Asymmetric Processes

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Reviewing the literature published between January 1994 and March 1995

1 Introduction

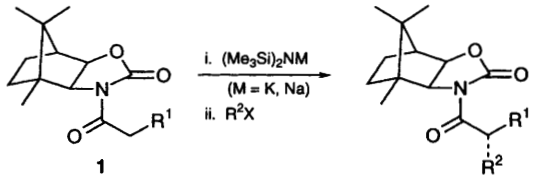
This review covers the literature from January 1994 to March 1995. Since asymmetric synthesis is such an active area, it would be impossible to be exhaustive, and a highly selective choice of examples has had to be made.

2 Chiral auxiliaries

2.1 Reactions of enolates

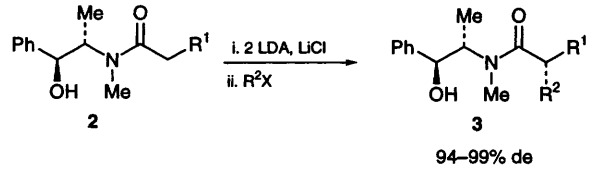
2.1.1 Alkylation

New chiral auxiliaries for the alkylation of enolates continue to appear, with various advantages being claimed for their use. The camphor-derived acylated auxiliary **1** gives uniformly high diastereoselectivities (>99.1:0.1) for alkylations of the sodium or potassium enolates, with only one example of slightly worse selectivity, of 99:1 for reaction with methyl iodide (**Scheme 1**).[1] It is noteworthy that such high selectivities are obtained even for reactions with small electrophiles (such as methylation) since this is not the case for some widely used auxiliaries. Conjugate addition of the enolates to crotonate derivatives is also described, and the auxiliary is removed conventionally by reduction with $LiAlH_4$.



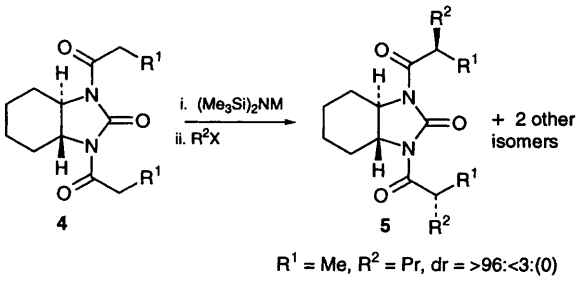
Scheme 1

The use of pseudoephedrine as a chiral auxiliary for alkylations has been advocated by Myers.[2] It was found to be superior to ephedrine, giving different selectivities, and also conferring crystallinity on the derivatives. As with ephedrine, both enantiomers are available at a similar price to each other, although pseudoephedrine is currently substantially more expensive than ephedrine. Alkylations of the lithium enolates of *N*-acylpseudoephedrines **2** proceed in selectivities of 94 to >99% de, with lithium chloride being used to accelerate the reactions (**Scheme 2**). The auxiliary can be removed from the products **3** by several different methods, such as acidic hydrolysis, or reduction with either borane–lithium pyrrolidide or $LiAl(OEt)_3H$. It is also possible to convert the products directly into aldehydes (with $LiAlH_4$ + EtOAc) or ketones (with RLi).



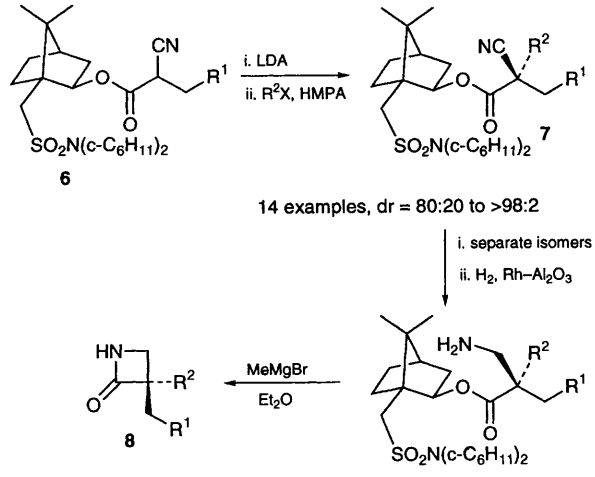
Scheme 2

Davies has introduced the cyclic urea derivative of *trans*-cyclohexane-1,2-diamine as an auxiliary with C_2 symmetry.[3] Both nitrogen atoms can be reacted to give the diacyl derivative **4**, and both acyl groups can be alkylated *via* a chelated bis-*syn*-enolate (**Scheme 3**). The C_2 symmetry means that there are only three possible diastereoisomers of the alkylation products **5**, and the diastereoselectivity of each alkylation is greater than the ratio of isomers of products obtained (for example a ratio of products of 85:14:1 represents a 92:8 selectivity at each alkylation). The auxiliary is removed reductively using Et_3B–AcOH followed by $LiAlH_4$. The thione analogues were also investigated, but proved not to be useful because the enolates decompose.



Scheme 3

The alkylation of 2-cyano esters of an isoborneol sulfonamide auxiliary **6** gives moderate (80:20) to good (>98: 2) diastereoselectivities (**Scheme 4**).[4] The isomers **7** can be separated and then, unusually,



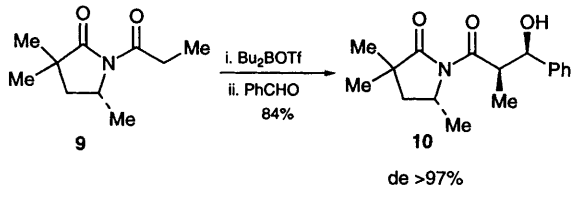
Scheme 4

the auxiliary is removed by hydrogenation of the nitrile, followed by cyclisation to form enantiomerically pure disubstituted β-lactams **8**.

A new benzopyranoisoxazolidinone auxiliary for amide enolate alkylations has been reported;[5] rather than being derived from a starting material from the chiral pool, it is prepared in racemic form by a [3+2] nitrone cycloaddition, and then resolved with camphorsulfonic acid.

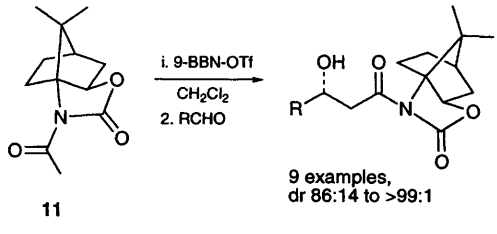
2.1.2 Aldol reactions

The acylated chiral lactam **9** gives good selectivities for the *syn*-aldol products **10** (>97% de) in the boron enolate aldol reaction,[6] with the methyl group being a sufficiently bulky substituent on the lactam ring to give good stereocontrol (**Scheme 5**). The auxiliary is readily removed by LiOH, since the *gem*-dimethyl group hinders attack on the lactam carbonyl (attack of hydroxide on the oxazolidinone carbonyl of Evans' auxiliaries can be a problem during removal). Alkylation reactions give similar stereoselectivities to those obtained using Evans' oxazolidinone auxiliaries.

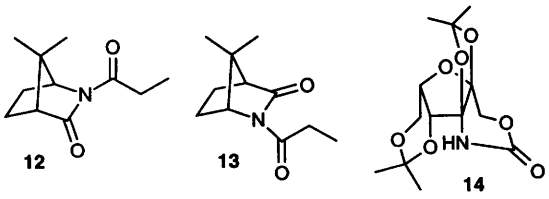


Scheme 5

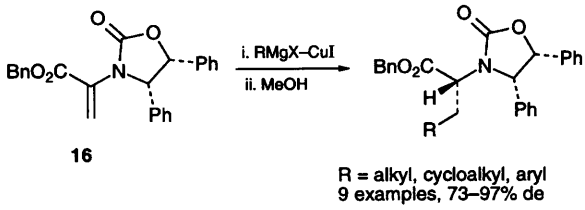
Other new auxiliaries reported for asymmetric aldol reactions include a camphor-derived oxazolidinone which, unusually, gives good selectivities (86:14 to >99:1) for boron aldol reactions of the unsubstituted *acetyl* derivative **11** (**Scheme 6**).[7] The stereoselectivities are explained by invoking a boat-like non-chelated transition state. The acylated camphor-derived bicyclic lactam **12** gives reasonably good selectivity for one of the *syn*-aldol products; however the isomer **13** gives a *syn*:*anti* ratio of only 2.2:1 with isobutyraldehyde (**Scheme 7**).[8] The oxazinanone auxiliary **14** is derived from gulonic acid *via* a nitrene insertion reaction, and its *N*-propionyl derivative gives good *syn*-selectivity in a lithium enolate aldol reaction



Scheme 6



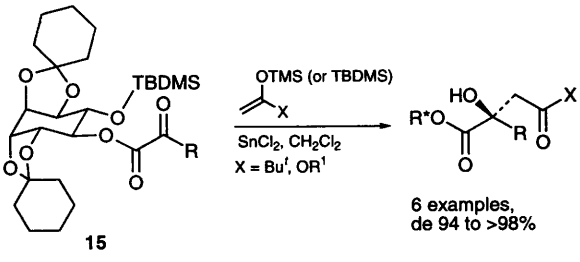
Scheme 7



Scheme 9

with benzaldehyde.[9] Diels–Alder reactions using the corresponding α,β-unsaturated amides as dienophiles with cyclopentadiene are also successful. The auxiliary can be removed from the products by reduction with $LiBH_4$ without epimerisation, in contrast to a similar galactose-derived auxiliary.

Asymmetric aldol additions of chiral enolates on to *ketones* are not generally as reliable as those on to aldehydes. To circumvent this problem the aldol reaction of an *achiral* silyl enol ether or silyl ketene acetal on a *chiral* α-keto ester **15** has been described (**Scheme 8**).[10] The auxiliary is derived from L-quebrachitol, a natural cyclitol from the rubber tree. The tin-mediated aldol reaction proceeds in 94–98% de and allows access to tertiary alcohol products.



Scheme 8

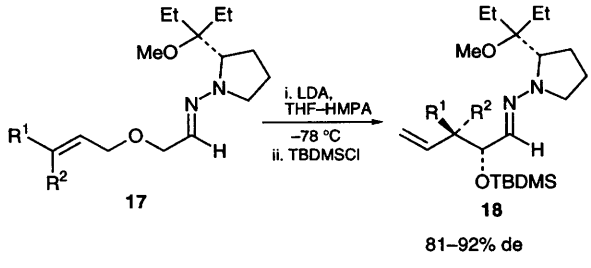
2.1.3 Other reactions

A new synthesis of α-amino acids is based on the copper-catalysed addition of Grignard reagents to the α,β-unsaturated oxazolidinone **16** (**Scheme 9**).[11] The stereoselectivity arises during protonation of the intermediate chiral enolate formed during the Michael addition step. The use of aryl and vinyl Grignard reagents results in complete selectivity, however alkyl Grignard reagents are less selective. The stereoselectivity is *improved* at higher temperature and the auxiliary can be removed by hydrogenation, although it is destroyed during this process. Another asymmetric synthesis involving Michael addition uses a chiral imidazolidinone enolate as the nucleophile reacting with an achiral acceptor; the addition is followed by intramolecular alkylation to generate chiral cyclopropanes of potential biological interest.[12] Finally, lithium enolates of acylated Evans' oxazolidinones have been coupled using titanium tetrachloride to give dialkyl succinic acid derivatives, with good selectivity for one of the chiral isomers over the *meso*-form.[13]

2.2 Reactions of carbanions

2.2.1 SAMP and RAMP hydrazones

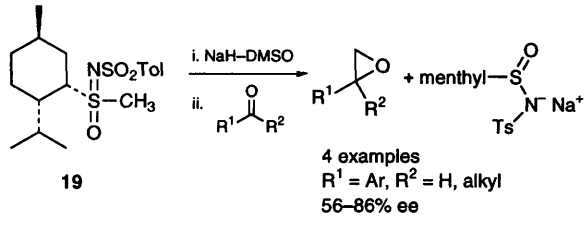
New applications of Enders' SAMP, RAMP [(*S*)-(−)- and (*R*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine] and related hydrazones continue to be reported. The SAEP [(*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine] hydrazones of allyloxy aldehydes **17** are deprotonated by lithium diisopropylamide (LDA) and then undergo [2,3] Wittig rearrangement with good diastereoselectivity (**Scheme 10**), which is higher than with the corresponding SAMP hydrazones.[14] Previously used chiral auxiliaries for the [2,3] Wittig rearrangement have generally been carboxylic acid derivatives. As well as hydrolysis to the protected α-hydroxy aldehydes, the hydrazone products **18** can also be converted to nitriles, using a method which has also been reported for alkylated hydrazones.[15] SAMP hydrazones of silyl protected α-hydroxy aldehydes undergo alkylation with good selectivity (>87% ee after removal of hydrazone), but in low yield because of difficult deprotonation.[16] Changing the protecting group to benzyl or BOM (benzyloxymethyl) gives higher yields but lower selectivities. Allyl Grignard reagents add to SAMP hydrazones of aldehydes in the presence of $CeCl_3$; cleavage of the hydrazine product with methyl chloroformate results in protected homoallylic amines in 90–98% ee, which have been ozonolysed to give optically active protected β-amino acids.[17] Radical addition of Bu_3SnH to an allene results in an alkenyl radical which undergoes intramolecular attack onto a SAMP hydrazone to give a cyclopentene; however the selectivity is only 50% de.[18]



Scheme 10

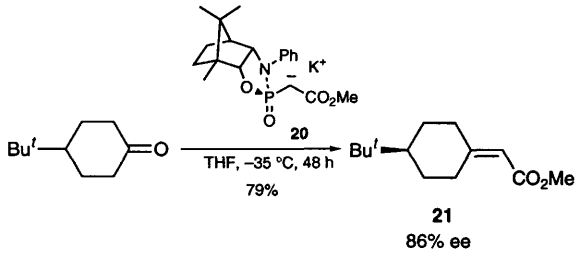
2.2.2 Other carbanions

An asymmetric synthesis of epoxides depends upon methylene transfer to ketones from a sulfoximine **19** which also bears a chiral ligand derived from menthol (Scheme 11).[19] Previous examples involving methylene transfer from sulfoximines with stereogenic sulfur atoms rather than chiral ligands have given low ees (<40%).



Scheme 11

Asymmetric Wadsworth–Emmons reactions can be used to desymmetrise ketones during the alkene synthesis. Menthol-derived phosphonates have previously given only moderate selectivities; however the camphor-derived phosphonate **20** gives the alkene **21** in 86% ee (**Scheme 12**).[20] The isomer of **20** which is epimeric at the phosphorus atom is much less selective.

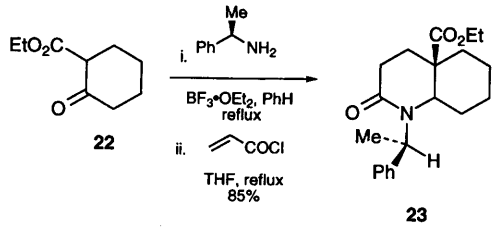


Scheme 12

The anions of chiral phosphonamides derived from cyclohexane-1,2-diamine can be reacted with sulfonyl azides, which following hydrolysis and reduction results in an asymmetric synthesis of α-aminophosphonic acids (in 63–99% ee), which are of interest as analogues of α-amino acids and peptides.[21] A chiral auxiliary has been applied for the first time to the [2,3] sigmatropic rearrangement of sulfonium ylides;[22] the auxiliary is attached directly to the sulfur by a rhenium atom, and gives products in 86–98% de.

2.3 Michael additions of chiral nucleophiles

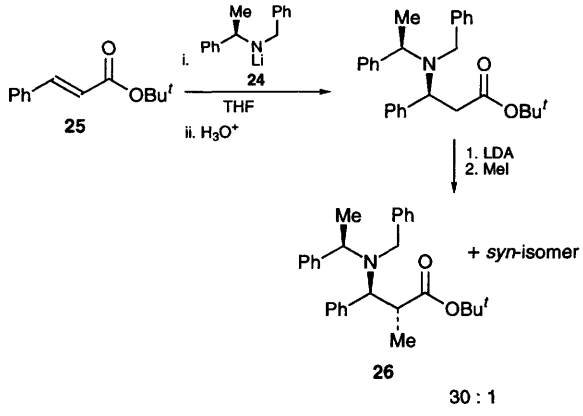
The enamine derived from the cyclic β-keto ester **22** and α-methylbenzylamine adds to acryloyl chloride in the presence of a Lewis acid to give **23**, which has a stereogenic quaternary centre (**Scheme 13**).[23] The ester group in **22** deactivates the enamine, which then requires a reactive electrophile for satisfactory



Scheme 13

reaction. A closely related enamine has been deprotonated with LDA, and undergoes Michael addition to an alkene with two ester activating groups in 95% ee after hydrolysis.[24] Opposite selectivities are obtained in THF and in toluene with addition of hexamethylphosphoramide (HMPA). The enamine formed between α-methylbenzylamine and acetylbutyrolactone adds to acrolein or methyl vinyl ketone; cyclisation *via* an aldol–dehydration sequence gives spiro bicylic ketones with a stereogenic spiro centre.[25] The same chiral amine has been used to form enamines with 4,4-disubstituted cyclohexanones; intramolecular Michael addition followed by hydrolysis then gives bridged bicyclic ketones (for certain bridge sizes) in up to 90% ee.[26]

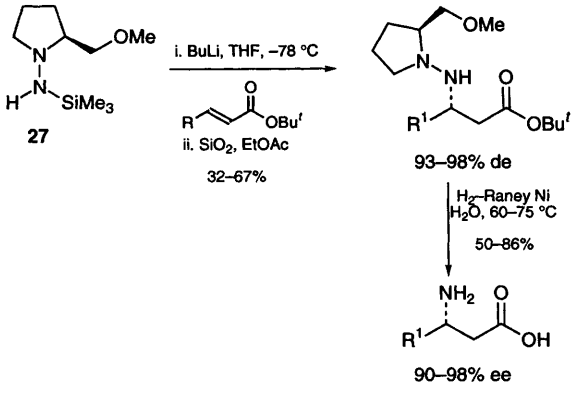
A number of examples of Michael addition of chiral nitrogen-centred nucleophiles to α,β-unsaturated esters have been reported, as a route to β-amino acid derivatives. Trapping of the intermediate enolates with electrophiles has also been studied. For example, Davies has found that the alkylation of the intermediate enolate formed by addition of the lithium amide **24** to the ester **25** is not very selective.[27] However if the enolate is generated in a separate second step, a high selectivity for the *anti*-isomer **26** is obtained, because of different enolate geometries being involved (**Scheme 14**). On the other hand, using the *magnesium* analogue of **24** does allow methylation of the intermediate enolate to give the opposite *syn*-isomer in 90% de.[28] If the unsaturated ester is already substituted with α-methyl group, then



Scheme 14

protonation of the intermediate lithium enolate gives the same *syn*-isomer in 98% de.[29] Electrophilic hydroxylation of the intermediate lithium enolate using Davis' oxaziridine gives the *anti*-α-hydroxy-β-amino ester, usually in >90% de,[30] and this has been applied to the synthesis of the Taxol side chain.[31]

Similar types of Michael addition to *tert*-butyl esters are possible using the lithium amides of TMS-SAMP **27** (**Scheme 15**).[32] If methyl esters or unsilylated SAMP are employed instead, then 1,2- rather than 1,4-addition is observed. The intermediate lithium enolates have also been alkylated, using HMPA as an additive, to give the *anti*-isomers in >96% de.[33] The enantiomeric *anti*-α-methyl-β-amino ester has also been formed by methylation of the enolate resulting from Michael addition of the lithium amide of a resolved dinaphthazepine.[34]



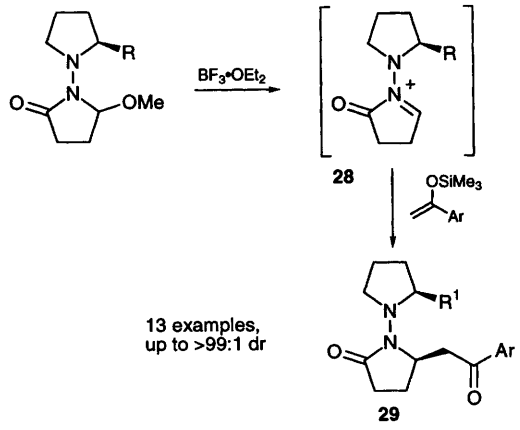
Scheme 15

Related to the above methods, achiral lithium amides have been added in conjugate fashion to a chiral oxazole derivative of naphthalenecarboxylic acid, with methylation of the intermediate anion, in 99% de.[35]

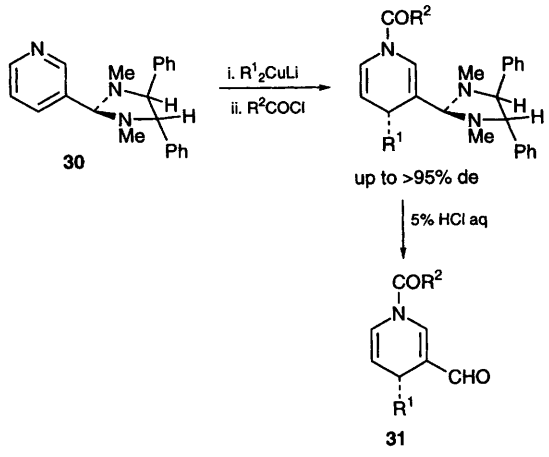
2.4 Other addition reactions

Nucleophilic addition of silyl enol ethers or allyl silanes to iminium ions **28** substituted with a chiral pyrrolidine auxiliary results in alkylpyrrolidinones **29** in up to 98% de (**Scheme 16**).[36] The auxiliary can be cleaved by borane and recycled. In a similar process, a silyl ketene acetal adds to a chiral imine of benzaldehyde to give, after cleavage of the auxiliary, β-amino esters in 88% ee.[37] Chiral primary amines can be prepared using a similar strategy, by addition of Grignard reagents to benzaldehyde imines which are *N*-substituted by camphor-derived sulfenimines or sulfinimines.[38] Imines prepared from α-methyl-benzylamine and highly substituted ketones can be reduced by borohydride, followed by destructive removal of the auxiliary by hydrogenation, to give neopentyl primary amines in 84–97% ee.[39]

Lithium organocuprate reagents have been added to pyridine-3-carbaldehyde derivatised as a chiral



Scheme 16



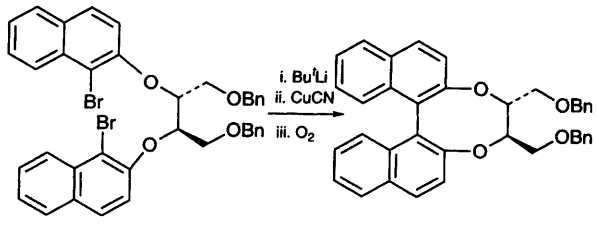
Scheme 17

N,N-acetal **30** (**Scheme 17**), with high selectivity for attack at C-4, and in up to 95% de in a route which gives access to protected chiral 1,4-dihydropyridines **31**.[40,41]

The well-known Diels–Alder addition of chiral fumarate esters as dienophiles has been extended to the use of chiral maleate esters of 2-phenylcyclohexanol.[42] Lewis acid-catalysed addition to cyclopentadiene gives the *endo*-adduct in 99:1 dr. The *N*-acryloyl derivative of proline benzyl ester has been used in a 1,3-cycloaddition to an azomethine ylide to give substituted pyrrolidines in 82–98% de.[43]

2.5 Miscellaneous uses of chiral auxiliaries

A chiral binaphthyl has been prepared by asymmetric Ullmann coupling of two molecules of a bromonaphthalene bearing an oxazoline chiral auxiliary, in a dr of 32:1.[44,45] Ullmann coupling of bromoaryl oxazolines results in chiral biaryls in a de which increases with time from 26% to 86%, as a result of thermodynamic equilibration.[46] Intramolecular Ullmann coupling of two bromonaphthol

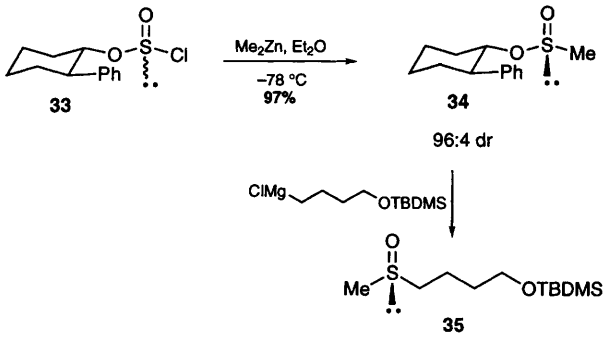


32

Scheme 18

units linked by a tartrate-derived tether as in **32** proceeds in 100% de (**Scheme 18**), and the tether can be removed with *N*-bromosuccinimide (NBS) to give binaphthol.[47]

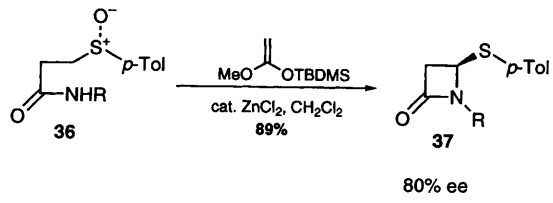
Several new syntheses of chiral sulfoxides employing auxiliaries have appeared. The mixture of isomeric chlorosulfite esters **33** reacts with dimethyl zinc to give mainly one sulfinate ester **34** (**Scheme 19**); the phenylcyclohexanol auxiliary is then displaced with a Grignard reagent with inversion to give the sulfoxide **35**.[48] The same type of Grignard reaction on *tert*-butylsulfinate esters of diacetone glucose has the attraction that either diastereoisomer of the sulfinate can be prepared depending upon the conditions of esterification, allowing access to either enantiomer of the sulfoxide.[49] Stoichiometric chiral ruthenium complexes of alkyl methyl sulfides can be oxidised quantitatively with dimethyldioxirane, and treatment with sodium iodide then releases the sulfoxide in up to 98% ee.[50]



33 34 35

Scheme 19

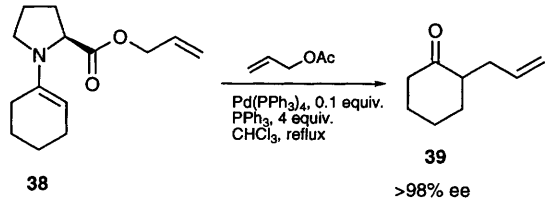
The optically pure sulfoxide **36** (R = Bn) undergoes an intramolecular Pummerer reaction with chirality transfer to give the β-lactam **37** in 80% ee (**Scheme 20**).[51] Replacement of the benzyl group with R = (*S*)-α-methylbenzyl results in a modest enhancement of the selectivity to 85% de. One approach to the synthesis of epoxides which also results in carbon–carbon bond formation is the reaction of a sulfonium ylide with an aldehyde or ketone. Sulfonium ylides bearing a chiral auxiliary have been prepared as diastereoisomeric mixtures at the sulfur atom, and reacted with aldehydes to give *trans*-disubstituted epoxides in variable ees of 0–43%.[52]



36 37

Scheme 20

The Pauson–Khand reaction has recently been extended to include the use of chiral auxiliaries, and an intramolecular example uses a chiral acetal auxiliary.[53] 2-Phenylcyclohexanol has also been used as an auxiliary for this reaction, in both inter-[54] and intra-molecular[55] examples. A polymer supported C_2-symmetric pyrrolidine auxiliary has been used for asymmetric iodolactonisaton reactions.[56] *anti*-β-Amino alcohols have been prepared in 90–93% ee by reaction between aldehydes and a chiral allyl borane containing a terminal nitrogen atom, in a process which unusually creates a 1,2-difunctional molecule by construction of the 1,2-C–C bond as well as the two chiral centres.[57] The proline-derived enamine of cyclohexanone **38** undergoes palladium-catalysed allylation to give **39** in >98% ee (**Scheme 21**).[58]

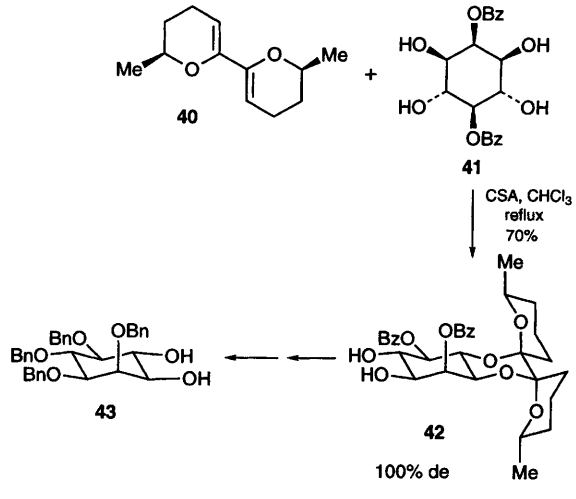


38 39

>98% ee

Scheme 21

Lastly, Ley has introduced the bis(dihydropyran) **40** as a chiral protecting group for polyols (**Scheme 22**).[59,60] Asymmetric protection of a symmetrical polyol such as **41** takes place with complete



40 41 42 43

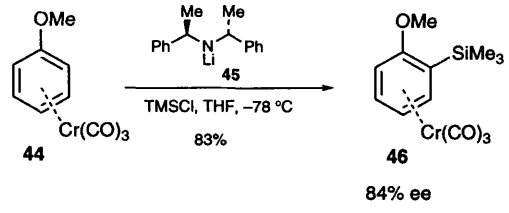
Scheme 22

selectivity to give the 'matched adduct' **42**, where both methyl groups are equatorial, and all the spiro oxygen atoms are mutually axial. The other hydroxy groups can then be manipulated conventionally, followed by removal of the dispiroketal, to give the chiral protected cyclitol **43.** Acrylate esters of dispiroketal diols have also been employed in asymmetric Michael and Diels–Alder reactions.[61,62]

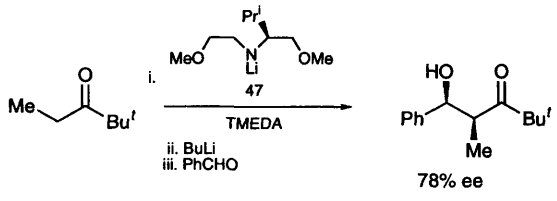
3 Chiral reagents

3.1 Chiral bases

Several applications of chiral lithium amide bases have appeared. Arene chromium tricarbonyl complexes, *e.g.* **44** have been deprotonated with **45** and trapped with TMSCl to give the chiral complex **46** (**Scheme 23**).[63] The base **47** has been used in aldol reactions to give *syn*-products from ketones and *anti*-products from hindered esters (**Scheme 24**).[64] In order to obtain good selectivity, both coordinating methoxy groups in **47** are required, and the amine also has to be deprotonated a second time with BuLi in the reaction, before addition of the aldehyde.

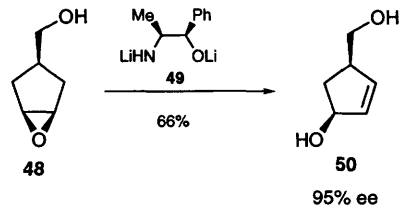


Scheme 23



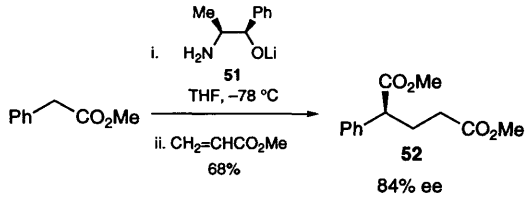
Scheme 24

Koga has reported full experimental details for the preparation of his phenylglycine-derived bases,[65] and Majewski has used this type of base with LiCl as an additive to deprotonate tropinone in up to 92% ee.[66] The symmetrical cyclopentene epoxide **48** has been deprotonated and ring opened in 95% ee using the readily available dilithiated norephedrine **49** to give **50** (**Scheme 25**),[67] which is an intermediate for the sythesis of carbovir. Similar work on the silyl-protected *trans*-epoxide using a proline-derived base has also been reported, including the conversion of the product into (−)-carbovir.[68] The same group has also used *catalytic* amounts of the same base, with a stoichiometric amount of LDA, to open cyclohexene epoxide in 75% ee with 0.2 equiv. of base, and 59% ee with only 0.05 equiv. of base.[69]



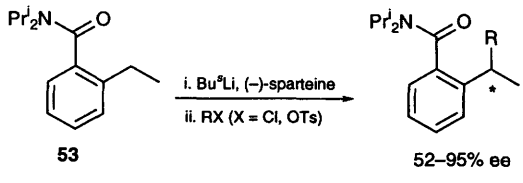
Scheme 25

Chiral metal alkoxide bases have been much less studied, however **51** has been used for the Michael addition shown in **Scheme 26**, giving **52** in 84% ee, with other examples showing less selectivity.[70] Exactly the same reaction has also been carried out using sodium hydride or *tert*-butoxide in the presence of 0.1 equiv. of a camphor-derived crown ether, in 83% ee, although other examples showed moderate selectivity.[71] A norephedrine-derived potassium alkoxide has been used for an elimination reaction on a symmetrical 1,2-dibromide, to give a chiral exocyclic bromoalkene in good yield and >99% ee after recrystallisation.[72] Chiral lithium amide bases were not effective in this reaction.



Scheme 26

Butyllithium in the presence of the natural chiral diamine (−)-sparteine has been used by Beak in a number of asymmetric reactions. *N-tert*-Butoxycarbonylpyrrolidine is deprotonated by this system, and the anion can be reacted with a range of electrophiles in 59–96% ee.[73] The anion generated by *ortho*-lithiation of the benzamide **53** reacts with alkyl chlorides in up to 95% ee (**Scheme 27**),[74] and interestingly gives the opposite enantiomer of the products using alkyl toluene-*p*-sulfonates instead of bromides.

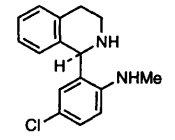
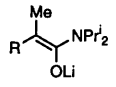
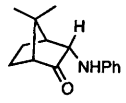
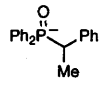
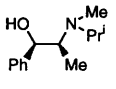
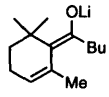
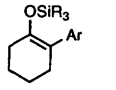
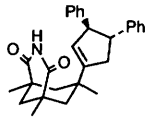
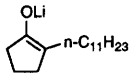
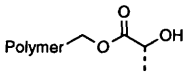
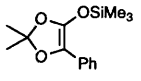


Scheme 27

3.2 Asymmetric protonation

Several examples of protonation of achiral enolates or enol equivalents by chiral proton donors have appeared, and some of these are shown in Table 1.

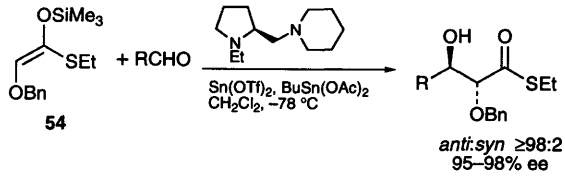
Table 1 Asymmetric protonation reactions

Entry	Proton Donor	Substrate	ee	Ref.
1			95–97%	75
2			81–83%	76
3			94%	77
4	binaphthol + $SnCl_4$		79–96%	78
5			96%	79
6			94%	80

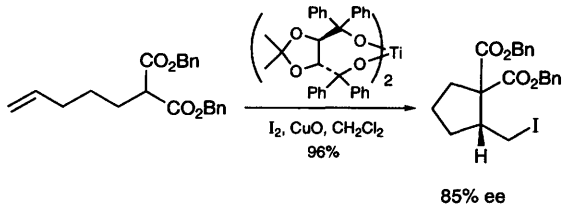
There are now several examples of protonation in high ee using simple chiral reagents, some of which are commercially available (*e.g.* entry 1). Protonation using a *catalytic* quantity (0.2 equiv.) of *N*-isopropylephedrine is possible (entry 3), with a ketone present as the stoichiometric proton source. Silyl enol ethers are represented by entry 4, where the commercially available binaphthol is the protic acid, assisted by $SnCl_4$ as a Lewis acid. In entry 5, a silyl enol ether is first converted into the lithium enolate, and in entry 6 it is protonated by a polymer-bound ester of a chiral α-hydroxy acid in high ee, whereas use of the methyl ester instead surprisingly gives no asymmetric induction at all.

3.3 Other chiral reagents

Several applications of enolates generated by chiral reagents have appeared. Mukaiyama has extended his tin-mediated aldol reaction to protected α-hydroxy thioesters **54** (**Scheme 28**),[81] where the choice of protecting group determines whether the reaction proceeds by a chelated or open transition state, allowing access to either the *syn*- or *anti*-aldol products. Chiral boron reagents designed with the aid of molecular modelling have also been used for aldol reactions of α-alkoxy and α-halo thioesters.[82] A boron enolate is also involved in the first example of a [2,3] Wittig rearrangement involving a chiral reagent (Corey's bis-sulfonamide),[83] rather than a chiral auxiliary. A titanium enolate is presumed to be an intermediate in the reaction of diketene with benzaldehyde, promoted by titanium tetraisopropoxide and a chiral Schiff base,[84] and the product is



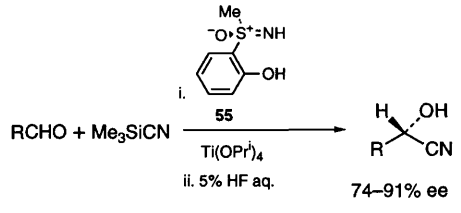
Scheme 28



Scheme 29

equivalent to an aldol reaction between benzaldehyde and the γ-carbon of isopropyl acetoacetate, in 84% ee. **Scheme 29** shows an intramolecular iodine-promoted alkylation of a malonate, which is also presumed to proceed *via* a chiral titanium enolate.[85]

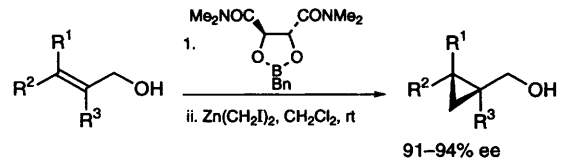
Other titanium-based chiral reagents include the use of a titanium dichloride coordinated by a tartrate-derived diol for the conjugate addition of dialkyl zinc reagents to nitroalkenes in 68–90% ee.[86] A chiral titanium reagent has also been used for the addition of trimethylsilyl cyanide to aldehydes shown in **Scheme 30**.[87] The chiral sulfoximine reagent **55** is prepared by a Kagan asymmetric oxidation, and the reaction is useful in that it forms the silyl-protected cyanohydrins directly, and as the (*S*)-enantiomers, which are less readily available by enzymatic methods.



Scheme 30

Thiols have been used for the asymmetric ring-opening of symmetrical aziridines in up to 88% ee, using a reagent prepared from diethylzinc and diisopropyl tartrate.[88] A rather different reaction which also uses zinc and tartrate-derived reagents is the asymmetric Simmons–Smith cyclopropanation shown in **Scheme 31**,[89] which has also been more recently improved for larger scale reactions.[90]

A chiral aluminium tris(binaphtholate) has been used to promote an asymmetric Claisen rearrangement at −78 °C in 61–92% ee,[91] and the selectivity has been rationalised by modelling studies, with the aluminium reagent creating a chiral pocket which



Scheme 31

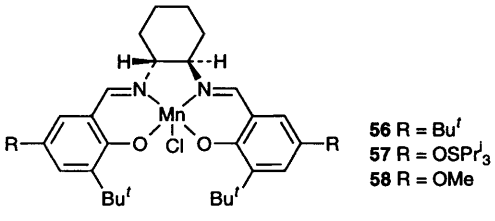
folds the ether in the correct conformation for rearrangement.

4 Chiral catalysts

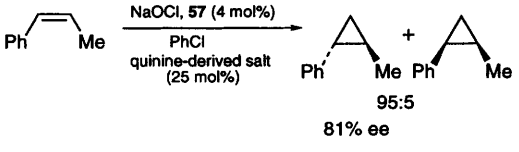
4.1 Oxidations

4.1.1 Epoxidation

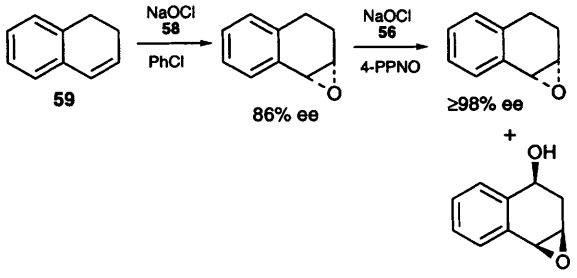
Several developments in the asymmetric epoxidation of unfunctionalised alkenes using Mn–salen catalysts, *e.g.* **56**, have been reported by Jacobsen (**Scheme 32**). An improved synthesis of the catalyst allows the preparation of **56** on both laboratory and 100 kg scales.[92] A detailed study of epoxidation of *cis*-cinnamate esters found that steric effects were important, with isopropyl esters giving higher ees than methyl or ethyl esters.[93] The Jacobsen method works well for conjugated *cis*-disubstituted alkenes, but gives slower rates and poorer ees (<65%) for *trans*-disubstituted alkenes. However, *cis*-disubstituted alkenes can be converted into the *trans*-epoxides in a non-concerted oxidation, allowing rotation about the C–C bond in an intermediate, using catalyst **57** with the addition of a quinine derivative (**Scheme 33**).[94] Epoxidation of cyclic conjugated dienes usually gives only moderate ees, with catalyst **57** being more selective than **56**, although 2-acetoxycyclohexa-1,3-diene reacts in 90% ee.[95] Dihydronaphthalene **59** is epoxidised in 86% ee, however this can be improved to >98% ee by selectively removing the minor enantiomer of the product in a kinetic resolution by an unusual



Scheme 32



Scheme 33

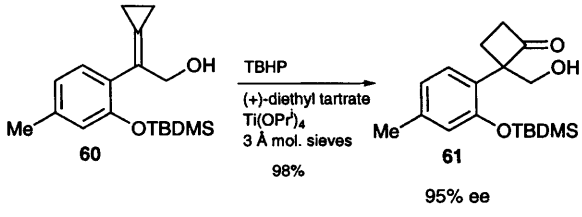


Scheme 34

asymmetric C–H hydroxylation (**Scheme 34**), with this second step requiring a change of catalyst.[96] The same substrate **59** has also been epoxidised in 70% ee using a manganese complex of a chiral porphyrin, which can itself be prepared in one step from pyrrole and an optically active aldehyde.[97]

Trisubstituted alkenes have been found to be good sustrates for the Jacobsen epoxidation, but give the opposite sense of induction to that expected by extrapolation of results from the *cis*- and *trans*-disubstituted cases.[98] A different Mn–salen complex has also been used for epoxidation of trisubstituted alkenes by Katsuki.[99]

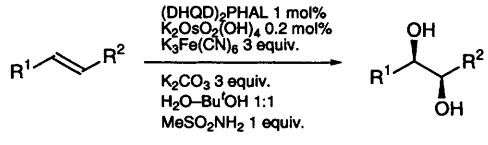
A synthesis of optically active cyclobutanones relies on Sharpless epoxidation of the cyclopropane **60** (**Scheme 35**); the spiro epoxide intermediate is not isolated, but underogoes spontaneous ring expansion to give **61** in very high yield and enantioselectivity.



Scheme 35

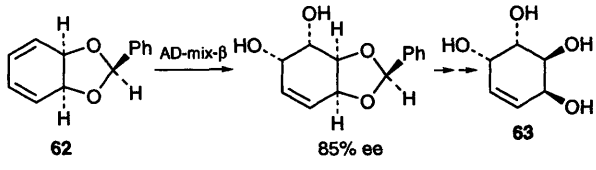
4.1.2 Dihydroxylation

A considerable amount of work has appeared on the Sharpless asymmetric dihydroxylation (AD) reaction, which is successful for many types of unfunctionalised alkene (**Scheme 36** shows typical conditions). A comprehensive review by Sharpless has appeared,[100] and must be considered essential reading for any chemist planning to use this reaction. Sharpless has also made a comparison of



Scheme 36

the various ligands which have been proposed for the AD reaction, and concludes that his $(DHQD)_2PHAL$ ligand (hydroquinidine 1,4-phthalazinediyl diether) is superior to those suggested by others.[101] The asymmetric AD reaction has been extended to several different classes of alkene. *trans*-1,2-Disubstituted allylic halides react successfully if the reaction is buffered with $NaHCO_3$ to suppress hydrolysis of the halide and epoxide formation,[102] although unsubstituted allyl iodide reacts in only 70% ee. The halo diol products were also converted to hydroxy epoxides with NaOH. Alkenes containing allylic sulfide, disulfide and dithiane functionalities react preferentially at the alkene double bond without oxidation of the sulfur atom, for reasons which are unclear.[103] *cis*-1,2-Disubstituted alkenes are normally poor substrates for the asymmetric AD reaction, however with *cis*-allylic alcohols the free OH group enhances the selectivity, presumably *via* hydrogen bonding.[104] On the other hand, in a *trans*-allylic alcohol, the hydroxy group has a varying and deleterious effect,[105] and in some geraniol derivatives the AD reaction is selective for the double bond remote to the hydroxy group. Cyclic *cis*-disubstituted conjugated alkenes have also been studied, and give variable ees, with a few being greater than 90%.[106] A protected benzene-1,2-diol **62** gives much better selectivity than cyclohexa-1,3-diene (**Scheme 37**) and has been used as the basis of an asymmetric synthesis of conduritol E **63**.[107,108] Allyl and vinyl silanes undergo the AD reaction with moderate ees, except when the alkene is *trans*-1,2-disubstituted.[109] A study of the AD reaction of polyenes concludes that, for non-conjugated cases the subsititution pattern and steric effects determine the regioselectivity, and for conjugated polyenes the more electron rich double bond reacts if it is sterically accessible. However there are several exceptions, and the level of predictability is not high.[110] Anomalous stereoselectivity has been reported in the case of 1,1-disubstituted alkenes, which give the opposite enantiomer to that predicted by the general empirical rule.[111]



Scheme 37

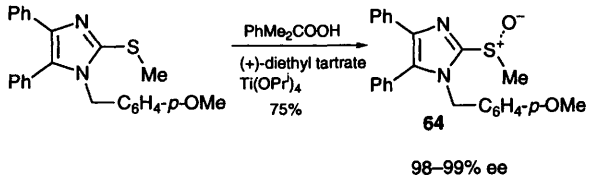
A polymer-supported AD catalyst has been prepared by polymerising alkenes derived from DHQ and DHQD with ethylene glycol dimethacrylate.[112] This gives a heterogeneous AD reaction which is almost as enantioselective as the normal reaction.

Several useful applications of the AD reaction have been reported, including experimental details for the conversion of stilbene into hydrobenzoin on a 1 kg scale in a flask of only 5 l volume.[113] Other applications include the preparation of the Taxol side chain,[114] preparation of carbohydrates by combining the AD reaction with an enzymatic aldol reaction,[115] and the preparation of a precursor for Mosher's acid.[116]

Corey[117] and Sharpless[118] have each proposed models to rationalise the stereoselectivity. The models are similar, but differ in the conformation of the aromatic spacer in the transition state, and in the location of the alkene. Sharpless also proposes an L-shaped cleft, as opposed to Corey's U-shaped pocket. Sharpless has made a detailed kinetic study of the reaction, showing that the rate is influenced mainly by the O-9 substituent of the alkaloid ligand.[119] It is proposed that this substituent gives to rise to a stabilising stacking interaction with the alkene in the transition state, and molecular modelling studies on the osmaoxetane intermediate in the [2+2] pathway support this.[120] A revised mnemonic to predict the outcome of asymmetric AD reactions is also given.[119]

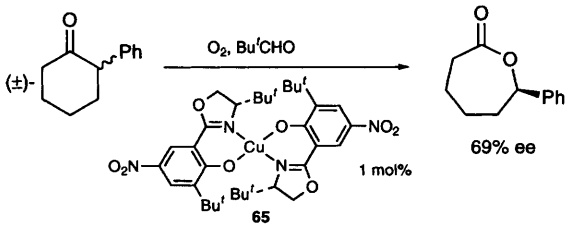
4.1.3 Other oxidations

The Kagan asymmetric oxidation of aryl sulfides to sulfoxides has been scaled up to the multi-kilogram level in the synthesis of a pharmaceutical intermediate **64** (**Scheme 38**).[121] This asymmetric oxidation has also been applied to some organometallic sulfides, including ferrocenyl[122] and tricarbonyl(η^6-arene)chromium[123] examples. Sulfides have also been oxidised in moderate ees using a stoichiometric amount of a camphorsulfonylimine and hydrogen peroxide;[124] however catalytic turnover of the imine is possible using smaller amounts, and interestingly, dialkyl sulfides are the substrates which give some of the best results.



Scheme 38

Kinetic resolution in the asymmetric Baeyer–Villiger oxidation of cyclic ketones to lactones has been achieved using a chiral copper catalyst **65** and molecular oxygen, with an aldehyde present as an oxygen atom acceptor (**Scheme 39**). The asymmetric Baeyer–Villiger oxidation has previously only been effectively achieved using enzymes. Cyclohexene undergoes allylic oxidation using a copper catalyst and a bis-oxazoline ligand in 77% ee, which is the best enantioselectivity yet achieved for catalytic allylic oxidation.[125]

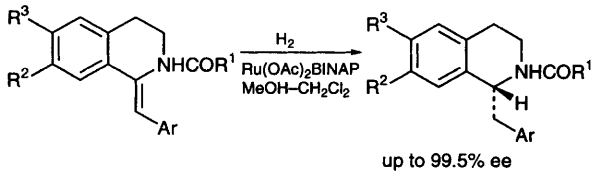


Scheme 39

4.2 Reductions

4.2.1 Hydrogenation

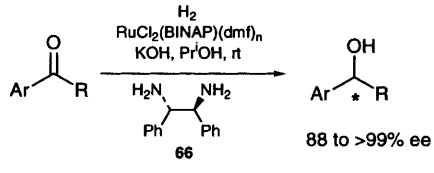
Asymmetric hydrogenation of alkenes using Rh or Ru catalysts and chelating diphosphine ligands has been intensively studied for many years now. Full details have appeared of the preparation of isoquinolines by hydrogenation of (*Z*)-enamides (**Scheme 40**);[126] the *N*-acyl function is essential as a tether for the catalytic metal centre, and this is a common feature of this type of asymmetric hydgrogenation. A new ferrocenyl diphosphine ligand[127] has been used for enantioselective hydrogenation of α,β-unsaturated ketones and β-keto esters, and also for allylic alkylation and hydroboration. A new cationic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)–Ru catalyst is useful for hydrogenation of α-substituted β-keto esters, α-keto and α-hydroxy esters, and also allylic alcohols and α,β-unsaturated acids.[128]



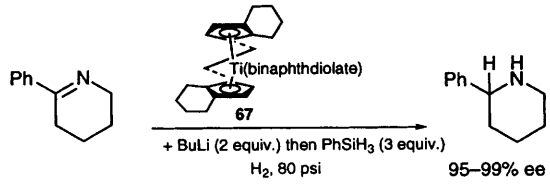
Scheme 40

The asymmetric hydrogenation of ketones which lack an extra heteroatom to anchor the Ru or Rh catalyst is much more difficult to achieve; however Noyori has developed a practical method for aromatic ketones (**Scheme 41**),[129] which uses a chiral 1,2-diamine **66** to enhance the activity of the catalyst, which would normally not be active for this reduction.

Buchwald has used a catalyst prepared from the chiral titanium–binaphthol complex **67** for the



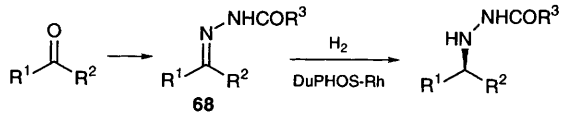
Scheme 41



Scheme 42

hydrogenation of imines[130] (**Scheme 42**) and enamines.[131] Cyclic imines work well, usually giving 95–99% ee at 80 psi of hydrogen; acyclic imines require up to 2000 psi and give lower enantioselectivities. Enamines also work well, giving products in 89–98% ee at 15 or 80 psi of hydrogen. The same complex **67** has also been used with polymethylhydrosiloxane to give asymmetric hydrosilylation of alkyl aryl ketones;[132] desilylation gives the secondary alcohols, usually in >95% ee, however the enantioselectivities are much lower for dialkyl ketones.

Hydrogenation of acyl hydrazones **68** using a DuPHOS–Rh catalyst (**Scheme 43**) has been used to achieve overall asymmetric reductive amination of ketones.[133] The acyl hydrazine products are reductively cleaved with SmI_2 to give the chiral primary amines, or alternatively can be hydrolysed to the hydrazines.



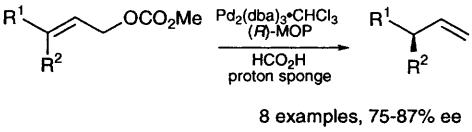
DuPHOS = 1,2-bis[(2*S*,5*S*)-2,5-dialkylphospholan-1-yl]benzene

Scheme 43

4.2.2 Other reductions

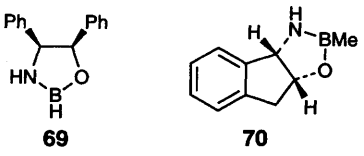
Palladium-catalysed asymmetric reduction of allylic carbonate esters has been used to form α-chiral terminal alkenes with transposition of the double bond (**Scheme 44**).[134] Formic acid is used as the reducing agent, and unusually, a monodentate phosphine ligand, *e.g.* (*R*)-MOP, is required, since with BINAP the reaction is both slow and not very selective. The same reaction has been used on vinyl silanes to give chiral allyl silanes.[135]

Chiral oxaborolidines are now widely used catalysts for asymmetric reductions using borane. New oxaborolidines have appeared, such as **69**, which is formed *in situ* from the corresponding



MOP = 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl

Scheme 44



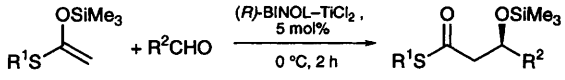
Scheme 45

amino alcohol (**Scheme 45**).[136] The oxaborolidine **70** is formed from the amino indanol, which is prepared in both enantiomeric forms *via* asymmetric epoxidation on an industrial scale, and is now commercially available.[137] Polymer-supported oxaborolidines have been used for reductions of aryl alkyl ketones, with enantioselectivities almost as good as with the non-polymer-supported catalyst.[138]

4.3 Carbon–carbon bond forming reactions

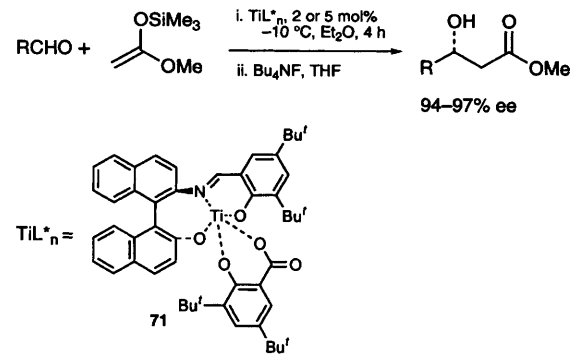
4.3.1 Catalytic asymmetric aldol reactions

The Mukaiyama aldol-type reaction of silyl ketene acetals of acetate thioesters (**Scheme 46**) is catalysed by 1,1′-bi(2-naphthol) (BINOL)–$TiCl_2$, and it has been established by crossover experiments that a

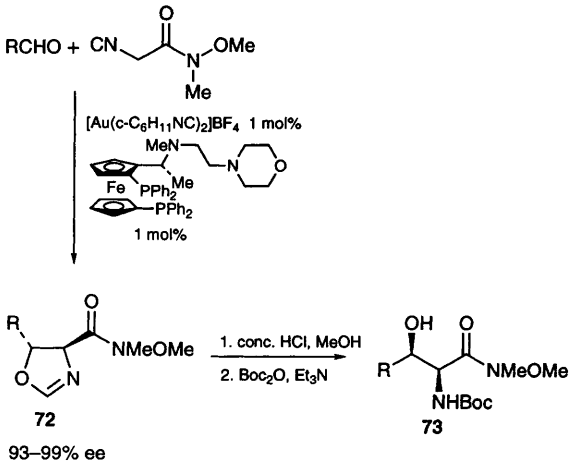


Scheme 46

direct intramolecular transfer of the silyl group to the aldehyde occurs.[139] With the ketene acetals of propionate thioesters, the *syn*:*anti* selectivity is dependent upon the geometry of the ketene acetal, and this suggests that a cyclic transition state is involved rather than an open one. These pieces of experimental evidence support a 'silatropic ene' pathway for this aldol-type reaction. Similar aldol-type reactions have been carried out using a catalyst prepared from BINOL and $Ti(OPr^i)_4$, with a wide range of aldehydes in good enantioselectivities (89–98%) which are highly solvent dependent.[140] Similar reactions with *O*-silylketene acetals, rather than *S*-silylketene acetals, had not previously given high enantioselectivities, however this has now been achieved using a catalyst **71** prepared from a tridentate ligand, $Ti(OPr^i)_4$, and 3,5-di-*tert*-butylsalicylic acid, in 94–97% ee for a wide range of aldehydes (**Scheme 47**).[141] A similar catalyst prepared without the salicylic acid is also effective for the aldol-type reaction of a simple enol ether, 2-methoxypropene, but gives good enantioselectivities only with straight chain aldehydes, and poorer ones with α-branched examples.[142] The Mukaiyama aldol reaction can also be promoted by a polymer-bound *N*-sulfonylvaline and borane, in similar ee to the non-polymeric reagent.[143] Although



Scheme 47



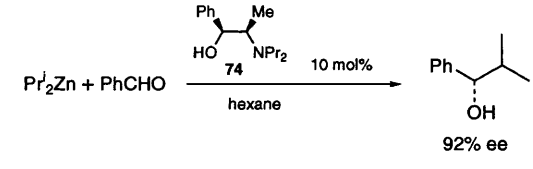
Scheme 48

the polymer-bound reagent is used in stoichiometric quantities, because the reaction is slow, it can easily be recovered and recycled several times.

A gold(I)-catalysed aldol reaction of an isocyano Weinreb amide initially gives the heterocyclic products **72**, which can then be readily converted into the protected α-amino-β-hydroxyamides **73** (**Scheme 48**).[144]

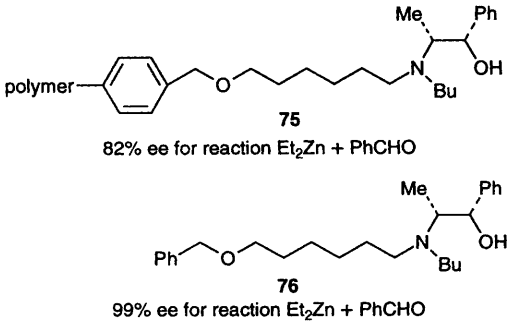
4.3.2 Other additions of carbon nucleophiles to carbonyl groups

The asymmetric addition of dialkylzinc reagents to aldehydes is currently receiving considerable attention, and the catalysts employed usually have two heteroatoms with a β-relationship, such as β-amino alcohols. A recent example shown in **Scheme 49** unusually employs the α-branched diisopropylzinc,



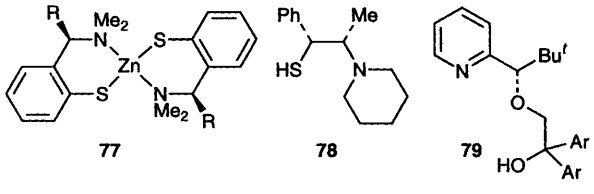
Scheme 49

propylzinc, rather than the commonly used diethylzinc, and *N*,*N*-dipropylnorephedrine is found to be slightly more effective than the *N*,*N*-dibutyl analogue, which is the best catalyst for diethylzinc.[145] The polymer-supported *N*-butylnorephedrine **75**, with a six-methylene spacer, is a reasonably efficient catalyst,[146] although not as good as the non-polymer-supported analogue **76** (**Scheme 50**); however without the spacer, polymer-supported catalysts are much less active and less stereoselective, presumably because of steric hindrance from the polymer matrix.



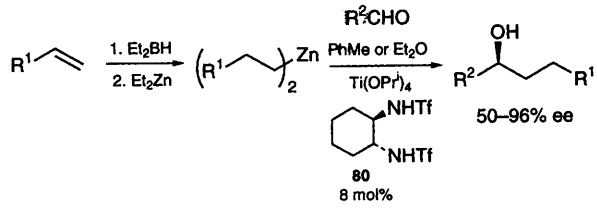
Scheme 50

New catalysts for the addition of diethylzinc to aldehydes include the air-stable zinc bis(arenethiolate) complex **77**[147] (**Scheme 51**), and the cyclic aminothiol **78**,[148] which is derived from norephedrine with retention of configuration, and gives good enantioselectivities for α-branched or aromatic aldehydes, but much lower ones for straight-chain aldehydes. Alkynylzinc reagents can be prepared from alkynes and diethylzinc, and add to aldehydes in 38–95% ee using a chiral β-alkoxy alcohol **79** as a catalyst.[149]

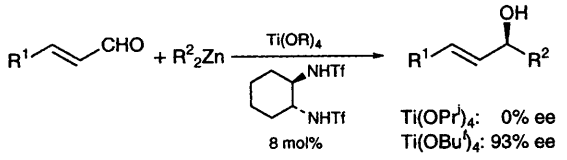


Scheme 51

Knochel has prepared a variety of organozinc reagents and studied their addition to aldehydes using the bis-trifluoromethanesulfonamide **80**. Hydroboration of terminal alkenes, followed by conversion of the organoboranes to organozinc reagents and addition to aldehydes, allows a one-pot synthesis of chiral alcohols resulting from the overall addition of alkenes to aldehydes (**Scheme 52**).[150] Asymmetric addition of functionalised dialkylzincs to α-silyloxy aldehydes results in a synthesis of mono-protected chiral 1,2-diols, and is an alternative to asymmetric epoxidation or dihydroxylation.[151] Addition of small dialkylzincs, *e.g.* Me_2Zn, to β-monosubstituted-α,β-unsaturated aldehydes usually gives poor enantioselectivities, however, compensating for the small alkyl group on zinc by increasing the steric bulk in the titanium alkoxide has a dramatic effect (**Scheme 53**).[152] Additions to β-silyl- and β-stannyl-α,β-unsaturated aldehydes have also been reported.[153]



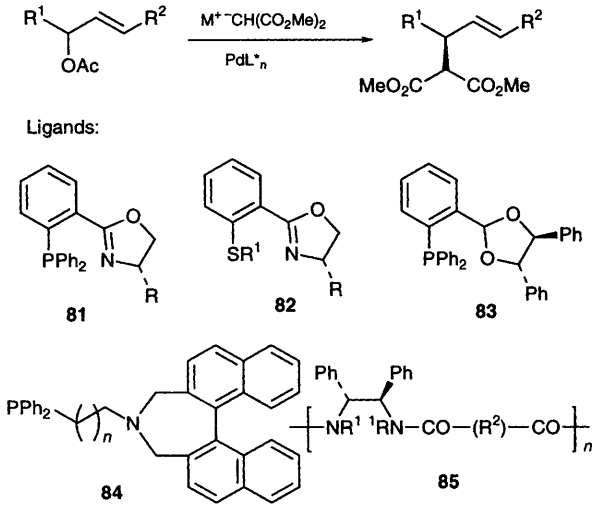
Scheme 52



Scheme 53

4.3.3 Palladium-catalysed reactions

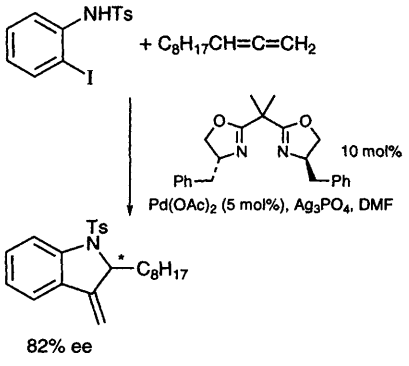
Palladium-catalysed allylic substitution reactions proceed in moderate to very good (40–96%) enantioselectivities using chiral dihydrooxazole ligands of the types **81** and **82** with a tethered phosphorus or sulfur atom (**Scheme 54**); the preparation of these ligands has been detailed,[154] and the origin of the enantioselectivity discussed in terms of a combination of steric and electronic effects.[155] Modifying the ligand to **83**, where a chiral



Scheme 54

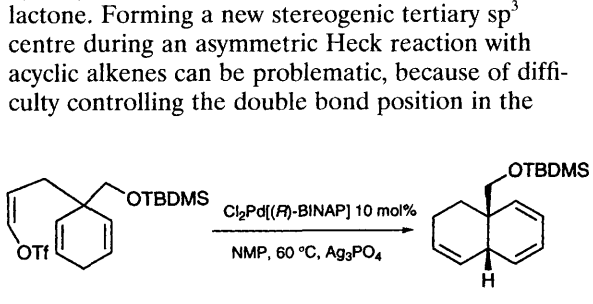
acetal replaces the dihydrooxazole, also results in an effective catalyst.[156] Generally, acyclic allylic acetates have been used, but cyclic systems have also been used successfully, with five- to eight-membered cycloalkenyl products being obtained in up to 85% ee.[157] A different type of catalyst for this reaction uses a C_2-symmetric binaphthyl-containing aminophosphine ligand **84**.[158] Isosparteine, a chiral diamine prepared in two steps from naturally occurring sparteine, has been found to be an effective ligand,[159] and is better than sparteine itself. The polymer **85**, prepared from a chiral C_2-symmetric 1,2-diamine gives good enantioselectivities for this reaction,[160] and has also been used for asymmetric reduction of acetophenone, for which it is rather less effective.

The related palladium-catalysed annulation of allenes shown in **Scheme 55** employs a bis-oxazoline ligand, and involves formation of an intermediate π-allyl palladium complex, followed by intramolecular substitution.[161]



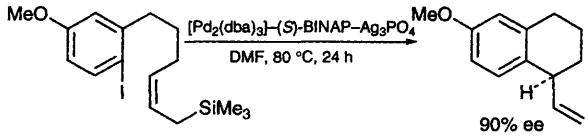
Scheme 55

The palladium-catalysed Heck reaction can result in the formation of a new stereogenic centre if the alkene double bond is reformed away from its original position, and making this process asymmetric is of current interest. An intramolecular example is shown in **Scheme 56**, where use of both the trifluoromethanesulfonate leaving group and the silver salt is essential for high enantioselectivity.[162] An intermolecular example employs a cyclic acetal of *cis*-butene-1,4-diol;[163] after the asymmetric Heck coupling with phenyl trifluoromethanesulfonate, hydrolysis and oxidation result in a chiral butyrolactone. Forming a new stereogenic tertiary sp^3 centre during an asymmetric Heck reaction with acyclic alkenes can be problematic, because of difficulty controlling the double bond position in the product. One solution to this is to employ a silyl group to terminate the reaction and control the double bond position, as shown in **Scheme 57**.[164]

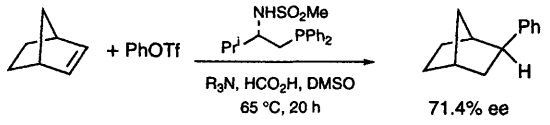


Scheme 56

The use of reductive Heck–coupling reactions, which employ formate salts to reductively cleave the organopalladium intermediates, is another way to preserve chirality formed during the coupling reaction, and asymmetric versions have appeared with reasonably good enantioselectivities on both norbornene and heterobicyclic alkenes (**Scheme 58**).[165–167] Again, aryl trifluoromethanesulfonate give much better enantioselectivities than aryl iodides.



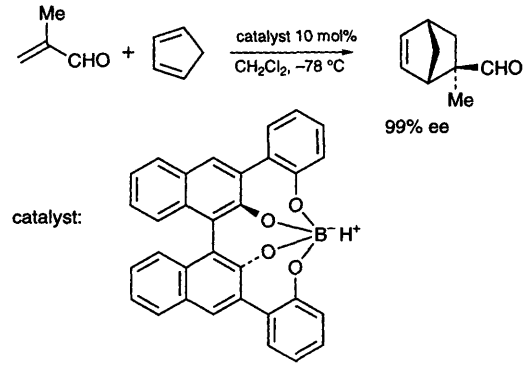
Scheme 57



Scheme 58

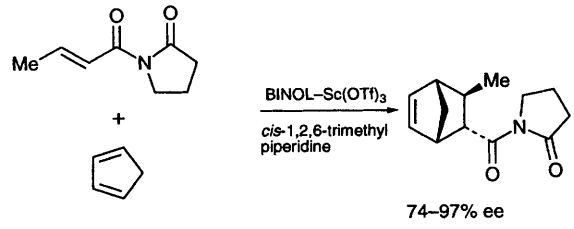
4.3.4 Cycloadditions

Asymmetric catalysis of Diels–Alder reactions using chiral Lewis acids has been widely studied, with boron- and aluminium-based catalysts being commonly used. A new BINOL-derived borate catalyst which is very effectively combined with a Bronsted acid is shown in **Scheme 59**. This gives very high ees with both cyclopentadiene and an acyclic diene.[168] Another boron-based catalyst is prepared from polymer-bound *N*-sulfonylvaline and borane,[169] similar to that discussed above for asymmetric aldol reactions, but gives only a moderate 65% ee. A hetero-Diels–Alder reaction of a glyoxylate ester is catalysed by an *N*-trifluromethanesulfonyloxaborolidine in 94% ee.[170]



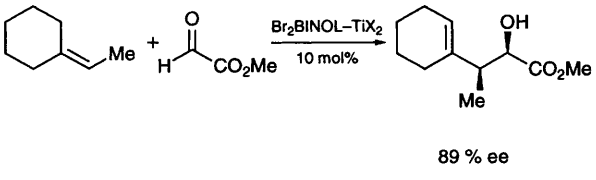
Scheme 59

Transition metals used as chiral Lewis acids for Diels–Alder reactions include a titanium–BINOL complex, which, using juglone as the dienophile, gives products in enantioselectivities of 79–96% which are highly dependent on the absence of molecular sieves.[171] Iron has also been used in a diphosphine–cyclopentadienyl complex,[172] which is very effective (up to 99% ee) using α-bromoacrolein as the dienophile. Kobayashi has reported asymmetric Diels–Alder reactions between cyclopentadiene and (achiral) α,β-unsaturated-*N*-acyloxazolidinones using a catalyst prepared by simply mixing together BINOL, $Sc(OTf)_3$, and *cis*-1,2,6-trimethylpiperidine (**Scheme 60**).[173] Interestingly, by using $Yb(OTf)_3$ together with different *achiral* additives, the enantioselectivity of this reaction can be reversed.[174]



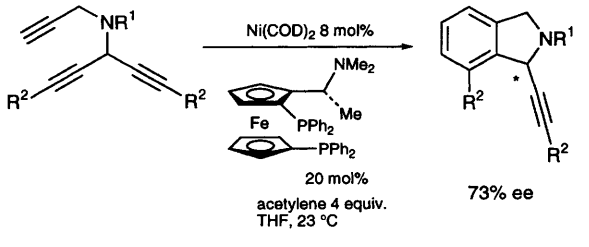
Scheme 60

Ene reactions of glyoxylates are also catalysed by a titanium–BINOL complex (**Scheme 61**)[175] similar to that used for Diels–Alder reactions above, and 1,4-asymmetric control has also been achieved in this process.[176]



Scheme 61

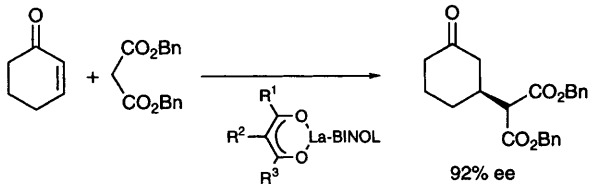
Whilst not a concerted cycloaddition, the formal [2+2+2] cocyclisation of three alkyne units has been achieved with 73% enantioselectivity, between two prochiral alkyne groups using a nickel catalyst with a chiral diphosphinylferrocene ligand (**Scheme 62**).[177]



Scheme 62

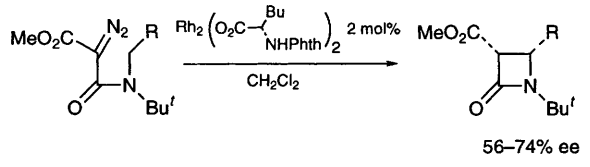
4.3.5 Other carbon–carbon bond forming reactions

The Michael addition of dibenzyl malonate to cyclohexenone is catalysed by a complex prepared from $La(OPr^i)_3$, a 1,3-diketone and BINOL, in 92% ee (**Scheme 63**).[178] The identical reaction is also catalysed in a lower 71% ee by a simple proline-derived ammonium salt, which is presumed initially to form an iminium ion with the cyclohexenone. Proline itself can also be used as its rubidium salt to catalyse the asymmetric Michael addition of nitroalkanes to cycloalkenones.[179]



Scheme 63

Carbenoids can be formed from α-diazo esters by catalysis by chiral metal complexes, and undergo a number of asymmetric reactions. Asymmetric cyclopropanation of styrene employs a catalyst formed *in situ* from a ruthenium complex and a chiral bis-oxazoline,[180] and a catalyst formed from $Cu(OTf)_2$ and a C_2-symmetric diamine is also effective for this reaction.[181] A different chiral bis-oxazoline has also been used with a Cu^I complex for addition of the carbenoid to the C=N double bond of an imine, resulting in aziridine formation with modest enantioselectivity.[182] Asymmetric intramolecular C–H insertion of a carbenoid can be achieved using a dirhodium salt of a protected α-amino acid (**Scheme 64**);[183] this has been previously used for carbocycle construction and here is used to form a β-lactam.

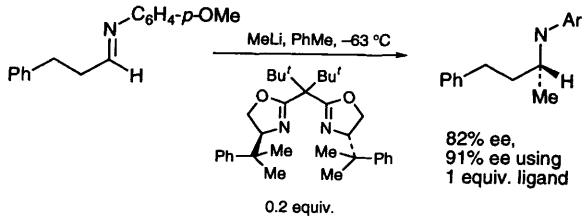


Scheme 64

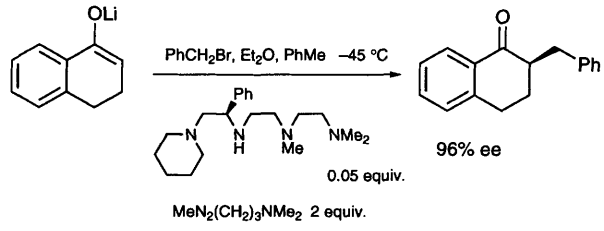
An entirely different use of a chiral bis-oxazoline is to promote the asymmetric addition of MeLi to *N*-arylimines (**Scheme 65**).[184] The enantioselectivity is increased from 82% to 91% if a stoichiometric, rather than a catalytic, amount of the bis-oxazoline is used.

Asymmetric alkylation of an achiral lithium enolate has been achieved using a catalytic amount of a chiral tetraamine, and a stoichiometric amount of an achiral diamine, in excellent enantioselectivity (**Scheme 66**).[185]

Alk-1-ynylboranes, prepared *in situ* from alk-1-ynylstannanes, undergo addition to aldehydes in



Scheme 65

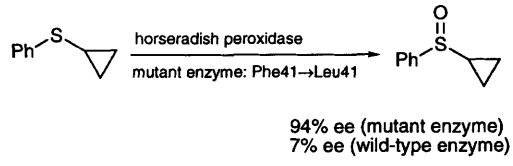


Scheme 66

the presence of catalytic to stoichiometric quantities of a chiral oxaborolidine to give alkynyl alcohols in 85–96% ee.[186] The catalyst is available as either enantiomer, and is readily recovered. Aldehydes are also involved in the intramolecular hydroacylation of pent-4-enals, using a Rh–BINAP catalyst, to give 4-alkylcyclopentanones in 17–99% ee.[187]

4.4 Enzymes and antibodies

Because of the wide and almost routine use of enzymes as asymmetric catalysts, and the availability of many reviews on this topic, only a few recent developments have been selected. Horseradish peroxidase catalyses not only its natural reaction, but also the two-electron oxidation of sulfides to sufoxides, and a single site-specific mutation of the enzyme (Phe-41→Leu-41) accelerates the reaction in **Scheme 67** by a factor of ten, and dramatically improves the enantioselectivity from 7 to 94%.[188]



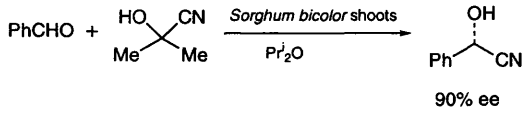
Scheme 67

A multi-gram scale enantioselective antibody-catalysed hydrolysis of an enol ether gives an α-substituted cyclopentanone in 86% ee, and this involves recovering the antibody and reusing it five times in conventional laboratory apparatus.[189] The first antibody-catalysed oxidation at a carbon atom has been reported,[190] and is the epoxidation of an unfunctionalised trisubstituted alkene, using hydrogen peroxide as the stoichiometric oxidant.

The asymmetric oxidation of monosubstituted benzenes to 'benzenediols' by *Pseudomonas putida* is well-known. The oxidation of 1,4-disubstituted benzenes gives only moderate enantioselectivities using the *P. putida* mutant UV4; however after removal of the 4-iodo group by hydrogenation, a wild type *P. putida* can be used to remove the (3*S*) enantiomer selectively, leaving the (3*R*) product in good ee.[191]

Kinetic resolution of racemic α-amino esters by alcalase has been combined with *in situ* racemisation of the unreacted material by pyridoxal-5-phosphate, to give almost complete conversion to the amino acid product, which precipitates out of the reaction mixture in 87–95% yields and 90–98% ee.[192]

Resolution of chiral alcohols by enzyme-catalysed esterification is well-established; more unusual is that an alcohol containing a stereogenic silicon atom undergoes kinetic resolution using papain to give the ester in 67% ee, and unreacted alcohol in 92% ee.[193] The asymmetric synthesis of (*R*)-cyanohydrins using oxynitrilase from almonds is likewise widely known. The enzyme from the plant *Sorghum bicolor*, which gives the (*S*)-cyanohydrins, has previously been laborious to obtain. However it has been reported that the shoots of the plant can be simply lyophilised, powdered and washed, and used without any purification or immobilisation of the enzyme being necessary (**Scheme 68**).[194]

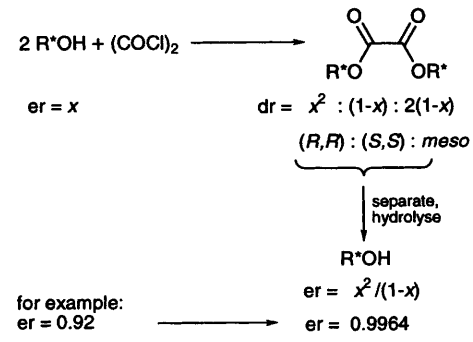


Scheme 68

The development of artificial enzymes is a continuing but elusive goal for chemists. One example of current endeavours is a polymer prepared by copolymerisation, using a small amount of a chiral α-aminophosphinate ester as a template. After removal of the phosphinate template the imprinted polymer shows modest enantioselectivity in the hydrolysis of esters of the corresponding α-amino acids.[195]

5 Miscellaneous asymmetric processes

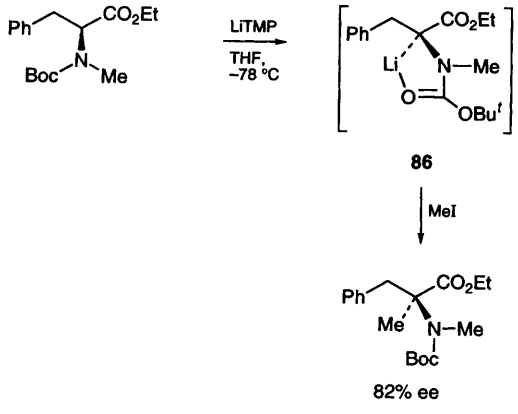
The enantioselective monoesterification of *meso*-diols by (−)-camphanoyl iodide gives mono-esters in 74–88% de, which can be readily improved to 97–98% after recrystallisation.[196] The enantiomeric purity of partially resolved alcohols can be improved by reaction with a difunctional reagent such as oxalyl chloride, after removal of the *meso*-diastereoisomer and hydrolysis (**Scheme 69**).[197] A simple method for enriching the enantiomeric purity of methyl tolyl sulfoxide of 86% ee is by flash chromatography on ordinary silica gel, which gave 14 fractions, varying from 99% ee for the first fraction to 63% ee for the last.[198] There are only a few examples known of fractionation of enantiomers



Scheme 69

by chromatography on an achiral phase, and this phenomenon presumably depends upon auto-association of the sulfoxide in the mobile phase to give diastereoisomeric aggregates of differing mobilities.

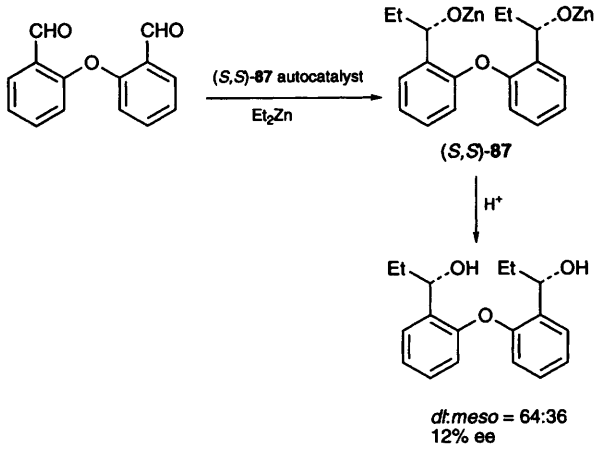
Enolate formation from enantiomerically pure α-amino acid derivatives usually gives racemised products; however the alkylation shown in **Scheme 70** proceeds in 82% ee with no external chiral ligand, and so the enolate is presumed to retain its stereochemistry, as in **86**.[199]



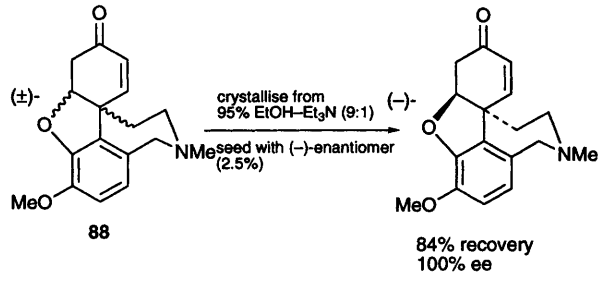
Scheme 70

An asymmetric *autocatalytic* reaction can occur when the product of the reaction is itself the chiral catalyst, and an example of this is shown in **Scheme 71**,[200] and although the enantioselectivity is currently modest, this is an unusual type of effect.

The total spontaneous resolution of a racemate has been observed in the crystallisation of (±)-narwedine **88**, an intermediate required for the synthesis of the alkaloid (−)-galanthamine, which is being investigated for the treatment of Alzheimer's disease.[201] Racemic **88** in supersaturated solution can be seeded with either enantiomer, and crystallisation gives 84–85% recovery of enantiomerically pure material (**Scheme 72**). Deuterium labelling experiments suggest that racemisation occurs in solution in the presence of triethylamine, by a retro-Michael ring-reclosure sequence.



Scheme 71



Scheme 72

Finally, a remarkable and fantastic report claimed that enantioselective addition of Grignard reagents to aldehydes in high ee (*e.g.* 98% ee for methyl magnesium iodide and naphthaldehyde), was effected only by an external *static* magnetic field, with no chiral reagents being present.[202] The report that *either* enantiomer of the products could be formed randomly, but with consistently high ee, and the lack of any known theoretical basis for these results (since a static magnetic field is not chiral) gave rise to considerable interest among chemists, and in the secondary literature. However, the claims turned out to be spurious, for there later appeared, in a single issue of the same journal, two independent attempts to reproduce the work,[203,204] which failed even in the original authors' laboratory and using their magnet, and also a retraction and an editorial statement.[205]

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