reaction with electrophiles usually occurs at the γ-position to give the enecarbamates **147** (Scheme 58).[142] Again, the opposite enantiomer of **147** is accessible *via* the intermediate γ-stannylated compound. Enantioselectivities of these types of reactions involving chiral benzyllithium species complexed with sparteine can be affected by equilibration, and also by kinetic resolution in reactions with limiting quantities of the electrophile.[143]

Alternatives to the naturally-occurring sparteine as a chiral



Scheme 58

solvating agent are the synthetic cyclic ureas (*e.g.* **149**) prepared by Koga and co-workers.[144] Reaction of the lithium enolate of tetralone **148** with methyl iodide in the presence of **149** gives **150** in 92% ee (Scheme 59). The enantioselectivity is affected by the base used to generate the enolate, being higher for LiHMDS than LDA or LiTMP, and it is also improved by the addition of HMDS.

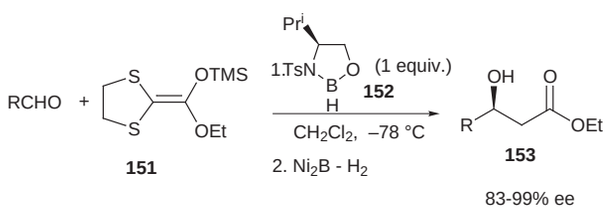


Scheme 59

The deprotonation–cyclisation of *O*-tosylketoximes using chiral amine bases has been reported.[145] The *O*-tosylketoximes are formed from β-ketoesters which allows the doubly-activated α-position to be deprotonated by tertiary amine bases. 2*H*-Azirines are formed in up to 80% ee using quinidine as the chiral base, which was found to be the most effective among several naturally occurring chiral amines tested.

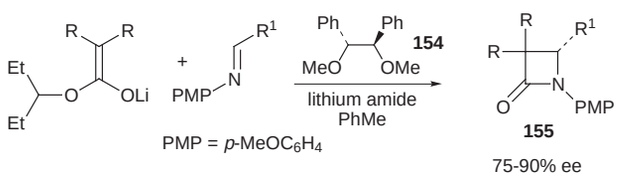
3.2 Miscellaneous uses of chiral reagents

Asymmetric aldol reactions of acetate enolate equivalents attached to chiral auxiliaries often use alkylthio groups as "dummy" substituents at the α-position to enhance stereoselectivity, and the same strategy has been used for aldol reactions using chiral reagents. In Scheme 60 an achiral dithiolane ketene acetal **151** undergoes an aldol reaction promoted by the oxazaborolidine **152**, and subsequent reductive removal of the dithiolane gives the acetate aldol **153**.[146] A similar strategy can be applied to (methylthio)acetic acid involving formation of an intermediate chiral boron enolate with terpene-derived ligands on the boron atoms.[147]



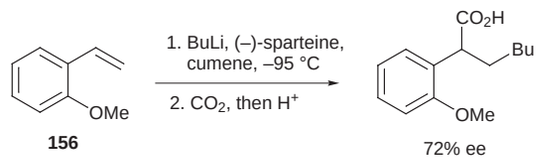
Scheme 60

Addition of lithium enolates of esters to imines mediated by a chiral C_2-symmetric ether **154** results in β-lactams **155** in up to 90% ee (Scheme 61).[148] Addition of extra lithium amide base over that required to generate the enolate improves the enantioselectivity, and the chiral ligand **154** also enhances the reactivity of the enolate complex at low temperatures. Another addition to imines involves chiral menthone-derived boron enolates of α-halothioesters, where the products can subsequently be cyclised to give aziridines in 94–99% ee.[149] Lithium enolates, this time of aryl methyl ketones, are also involved in asymmetric Michael addition to doubly-activated electrophiles, promoted by a chiral chelating amine, in up to 94% ee.[150]



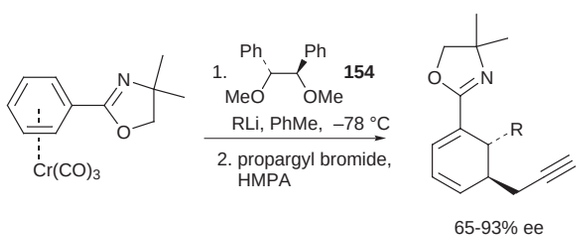
Scheme 61

Addition of organolithium reagents to carbonyl groups in the presence of chiral ligands has been one of the longest-studied processes in asymmetric synthesis. New examples include the addition of lithium trimethylsilylacetylide to cyclohexanones using proline-derived chelating amines.[151] The chiral ether **154** (which was used above for addition of an enolate to an imine) has also been used to control the ring opening of cyclohexene oxide by phenyllithium, in moderate enantioselectivity of 43%.[152] A more unusual reaction of organolithium reagents is the addition to styrenes, *e.g.* 2-methoxystyrene **156** (Scheme 62) in the presence of (−)-sparteine, where the electrophilic trapping with CO_2 is the enantioselective process.[153] Other 2-substituted styrenes and styrene itself are less effective.



Scheme 62

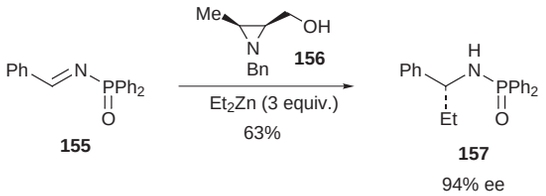
Addition of organolithium reagents to prochiral arene chromium tricarbonyl complexes is mediated by chiral ligands, and is followed by electrophilic trapping to give substituted cyclohexadienes (Scheme 63).[154] The chiral ether **154** again features, and is the best ligand among four that were investigated.



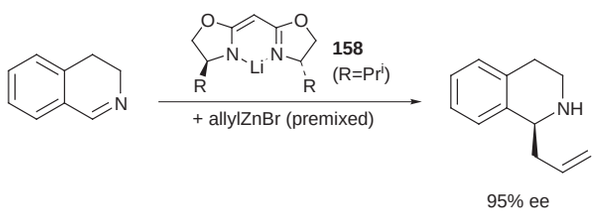
Scheme 63

Other types of organometallic reagents used with chiral ligands include organocerium reagents in the presence of TADDOLs (tetraaryl-1,3-dioxolane-4,5-dimethanols), which add to aldehydes in up to 92% ee.[155,156] Asymmetric reactions of diethylzinc are usually additions to aldehyes with catalytic amounts of chiral ligands. However the addition of diethylzinc to imine **155** shown in Scheme 64 uses a stoichiometric amount of the chiral aziridine **156** as the ligand, forming the amine **157** in 94% ee.[157] Another addition of organozinc reagents to imines (Scheme 65) uses an allylzinc reagent and a lithiated bis-oxazoline ligand **158** (R = Pr^i), previously used by the same group for addition of allylzinc reagents to cyclopropenone acetals.[158] Addition to the acyclic *(E)*-*N*-phenyl benzaldehyde imine gives little enantioselectivity, but much better results are obtained with cyclic imines, which are geometrically constrained to the (*Z*)-geometry. A very similar lithiated bis-oxazoline ligand to **158** (R = Ph) has also been used by Hanessian and Yang for the addition of allylzinc reagents to oximes of α-ketoesters.[159] The bis-oxazoline **159** (which is lithiated to form **158**) has also been used as a chiral ligand for a zinc Lewis acid in the radical allyl transfer reaction shown in Scheme 66.[160] Better enantioselectivities are observed in this reaction when the intermediate radical is generated by Michael addition rather than bromine atom abstraction.

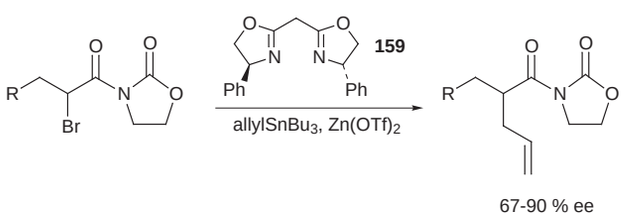
An intermediate *N*-sulfonylimine undergoes addition of organoaluminium reagents formed from trimethyl- or triethylaluminium and binaphthol in 52–62% ee.[161] Six different ligands have been investigated for the asymmetric addition of lithium dimethylcuprate to chalcone, in order to tune the enantioselectivity, which is 90% in the best case.[162] The same



Scheme 64



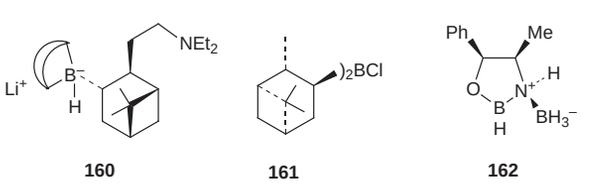
Scheme 65



Scheme 66

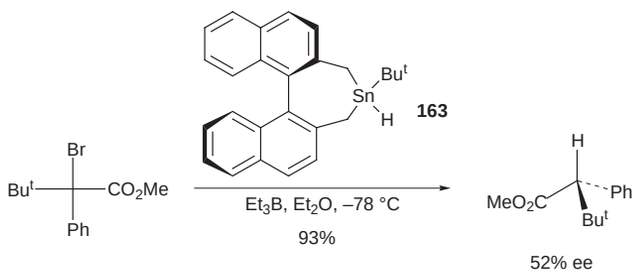
ligand also mediates the addition of magnesium dibutylcuprate to cyclohexenone in 96% ee.

The use of metal hydride reagents bearing a chiral ligand for the asymmetric reduction of ketones has been a popular approach for many years, however reduction of simple straight-chain aliphatic ketones is often difficult. A new chiral borohydride reagent **160**, where the ligand is derived from β-pinene, shows better selectivity for the reduction of octan-2-one than Midland's similar benzyloxy reagent.[163] The neutral borane (+)-*B*-chlorodiisopinocampheylborane (Ipc_2BCl) **161** gives poor selectivities in the reduction of unhindered dialkyl ketones; however reduction of α- and β-hydroxyketones with this reagent is much better (84–92% ee) since initial formation of a borinate allows reduction to occur in an intramolecular fashion.[164] The same reagent **161** also reduces diacylaromatic compounds to chiral C_2-symmetric diols in >99% ee, with only small amounts of the *meso*-diols being formed.[165] Asymmetric reduction using borane together with a chiral oxazaborolidine has previously been applied to many ketones and has been extended to the case of α-alkynylketones, which are reduced in 71–98% ee using an excess of the chiral ligand.[166] Asymmetric reduction of a C=N bond in oxime ethers can also be achieved using a chiral borane reagent **162**, which is prepared *in situ* from borane and norephedrine.[167]



Asymmetric hydroboration of alkenes using pinene-derived reagents has been studied extensively, and Brown and co-workers have now reported on a comparison of methods for the synthesis of optically pure isopinocampheylchloroborane (IpcBHCl) and have also compared IpcBHCl with $IpcBH_2$ for the hydroboration of representative alkenes.[168] The corresponding bromo-compound IpcBHBr has also been prepared, and reacts with alkenes at lower temperatures than does IpcBHCl, and often with higher enantioselectivities.[169]

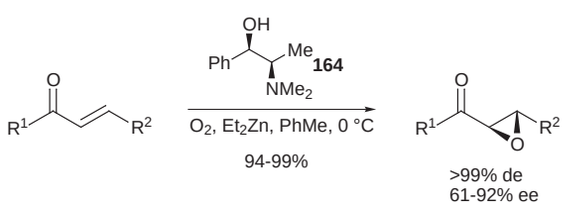
Asymmetric hydrogen transfer from a chiral tin hydride to a prochiral radical has been achieved using the stannane **163**, which incorporates a binaphthyl unit (Scheme 67).[170] Although the enantioselectivity is modest, the tin hydride **163** can be regenerated with sodium cyanoborohydride with retention of configuration, allowing it to be used catalytically, and with the same enantioselectivity as for the stoichiometric reaction.



Scheme 67

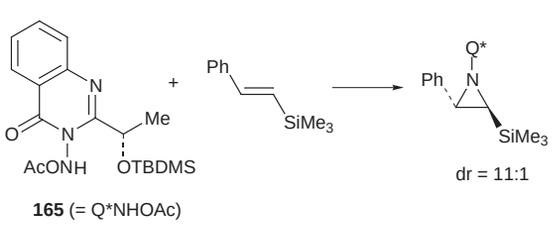
The asymmetric α-hydroxylation of 2′,4′-difluoropropiophenone using a camphorsulfonyl oxaziridine has been optimised from previously used literature conditions, including efficient recycling of the oxaziridine reagent, and this has allowed scale-up to the multi-kilo level for the preparation of potential antifungal drugs.[171]

A new method for asymmetric epoxidation of α,β-unsaturated ketones uses molecular oxygen as the oxidant, together with diethylzinc and *N*-methylpseudoephedrine **164** (Scheme 68).[172] In order to arrive at the use of **164**, 35 chiral alcohols were screened, together with 8 solvents. The enantioselectivities are mostly good (82–92%) except when the β-substituent on the enone is phenyl (61% ee). A chiral (ethylperoxy)alkoxyzinc species is proposed as the reactive intermediate.



Scheme 68

The asymmetric aziridination of β-trimethylsilylstyrene using the chiral acetoxyaminoquinazolinone **165** is much more selective than with the analogous reagent where the chiral centre has a bulky alkyl (Bu^t) substituent instead of the silyloxy substituent (Scheme 69).[173] This difference has been accounted for in terms of a preference for the C–O bond to eclipse the C=N bond of the heterocycle, and this is supported by a crystal structure.



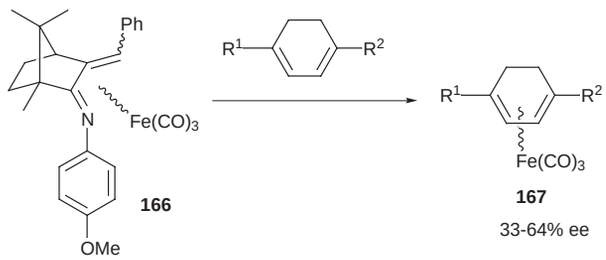
165 (= Q*NHOAc)

Scheme 69

Asymmetric cyclopropanation of allylic alcohols using a chiral dioxaborolane and $Zn(CH_2I)_2$ has been extended to cases where the substrate also contains other alkene double bonds.[174]

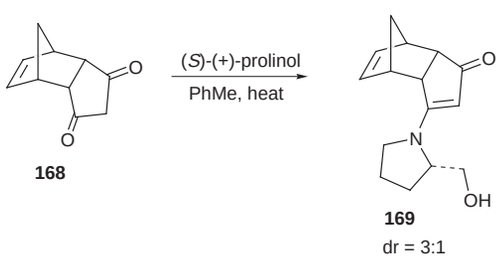
In most cases high chemoselectivity for the allylic alcohol is observed, with both conjugated and isolated polyenes, and in one problematic case, a glucose-derived auxiliary was superior to the chiral reagent.

Formation of optically active 1,3-diene irontricarbonyl complexes **167** directly from the corresponding prochiral dienes is possible using a chiral irontricarbonyl transfer reagent (Scheme 70).[175] The structure of the reagent is presumed to be **166**, although it has not been characterised, because of its air sensitivity and low stability.



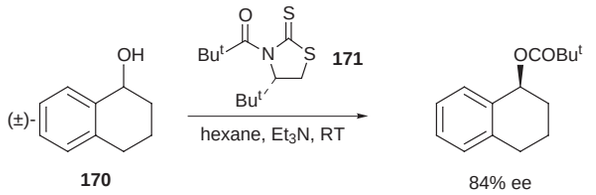
Scheme 70

Desymmetrisation of *meso*-substrates is a useful approach to chiral products, since, unlike resolution of racemic compounds, 100% conversion to a single enantiomer is possible, at least in principle. The *meso*-diketone **168** actually exists as a rapidly-equilibrating mixture of enols, and formation of the enamine **169** with prolinol occurs with a dr of 3:1 (Scheme 71).[176] The mixture can be enriched in the major diastereoisomer by fractional crystallisation, or alternatively, complete separation is possible by chromatography of the acetates. Tricyclic norbornane-derived *meso*-anhydrides have previously been desymmetrised by amide formation with methyl prolinate, and this approach has been extended to bicyclic anhydrides.[177] *tert*-Butyl prolinate has some practical advantages in this case, facilitating separation of the diastereoisomeric products, and in the case of a bridged bicyclic anhydride, complete diastereoselectivity is observed.



Scheme 71

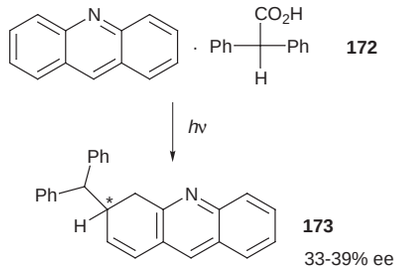
Kinetic resolution of secondary alcohols using the chiral acylating agent **171** gives widely varying enantioselectivities (19–84% ee) with different alcohols (Scheme 72), and the alcohol **170** gives much the best results.[178] In some cases, addition of MeMgBr as a base reverses the enantioselectivity.



Scheme 72

5 Miscellaneous asymmetric processes

An unusual example of absolute asymmetric synthesis (no chiral reagent or catalyst) is shown in Scheme 73, and relies on a two-component molecular crystal **172**.[179] Diphenylacetic acid forms achiral crystals, but when crystallised with acridine, the two-component molecular crystal **172** is chiral, and can be produced in either enantiomeric form by seeding methods. Photolysis of a pulverised single crystal of one enantiomeric form then causes decarboxylation and formation of **173** in about 35% ee.



Scheme 73

Enantiomeric enrichments of racemic compounds using circularly polarized light (CPL) usually give very low levels of enrichment (mostly <3% ee), and this may be due, at least in part, to the low intensities of light used, and to the use of mixed wavelengths.[180] Photolysis of a solution of DL-tartaric acid with high intensity right-CPL from an XeF excimer laser gives improved levels of enrichment of D-tartaric acid (about 7.5% ee), probably by selective decomposition of the L-isomer.

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