Asymmetric processes

Andrew C. Regan

Department of Chemistry, University of Manchester, Oxford Road, Manchester, UK M13 9PL

REVIEW PERKIN 1

Covering: April 1995 to March 1996

Previous review: *Contemp. Org. Synth.*, 1997, 4, 1

1 Introduction

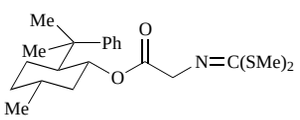
This article covers the literature from April 1995 to March 1996, and continues the coverage of the previous review. As before, since asymmetric synthesis is such a large area, a highly selective choice of examples has had to be made.

2 Chiral auxiliaries

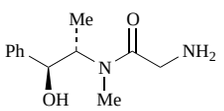
2.1 Reactions of enolates

2.1.1 Alkylation

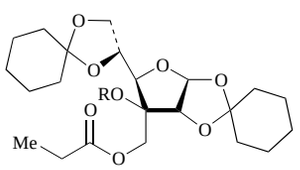
The 8-phenylmenthyl ester **1** has been used as a chiral glycine enolate, and by careful choice of conditions either diastereoisomer of the alkylated products can be obtained.[1] Use of KOBu^t and alkyl halides gives the (*R*)-configuration at the new stereocentre (95 : 5 dr), whereas use of LDA or BuLi and alkyl triflates gives the opposite configuration in up to 20 : 80 dr. Asymmetric glycine enolate alkylation has also been achieved by Myers *et al.*, by extending his previous use of pseudoephedrine as the auxiliary (available as either enantiomer) to the glycine ester **2**.[2] The alkylations of the enolate of **2** are performed without protection of the amino group, and removal of the auxiliary is particularly mild (reflux in pure water). Alternatively, *N*-protection followed by replacement of the auxiliary by a Grignard or alkyllithium reagent results in α-amino ketones.[3]



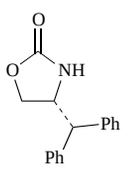
1



2



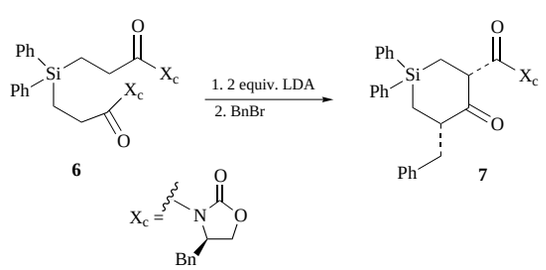
3 R = H
4 R = $SiMe_3$



5

Alkylation of the two closely related glucose-derived propionate esters **3** and **4** containing pseudo-C_2 symmetry gives opposite diastereoisomers in ⩾91% de, and requires the use of LiCl or HMPA as additives for **3** and **4** respectively, in order to obtain high selectivities.[4] The oxazolidinone **5** has been suggested as a more bulky version of the popular Evans' auxiliaries, and can be prepared from serine methyl ester.[5] It has been tested in alkylation, aldol and Diels–Alder reactions, and advantages claimed include crystalline aldol adducts and possible superiority in radical reactions.

An unusual tandem asymmetric alkylation–Dieckmann cyclisation is shown in **Scheme 1**, using the symmetrical bis-(acylimide) **6**.[6] Asymmetric α-alkylation at either terminal of **6**, followed by tandem Dieckmann cyclisation of the enolate formed at the other terminal gives the heterocyclic ketone **7** as the major isomer.



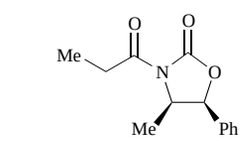
6 **7**

Scheme 1

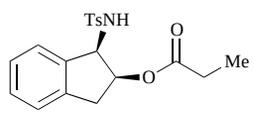
1,3-Dithiane-1-oxide has been used as a chiral auxiliary in the methylation of the enolate of a ketone side chain.[7] Destructive removal of the auxiliary followed by cleavage of the 1,2-diketone products gives α-arylpropanoic acids in up to 93% ee.

2.1.2 Aldol reactions

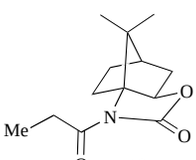
Several developments in the asymmetric synthesis of *anti*-aldol adducts have been reported. The *N*-propionyl Evans' oxazolidinone **8** reacts in an *anti*-manner with acetaldehyde (*anti* : *syn* = 7 : 1), where the only change from the standard Evans' conditions is the use of *two equivalents* of Bu_2BOTf in the enolisation step.[8] A novel tartaric acid work-up is also described. The titanium enolate of propionate ester **9** gives good selectivities (*anti* : *syn* 85 : 15 to 99 : 1) with several aldehydes which have been precomplexed with $TiCl_4$, but only a 44 : 55 dr with benzaldehyde.[9] Similarly, the enolate of the *N*-propionyl camphor-derived auxiliary **10** gives good *anti* : *syn* selectivities (99 : 1) after transmetallation with $TiCl_4$ or $SnCl_4$, but much lower selectivities with aromatic aldehydes.[10] The analogous *N*-acetyl oxazolidinone **11** affords no diastereoselectivity at all in the titanium aldol reaction, but the corresponding *N*-acetyloxazolidine-2-thione **12** performs much better (dr 93 : 7 to 95 : 5).[11]



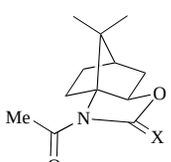
8



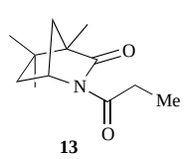
9



10



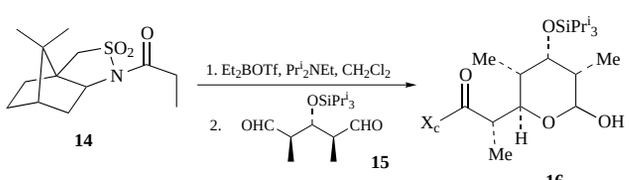
11 X = O
12 X = S



13

The *N*-propionyl bicyclic lactam **13** gives uniformly high selectivities for a single *syn* isomer (dr >98 : 2) in the standard boron enolate aldol reaction with a variety of aldehydes, including benzaldehyde.[12] The design of **13** is a development of a previous, much less selective auxiliary, and takes into account both dipole–dipole and steric interactions.

Desymmetrisation of *meso*-substrates is a popular current strategy in asymmetric synthesis, and Oppolzer has used boron aldol reactions of the *N*-propionyl camphor-derived sultam **14** to desymmetrise the *meso*-dialdehyde **15** (**Scheme 2**).[13] The lactol **16** is formed with 95% selectivity, without reaction at the second aldehyde group, and is an intermediate for the synthesis of the marine polypropionates Denticulatin A and B.



14 **15** **16**

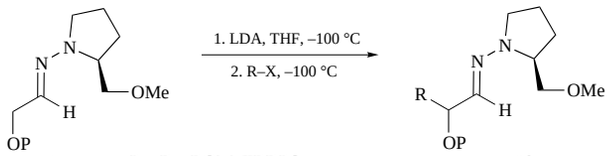
95%

Scheme 2

2.2 Reactions of carbanions

2.2.1 SAMP and RAMP hydrazones

Further recent developments in the uses of 1-amino-2-(methoxymethyl)pyrrolidine (SAMP and RAMP) hydrazones by Enders include the alkylation of the SAMP hydrazones of protected hydroxyacetaldehyde **17** (**Scheme 3**).[14] The products **18** are formed with diastereoselectivities which vary with the type of protecting group, and can either be cleaved to give the corresponding hydroxy aldehydes, or the C=N double bond can undergo nucleophilic addition to give vicinal amino alcohols with two adjacent stereogenic centres. Enders *et al*. have also reported two methods for the silylation of the anions of SAMP and RAMP hydrazones, involving either direct silylation with silyl triflates, or alternatively, silylation of the methyl group of hydrazones derived from acetaldehyde or methyl ketones, followed by α-alkylation.[15] This latter method allows the regioselective formation of α-silyl ketones, not accessible by the direct method.



17 P = Bn, BOM, TBDPS **18**

TBDPS gives best des (87–95%)
Bn gives higher yields, but lower des

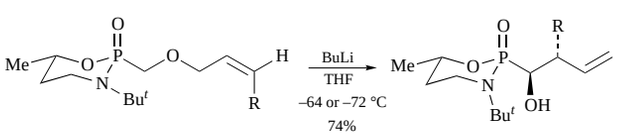
Scheme 3

The SAMP hydrazones of 6- and 7-membered cyclic lactones can be prepared by cyclisation of ω-chloroacyl hydrazides.[16] Diastereoselective alkylations (83–93% de) are then possible, but require 3.3 equiv. of LDA and 3.4 equiv. of alkylating agent, with final cleavage of the hydrazone by ozone providing an enantioselective route to 2-alkyl cyclic lactones.

Other uses of SAMP/RAMP hydrazone anions include α-phosphinylation,[17] and anionic Carroll[18] and [2,3]-Wittig rearrangements.[19,20]

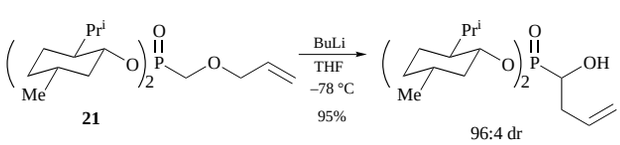
2.2.2 Other carbanions

Several other chiral auxiliaries have been employed in the [2,3]-Wittig rearrangement. Glucose methyl ethers give a high degree of asymmetric transmission from the anomeric centre, which is part of the carbon skeleton involved in the rearrangement.[21] Two groups have reported diastereoselective [2,3]-Wittig rearrangements using chiral phosphorus-stabilised anions containing chiral auxiliaries. The oxazaphosphorinanes **19** and **20** are prepared from the corresponding amino alcohols, and the anions undergo [2,3]-rearrangement with complete control of stereochemistry at the anionic carbon atom (**Scheme 4**).[22] The minor diastereoisomer formed from **20** has the methyl group *syn* to the hydroxy group. The auxiliary can be removed by vigorous hydrolysis (refluxing in 6 M HCl) to give the phosphonic acids. The phosphonates **21** are prepared from readily available menthol, and the [2,3]-Wittig rearrangement proceeds in 92% de.[23] As with the first case, vigorous conditions are required to remove the auxiliary by hydrolysis to give the corresponding phosphonic acid.



19 R = H
20 R = Me

R = H : dr >100:1
R = Me : dr 9:1



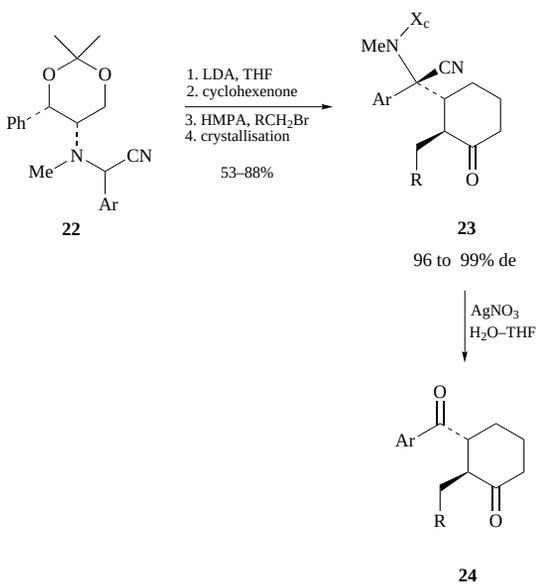
21

96:4 dr

Scheme 4

Another use of phosphorus-stabilised carbanions is the Horner–Emmons reaction, and phosphonates with a second anion stabilising group containing a chiral benzopyranooxazolidine auxiliary have been used for the synthesis of axially disymmetric alkenes from 4-substituted cyclohexanones.[24] The use of potassium hexamethyldisilazide (KHMDS) and 18-crown-6 to form the anion is essential for high diastereoselectivities, which are 90 : 10 to 96 : 4 dr for a range of ketones under optimum conditions.

Protected α-amino nitriles formed from aldehydes can be lithiated, giving 'umpoled' anions, and examples with a chiral auxiliary on the amino group *e.g.* **22** have been used for conjugate addition to cyclohexenones, followed by tandem α-alkylation (**Scheme 5**).[25] Hydrolysis of the α-amino nitriles **23** then removes the auxiliary, revealing the ketone. The 2-alkyl-3-aroylcyclohexanones **24** are formed in ≥97% ee, but the alkylation step requires activated alkyl halides and also the use of HMPA. Meyers has developed the use of chiral formamidine stabilised anions for the asymmetric synthesis of several types of heterocyclic system, and sequential bis-alkylation of an isoindoline formamidine gives (*S*,*S*)-1,3-dialkyl isoindolines in ≥95% ee.[26]



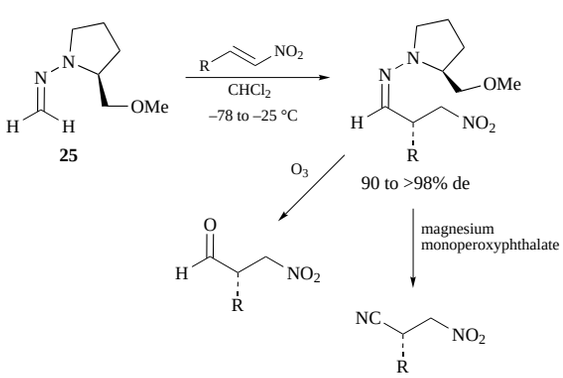
Scheme 5

A sulfimine-stabilised anion adds to carbonyl compounds with subsequent ring closure to give chiral epoxides; benzaldehyde reacts in 70% ee, but other examples are much less selective (21–45% ee).[27]

2.3 Michael addition reactions

2.3.1 Michael addition reactions of chiral nucleophiles

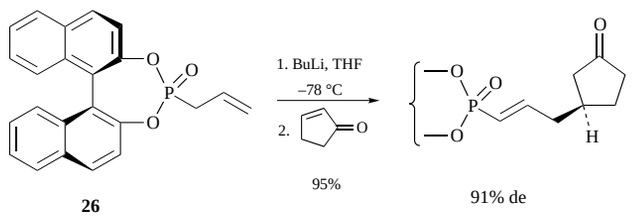
SAMP hydrazones have been used as nucleophiles for Michael reactions in two different ways. Lithiated SAMP hydrazones of methyl ketones are chiral enolate equivalents, and undergo Michael addition to alkenylphosphonates, to give 4-oxophosphonates in moderate to very good ees (20 to >95%).[28] On the other hand, the SAMP hydrazone of formaldehyde **25** is a neutral formyl anion or cyanide equivalent in its Michael additions to nitro alkenes (**Scheme 6**).[29]



Scheme 6

The lithium enolate of a chiral *N*-propionyloxazolidine reacts with α,β-unsaturated esters and amides in 87:13 to >99:1 dr; however small structural variations, or the use of the oxazolidine as the Michael acceptor, gives poor selectivities.[30] Davies has extended the use of chiral lithium amides to Michael additions to α,β-unsaturated Weinreb amides, which allows the products to be transformed into either β-amino aldehydes or ketones.[31]

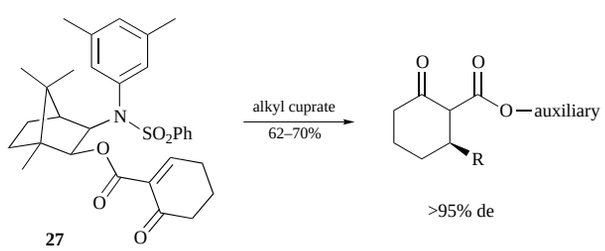
Two groups have described the Michael additions of chiral phosphorus-stabilised allyl anions to α,β-unsaturated cyclic ketones. One uses the allylphosphonate of binaphthol **26** (**Scheme 7**),[32] and the products can be oxidatively cleaved at the new alkene bond. Tandem methylation of the intermediate enolate is possible, and the crotylphosphonate analogous to **26** can also be used, forming two stereocentres during the addition step. A second approach utilises the anions of *P*-allyl oxazaphosphorinanes closely related to **19** shown in Scheme 4.[33]



Scheme 7

2.3.2 Michael addition reactions to chiral electrophiles

The well-established conjugate addition of cuprates to α,β-unsaturated esters of Helmchen's camphor-derived auxiliaries has been extended to the use of unsaturated 5- and 6-membered cyclic β-keto esters, *e.g.* **27** (**Scheme 8**).[34,35,36] The products are formed in uniformly high diastereoselectivities (>95%), and removal of the auxiliary is accomplished simply by heating in methanol, but requires a sealed autoclave at 125 °C.



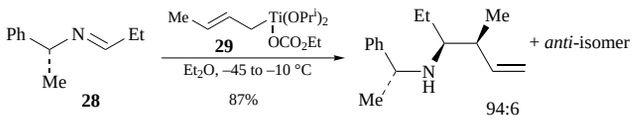
Scheme 8

Meyers has reported the conjugate addition of primary amines to his chiral bicyclic lactams in 95:5 to >98:2 dr, and the products can be transformed by reductive cleavage to chiral 3-aminopyrrolidines.[37] Lithium enolates of esters and ketones undergo Michael addition to chiral Fischer vinyl carbene complexes derived from 8-phenylmenthol.[38] 1,3-Oxathianes have previously been used as auxiliaries for addition to attached carbonyl groups; conjugate addition of organocuprates to the α,β-unsaturated acyl oxathianes gives chiral β-substituted ketones, and the addition of $YbCl_3$ improves the diastereoselectivity.[39]

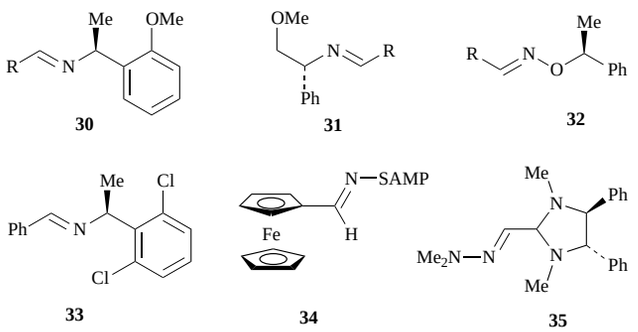
2.4 Additions to C=N double bonds

The addition of nucleophiles to imines prepared from 1-phenylethylamine *e.g.* **28** has been well studied, and reaction with crotyl titanium reagents **29** gives the *syn* homoallylic amines in 94:6 dr (**Scheme 9**).[40] Modification of 1-phenylethylamine by introduction of a methoxy group gives the imines **30**, which give better diastereoselectivities (93:7 to 98:2) in the addition of organolithium reagents, as a result of chelation.[41] The imine **31** also incorporates a chelating methoxy group, but in a different position, and the addition of lithium diethylphosphite provides a route to α-aminophosphonates.[42] Additions to chiral oxime ethers are much less well studied, and

examples bearing a chiral *O*-(1-phenylethyl) group *e.g.* **32** undergo addition of organolithium and Grignard reagents in the presence of $BF_3{\cdot}OEt_2$ in 35–95% de.[43] The bulky (2,6-dichlorophenyl)imine **33** gives fairly good selectivity (83 : 13) in the Staudinger addition of phenoxyketene to give β-lactams;[44] the unsubstituted phenyl analogue is almost unselective.



Scheme 9

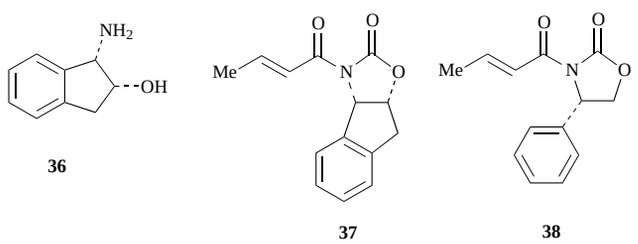


Asymmetric Strecker reactions using auxiliaries on the imine have in the past given mostly moderate selectivities, however Davis has reported that the addition of Pr^{i}OH to the reaction of Et_2AlCN with chiral sulfinimines gives dramatically improved results (82–86% de compared with 36–42% de without Pr^{i}OH).[45]

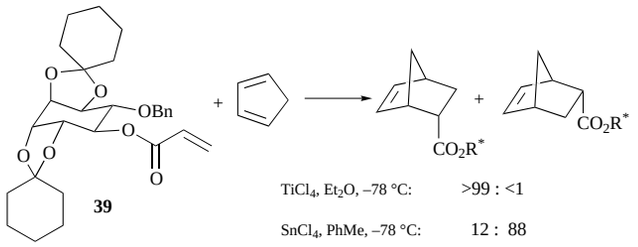
Two different strategies for the addition to the C=N bond of hydrazones are represented by the addition of organolithium reagents to SAMP hydrazones of ferrocene aldehydes **34** in ⩾98% de,[46] where the auxiliary is on the nitrogen atom of the hydrazone, and secondly, addition to a dimethylhydrazone of glyoxal **35**,[47] where the auxiliary is a chiral aminal formed on the second aldehyde group.

2.5 Cycloaddition reactions

New examples of auxiliaries for the dienophile component of Diels–Alder reactions continue to appear. The oxazolidinone **37** derived from aminoindanol **36** gives higher selectivities (87.5–98.4% de) than the structurally related but conformationally less restricted analogue **38**.[48] However, simple acrylate esters of **36** with an *N*-tosyl group are also quite selective (92 : 8 dr) in the $TiCl_4$-promoted reaction with cyclopentadiene.[49] Another α,β-unsaturated *N*-acyl oxazolidinone derived from camphor also gives good results with cyclopentadiene.[50] The Diels–Alder reaction of the acrylate ester **39** is unusual in that it gives an excellent selectivity under one set of conditions, which is reversed simply by changing the solvent and Lewis acid (**Scheme 10**).[51] Cyclic 2-methylene-1,3-bis-sulfoxides give >97 : 3 selectivity in the addition of various dienes, and serve as chiral ketene equivalents.[52]



Incorporation of the chiral auxiliary into the diene component is rather less common, however use of 2-(2-phenylcyclohexyl)oxy dienes gives moderate to high face selectivity.[53]

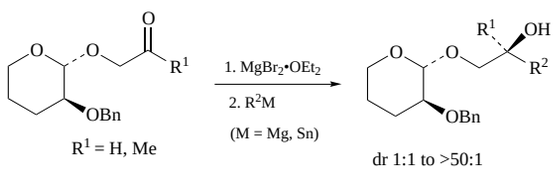


Scheme 10

Nitro alkenes serve as the 4-atom component in the [4 + 2] cycloaddition to chiral vinyl ethers; the resulting cyclic nitronates can be readily transformed into chiral pyrrolidines.[54]

2.6 Other addition reactions

A chiral version of the THP protecting group has been attached to α-hydroxy aldehydes and ketones (**Scheme 11**); addition of allyl stannanes or Grignard reagents occurs with 22 : 1 to 50 : 1 selectivity, and the auxiliary can be removed by conventional hydrolysis.[55,56] Chiral 2-phenoxycyclohexanols have been used as auxiliaries by forming esters with glyoxylic acid; addition of alkylzinc reagents to the aldehyde then affords a route to α-hydroxy acids.[57]

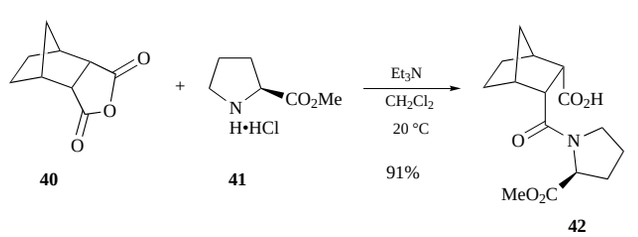


Scheme 11

Roush has reported an improved cyclic amide derivative of tartaric acid as an auxiliary for the addition of chiral allylboronates to aldehydes.[58] Allylsilanes undergo addition to ketones mediated by a norpseudoephedrine derivative;[59] this is a development of the same reaction with aldehydes, but surprisingly gives the opposite facial selectivity with ketones.

2.7 Miscellaneous uses of chiral auxiliaries

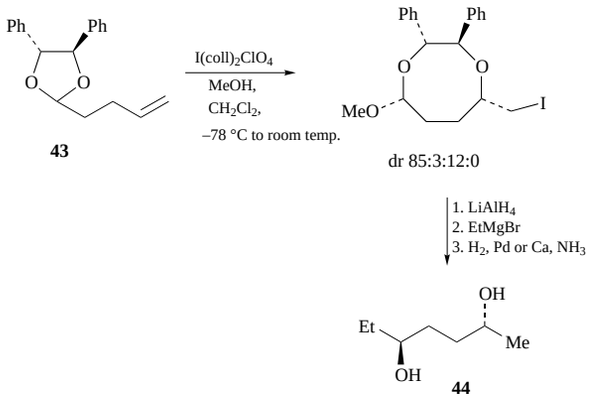
Desymmetrisation of cyclic *meso*-anhydrides is an attractive approach to diacid derivatives containing two or more stereogenic centres in a single step. Norbornene- and norbornane-derived anhydrides, *e.g.* **40,** react with proline methyl ester hydrochloride salt **41** to give the amide **42** with complete selectivity (**Scheme 12**);[60] however cyclohexane-derived anhydrides react non-selectively. Chiral titanium complexes have also been used to desymmetrise cyclic *meso*-anhydrides to give isopropyl monoesters.[61]



Scheme 12

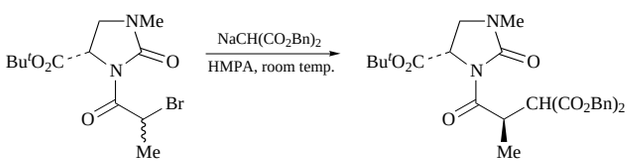
Chiral cyclic acetals have been widely used as auxiliaries in ring-opening reactions. A four-step sequence from the ene acetal **43** results in a synthesis of 1,4-diols **44** (**Scheme 13**).[62] A new dioxane acetal with a 2,6-dichlorophenyl substituent is effective for $TiCl_4$-mediated reaction with allylsilanes and silyl enol ethers, and the products are consistent with the operation of an S_N2-like mechanism.[63]

Dynamic kinetic resolution in the alkylation of dibenzyl



Scheme 13

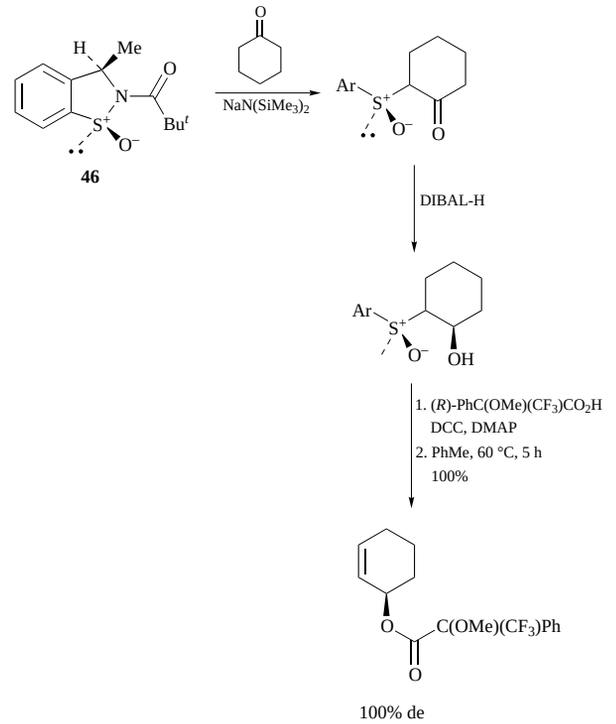
malonate has been achieved using the halide **45**, with rapid epimerisation of **45** occurring under the reaction conditions, and one diastereoisomer reacting selectively (**Scheme 14**).[64] HMPA is required for good selectivity, with other solvents being much less effective.



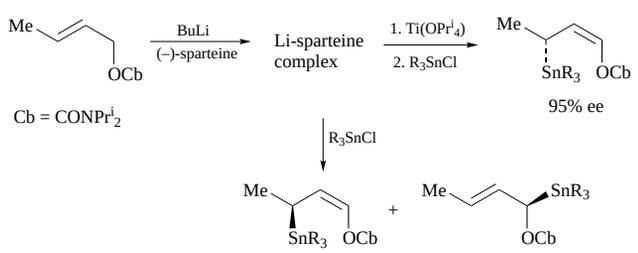
Scheme 14

Intramolecular palladium catalysed cyclisation of chiral enamines onto allylic acetates has been used to form cyclopentanes, with the best result being obtained using a pyrrolidine bearing a pendant phosphine group.[65] Another transition metal mediated cyclisation is the rhodium catalysed insertion of diazo amides containing a chiral ester auxiliary, to give 4-substituted pyrrolidinones.[66] *cis*-2,6-Disubstituted piperidines have been prepared from Meyers' chiral bicyclic lactams by an Eschenmoser sulfur contraction followed by stereoselective hydrogenation.[67]

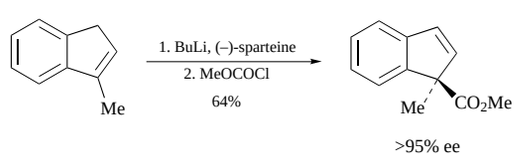
The sulfinamide **46** has been used to introduce a sulfoxide auxiliary by reaction with enolates of ketones (**Scheme 15**).[68] The auxiliary is used to direct the reduction of the ketone, and can then be eliminated thermally to give chiral allylic alcohols or their esters.



Scheme 15



Scheme 16



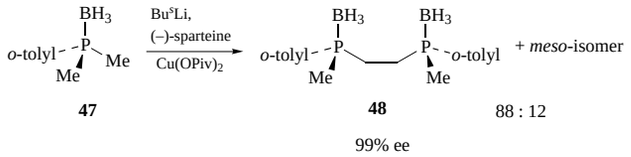
Scheme 17

3 Chiral reagents

3.1 Chiral bases

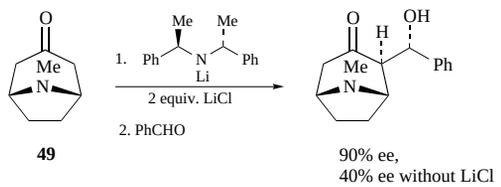
The combination of BuLi (or Bu^{s}Li) and the natural chiral diamine (−)-sparteine has been used for the asymmetric deprotonation of a number of substrates. Lithiated crotyl carbamates have been converted into allylstannanes in high regio- and enantio-selectivity (**Scheme 16**).[69] The opposite enantiomer can be obtained *via* an intermediate titanium species, and the allylstannanes can be reacted with aldehydes and ketones with complete chirality transfer. Reaction of indenes with BuLi–(−)-sparteine gives a configurationally labile organolithium species which undergoes thermodynamic equilibration controlled by the sparteine, before reaction with electrophiles in >95% ee (**Scheme 17**).[70] A similar phenomenon has been reported for the lithiation of *N*-Boc-*N*-methylbenzylamine, which undergoes enantioselective lithiation in the presence of sparteine followed by rapid racemisation and subsequent equilibration to an enantiomerically enriched species.[71] The asymmetric deprotonation of *N*-Boc-pyrrolidine using Bu^{s}Li and various chiral ligands has been studied by Beak,[72] with (−)-sparteine being the best ligand yet found. *N*-Boc-*N*-(3-chloropropyl)benzylamines undergo enantioselective deprotonation followed by rapid cyclisation which is faster than racemisation, to give 2-arylpyrrolidines, mostly in 84–96% ee.[73] Ferrocene bearing an electron-withdrawing amide group is lithiated enantioselectively by BuLi–(−)-sparteine; trapping with electrophiles then gives ferrocene derivatives with axial chirality in 81–99% ee.[74] A similar deprotonation of ferrocene bearing a diphenylphosphinyl group can be achieved using a chiral lithium amide base.[75] Selective deprotonation of enantiotopic methyl groups rather than enantiotopic protons by Bu^{s}Li–(−)-sparteine has been applied to the phosphine borane **47** (**Scheme 18**).[76] Trapping of the anions with benzophenone gives products in 79–87% ee, but homocoupling of the anions gives C_2-symmetric diphosphines **48** in higher 96–99% ee, since the coupling of opposite enantiomers gives the minor *meso*-diastereoisomer. Treatment of cinnamyl alcohol (and other cinnamyl derivatives) with BuLi–(−)-sparteine results not in deprotonation, but enantioselective carbolithiation of the alkene; protonation or trapping with electrophiles then gives products in up to 84% ee.[77]

Selective deprotonation of enantiotopic protons by chiral lithium amide bases has been quite extensively studied, and in some cases addition of LiCl dramatically improves the enantio-



Scheme 18

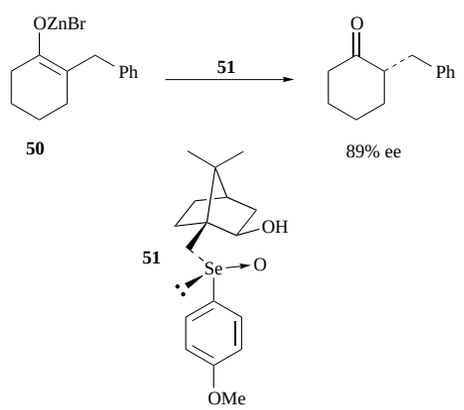
selectivity, *e.g.* from <40% to about 90% ee in the case of tropinone **49** (**Scheme 19**).[78] Preparation of the lithium amide from the hydrochloride salt of the amine and two equivalents of BuLi achieves the same effect.



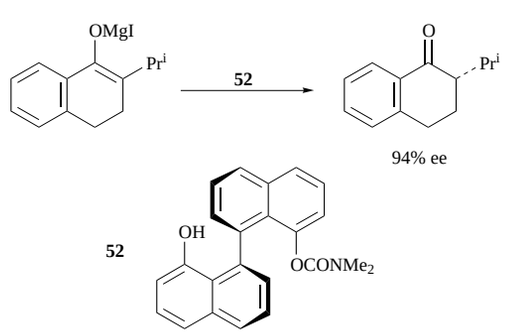
Scheme 19

3.2 Asymmetric protonation

Enantioselective protonation of enolates is possible using a variety of chiral protonating agents.[79] Chiral alcohols are usually not sufficiently acidic to be effective, however the γ-hydroxy selenoxide **51** (**Scheme 20**) gives 89% ee with the zinc enolate of 2-benzylcyclohexanone, **50**,[80] and internal hydrogen bonding is proposed as an important acidifying effect. Phenols are sufficiently acidic to be effective, and the novel chiral binaphthol carbamate **52** protonates substituted-tetralone enolates in up to 94% ee (**Scheme 21**),[79] with magnesium enolates giving much higher selectivities than lithium enolates.



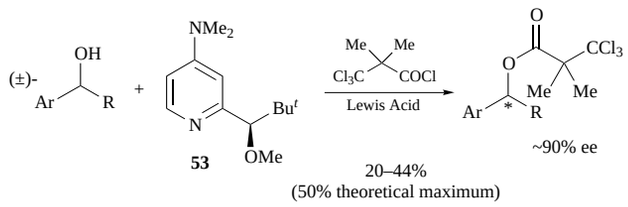
Scheme 20



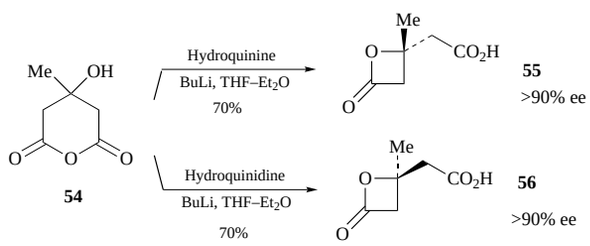
Scheme 21

3.3 Miscellaneous uses of chiral reagents

Kinetic resolution of alcohols, commonly achieved using enzymes, is also possible using synthetic chiral reagents. For example, 4-(dimethylamino)pyridine is a widely used nucleophilic catalyst for acylation, and the chiral derivative **53** resolves aromatic secondary alcohols when used in stoichiometric amounts (**Scheme 22**),[81] although turnover has not yet been achieved. Racemic secondary alcohols have also been resolved in the Mitsunobu reaction, using a chiral phosphine reagent derived from binaphthol.[82] The ester product is formed in low ee (0–39%), but the unreacted alcohol can be obtained in up to 99% ee at the expense of allowing the reaction to proceed to high conversion. The desymmetrisation of the cyclic anhydride **54** can be effected to give either enantiomer of the β-lactone product **55** or **56** using the lithium alkoxides of hydroquinine and hydroquinidine respectively (**Scheme 23**).[83] The β-lactones **55** and **56** can then be converted into various chiral half-esters or amides.

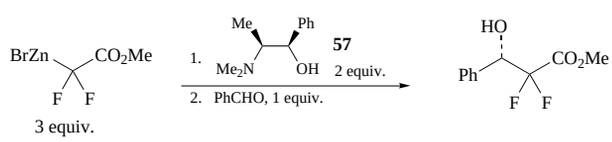


Scheme 22



Scheme 23

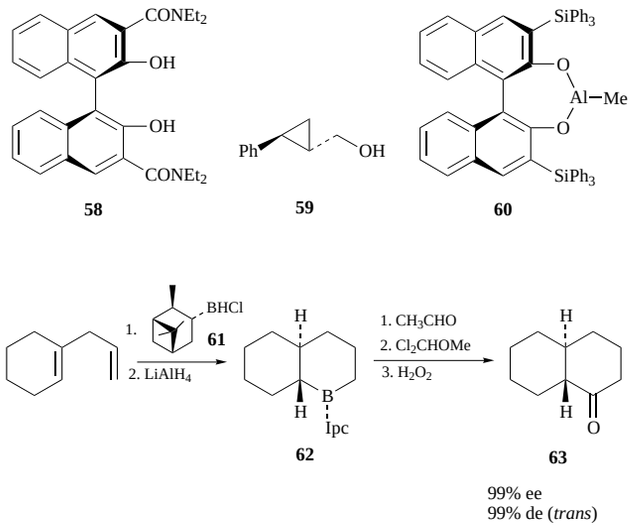
The use of chiral additives in the reaction of organometallic reagents with aldehydes and ketones has been a popular topic in asymmetric synthesis for many years now. Two recent examples use ephedrine derivatives; in one case for the addition of a lithium acetylide to a trifluoromethyl aryl ketone in 96–98% ee,[84] and in the second for an enantioselective Reformatsky reaction (**Scheme 24**).[85] Two equivalents of *N*-methylephedrine **57** are required to give the product in 84% ee, with three equivalents of organozinc reagent, since deprotonation of **57** occurs. Sub-stoichiometric amounts of **57** give reduced selectivities (54% ee with 0.1 equiv.), and the reaction resembles the intensively studied addition of dialkylzinc reagents to aldehydes.



Scheme 24

Modified binaphthols have been prepared to give improved reagents for particular applications. For example, the amide-substituted binaphthol **58** is effective in the Simmons–Smith cyclopropanation of cinnamyl alcohol, giving the cyclopropane **59** in 90% ee.[86] A silyl-substituted binaphthol has been used to prepare the aluminium compound **60**, and this has been used as a chiral Lewis acid to promote radical cyclisation reactions in up to 48% ee.[87]

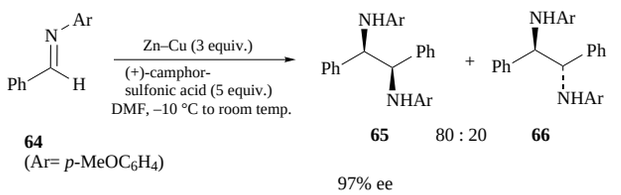
Chiral alkyl boranes have been used extensively for asymmetric hydroboration, and double *cyclic* hydroboration of a diene has been achieved using isopinocampheylchloroborane **61** (**Scheme 25**).[88] The cyclic borane intermediate **62** is then reacted with α,α-dichloromethyl methyl ether to insert a carbon atom, resulting in a synthesis of tetralone **63** in 99% ee. Two other terpene-derived chloroboranes, di-2- and di-4-isocaranyl-



Scheme 25

chloroborane, have been used to prepare enol borinates of substituted acetic acids; subsequent aldol addition to benzaldehyde occurs in >99% ee for several examples.[89]

Camphorsulfonic acid has been used as an additive in a pinacol coupling of the imine **64** (**Scheme 26**) to give the 1,2-diamine **65** in high enantiomeric purity, together with the *meso*-isomer **66** as a minor product.[90] This is an unusual approach to the asymmetric synthesis of 1,2-difunctional systems, since it forms the 1,2-C–C bond as well as the two asymmetric centres in a single reaction.



Scheme 26

Other uses of chiral reagents include a mannitol-derived selenide for methoxyselenation of alkenes,[91] chiral diols to give asymmetric aldol-ring cleavage reactions *via* the acetals,[92] and the allylation of aldehydes by diallyltin dibromide using chiral diamines as Lewis base promoters.[93]

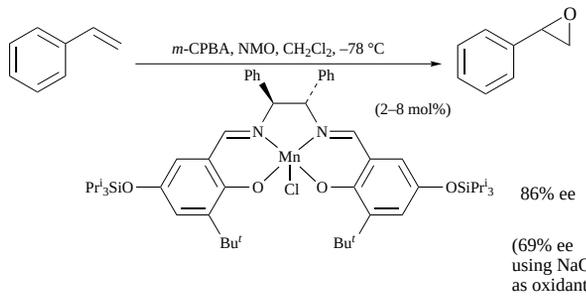
4 Chiral catalysts

4.1 Oxidations

4.1.1 Epoxidation

The Mn-salen catalysed epoxidation of alkenes generally employs aqueous sodium hypochlorite as the stoichiometric oxidant, but if a combination of *m*-CPBA and *N*-methylmorpholine *N*-oxide in dichloromethane at low temperature is used then enhanced enantioselectivities are seen in many cases, particularly for terminal alkenes (**Scheme 27**).[94] This method is also useful for substrates which are water-soluble, or which decompose in aqueous bleach.

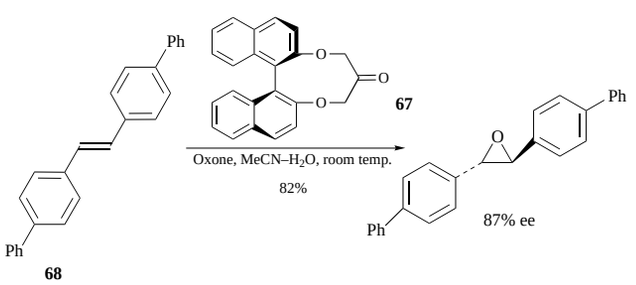
Tetrasubstituted alkenes would be expected to give poor enantioselectivities in the Mn–salen catalysed epoxidation, since their bulkiness prevents side-on approach to the metal-oxo intermediate. However, certain cyclic tetrasubstituted alkenes (*e.g.* chromene derivatives) have been found to react with high selectivities.[95] Nevertheless, small structural changes in the substrate can result in dramatically worse results. Cyclic 1,3-dienes have been epoxidised at low temperature (−18 °C) with improved enantioselectivity (82–94% ee; ≤70% ee obtained previously) using a catalyst with enhanced steric and π-



Scheme 27

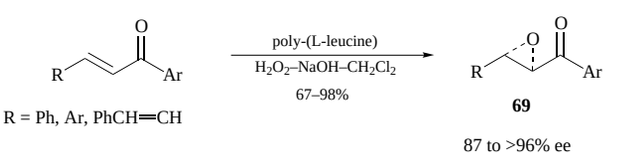
electronic interactions.[96] Enantioselective ring-opening reactions of symmetrical *meso*-epoxides with $Me_3Si–N_3$ are also catalysed by salen complexes in 81–98% ee, with a change of metal from Mn to Cr being essential to control selectivity.[97] Kinetic resolution of racemic terminal epoxides is also possible. A Cr–salen complex has also been employed for catalytic epoxidation of *cis*-β-methylstyrene in 77% ee using iodosylbenzene as the stoichiometric oxidant.[98] This reaction differs substantially from the Mn–salen catalysed reaction: a different mechanism operates, and *trans*-disubstituted alkenes react more selectively than do the *cis*-isomers.

The chiral ketone **67** is a non-transition metal catalyst for asymmetric epoxidation (**Scheme 28**).[99] Oxone is the stoichiometric oxidant, the reaction proceeding *via* a chiral dioxirane intermediate, but with alkenes other than **68** poorer selectivities are obtained (<5–50% ee). A binaphthyl-based iminium salt has also been used with Oxone as a chiral oxygen transfer catalyst for the epoxidation of alkenes.[100] An oxaziridinium salt is the intermediate and 1-phenylcyclohexene reacts with good selectivity (70% ee), but other examples react less selectively (8–45% ee).



Scheme 28

A variety of α,β-unsaturated ketones undergo asymmetric epoxidation with basic hydrogen peroxide using poly(leucine) as the catalyst (**Scheme 29**).[101,102] The epoxides **69** are formed in high yields and ees, and the poly(leucine) catalyst is commercially available, or easily prepared in both L- and D-forms.

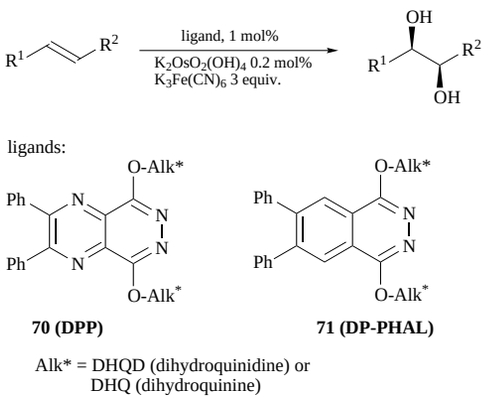


Scheme 29

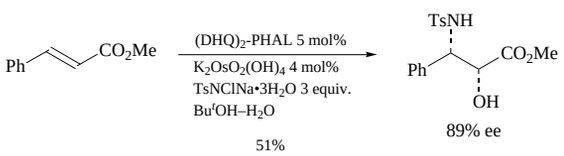
4.1.2 Dihydroxylation

Sharpless has reported several developments in the osmium-catalysed asymmetric dihydroxylation (AD) of alkenes (**Scheme 30**). Bis(cinchona) alkaloid ligands containing new diphenyl-substituted spacers DPP (diphenylpyrazinopyridazine) **70** and DP-PHAL (diphenylphthalazine) **71** give better ees than those used previously for most classes of alkenes, except for alkyl-substituted terminal alkenes.[103] A new spacer based on an anthraquinone core has been found to be effective for terminal

alkenes containing allylic substituents, and is better than previous ligands for this class of compound.[104] Sharpless proposes osmaoxetane intermediates for these reactions, and has studied them using DFT-calculations, concluding that they explain all the enantioselectivities so far observed in AD reactions.[105] The AD reaction has been extended to catalytic aminohydroxylation of alkenes, using Chloramine-T as the nitrogen source (**Scheme 31**).[106]

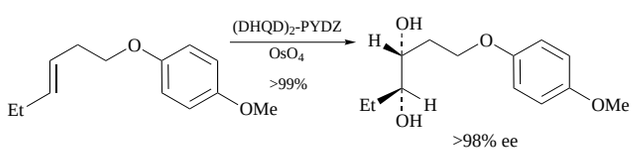


Scheme 30



Scheme 31

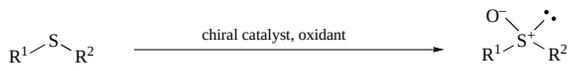
Corey has used his alternative mechanism, involving a complex with a U-shaped cleft and a [3 + 2] cycloaddition pathway, to develop the AD reaction on *p*-methoxyphenyl ethers of homoallylic alcohols (**Scheme 32**).[107] The same approach has also been used for the AD reaction of *p*-methoxyphenyl ethers of bishomoallylic alcohols,[108] and also ethers of 1,3-dienes containing an allylic or homoallylic hydroxy group at the 2-position.[109]



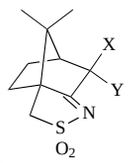
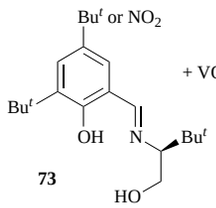
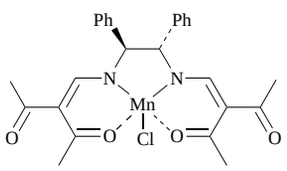
Scheme 32

4.1.3 Other oxidations

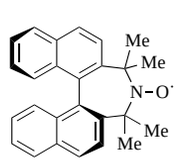
Asymmetric catalytic oxidation of sulfides to sulfoxides (**Scheme 33**) is currently attracting attention, using both synthetic catalysts and enzymatic methods. The widely used Kagan method, using a water-modified Sharpless titanium complex has been optimised, and experimental conditions reported for reproducibly high enantioselectivities for aryl alkyl sulfides.[110] Two recent sulfide oxidations both use hydrogen peroxide as the stoichiometric oxidant. In one, the catalysts are acetals of oxocamphorsulfonylimine **72**, and the reactive intermediate is proposed to be the corresponding α-hydroperoxyamine.[111] Dialkyl sulfides are oxidised in up to 86% ee for acyclic cases, and ⩾98% ee for 2-substituted dithianes. A second example uses a vanadium catalyst with an imine **73** derived from a salicylaldehyde and *tert*-leucinol as the chiral catalyst,[112] and is also more selective for cyclic dithioacetals than acyclic sufides. An Mn–aldiminato complex **74** in combination with pivalaldehyde and molecular oxygen oxidises aryl methyl sulfides in up to 72% ee,[113] and appears to involve the pivalaldehyde in the reactive intermediate.

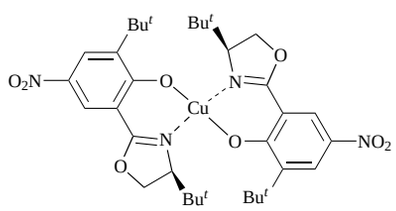


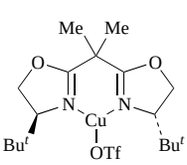
Scheme 33

Catalyst	Oxidant	ee
 **72**	H_2O_2	up to 86% (acyclic) ⩾98% (2-subst. dithiane)
 **73**	H_2O_2	53–70% (acyclic) 85% (2-Ph-dithiolane)
 **74**	O_2, Bu^tCHO	72% (R = 2-Cl-C_6H_4, R^2 = Me)

Other miscellaneous asymmetric oxidations include the resolution of chiral secondary alcohols using the aminoxyl **75** as catalyst together with commercial bleach,[114] the Baeyer–Villiger type oxidation of cyclobutanones using the copper catalyst **76** with pivalaldehyde and oxygen,[115] and the allylic oxidation of alkenes (Kharasch reaction), also using a copper catalyst **77**, and *tert*-butyl perbenzoate.[116]


75


76

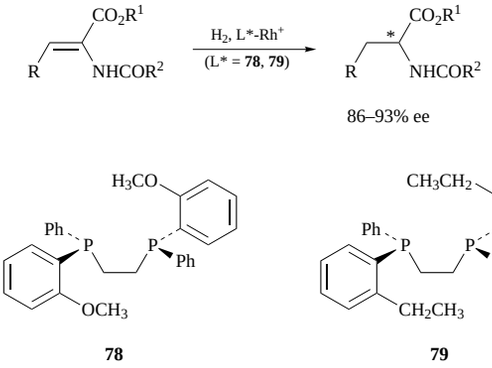

77

4.2 Reductions

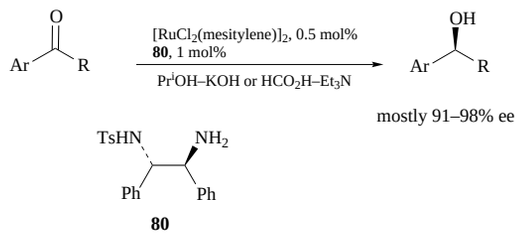
4.2.1 Hydrogenation

The rhodium-catalysed hydrogenation of α-(*N*-acylamino)-acrylic acids in the presence of chiral phosphines is probably the most used and intensively studied asymmetric hydrogenation reaction to date. One of the most widely used ligands is DIPAMP **78** (**Scheme 34**), its isosteric ethyl analogue **79** having also been prepared, and giving similarly high ees in hydrogenation reactions; this suggests that the steric effect of the *o*-MeO group in **78** is more important than coordination to the metal.[117]

Asymmetric transfer hydrogenation of aryl alkyl ketones can be achieved in very high selectivity using a ruthenium catalyst together with a chiral diamine derivative **80**, and Pr^iOH as the hydrogen source (**Scheme 35**).[118] An amino alcohol analogous to **80** is also effective.[119] Because the reaction is reversible, the ee becomes lower as the reaction proceeds, and low substrate con-



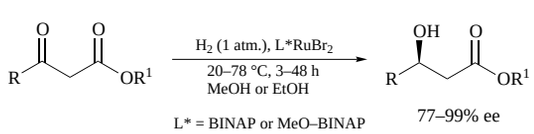
Scheme 34



Scheme 35

centrations are used to obtain high selectivity. However, by using formic acid instead of Pr^{i}OH as the hydrogen source the reduction becomes irreversible, allowing higher substrate concentrations.[120] This is then a very practical method, with the catalyst being prepared *in situ*, and the reaction being conducted in an open vessel. Helmchen has found that chiral phosphinooxazolines are also useful ligands for reduction of aryl alkyl ketones,[121] and they are also reasonably effective (60% ee) for a dialkyl example.

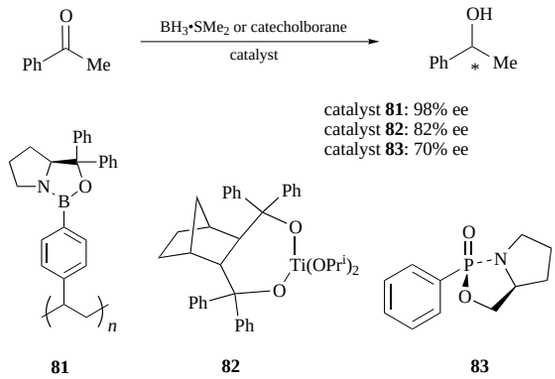
Asymmetric hydrogenation of β-keto esters using a BINAP–Ru catalyst was developed by Noyori several years ago, but most reductions of this type using chiral Ru complexes required elevated pressures of hydrogen (35–100 atm). Catalytic systems have now been developed which allow the reaction to proceed at atmospheric pressure (**Scheme 36**),[122] or slightly above (4 atm).[123]



Scheme 36

4.2.2 Other reductions

Various chiral catalysts have been introduced for the reduction of ketones using borane (**Scheme 37**), following Corey's use of oxaborolidines. A polymer supported version **81** can easily be recovered although the selectivity does begin to diminish after more than one reuse.[124] The chiral titanium alkoxide **82** represents the first titanium-catalysed borane reduction of a ketone,[125] giving 82% ee for acetophenone. The oxazaphospholidine oxide **83** becomes more effective as a catalyst for the reduction of acetophenone as the temperature is increased (70% ee at 60 °C; 40% ee at 20 °C).[126] It is very effective for chloroacetophenone (94% ee) but much less so for alkyl ketones (25–49% ee). Sodium borohydride reductions of ketones can also be made enantioselective by chiral catalysts, and aldiminato cobalt complexes have been used in 68–92% ee.[127] Cyclic *meso*-*N*-phenyl imides have been reduced using a phenoxyborane and a catalyst prepared from diethyl zinc and a chiral α-amino thiol;[128] the products are formed in 70–99% ee and are readily transformed into chiral lactones.

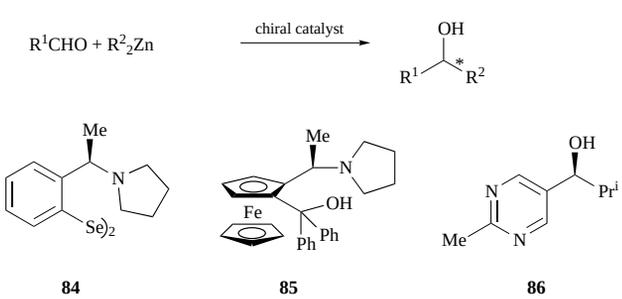


Scheme 37

4.3 Carbon–carbon bond forming reactions

4.3.1 Additions of carbon nucleophiles to carbonyl groups

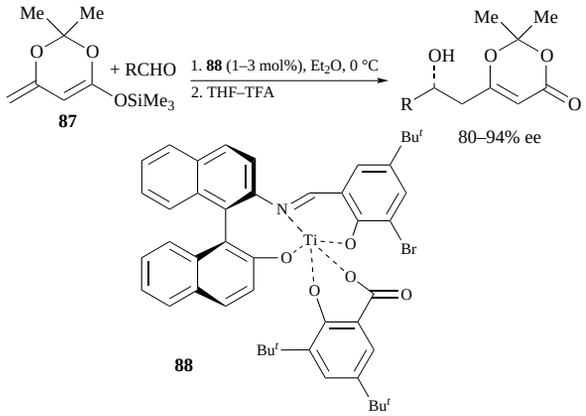
The addition of dialkylzinc reagents to aldehydes in the presence of chiral catalysts (**Scheme 38**) has been intensively studied, and continues to attract new developments. Most catalysts are 1,2-amino alcohols or 1,2-diamines, but new examples include the diselenide **84**, which is derived from 1-phenylethylamine, and is thus accessible in either enantiomeric form.[129] Only 1 mol% of **84** is required for good enantioselectivities using Et_2Zn, with lower selectivities being obtained for non-aromatic aldehydes and other organozinc reagents. The ferrocenyl amino alcohol **85** gives 98.6% ee in the addition of dimethylzinc to ferrocenecarbaldehyde, and the product can be transformed into the opposite enantiomer of the catalyst.[130] Automultiplication of the catalyst, where the product of the reaction is itself the catalyst, has been studied for this type of reaction before, but only low ees had previously been obtained. The pyrimidyl alcohol **86** is the first example of a catalyst giving high ee (93.8%) for automultiplication,[131] although a fairly large amount of catalyst (20 mol%) is required. The use of amino alcohols as catalysts in this reaction gives dramatic non-linear effects, with high ees of products being obtained even with catalysts of low ee. This effect has been studied in detail by Noyori, and discussed in terms of self-recognition of the catalyst in the formation of dimeric species.[132]



Scheme 38

A similar type of non-linear effect is seen in the BINOL-catalysed addition of allylstannanes to aldehydes,[133] where titanium complexes can also be used to poison the racemic catalyst and thus improve enantioselection. The same reaction is also catalysed by a BINOL–zirconium alkoxide complex,[134] again showing positive non-linear effects dependent on the enantiomeric purity of the catalyst. Catalysts prepared from substituted BINOLs and lanthanum alkoxides are effective in the nitroaldol reaction,[135] which is diastereoselective for the *syn*-product (up to 92 : 8) and also shows good enantioselectivity (up to 97%).

The dienol derivative **87** undergoes addition to aldehydes catalysed by the titanium complex **88** to give products which are the equivalent of enantioselective aldol reactions at the γ-position of acetoacetate (**Scheme 39**).[136] Very similar products



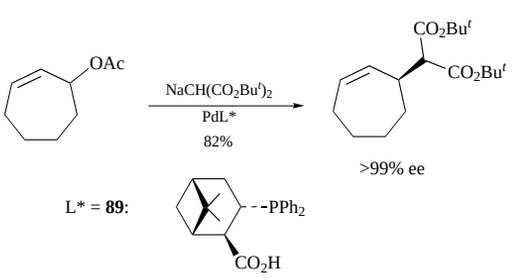
Scheme 39

can also be obtained in 75–91% ee by the reaction of diketene and aldehydes, catalysed by a titanium complex containing a valinol-derived imine.[137]

The Baylis–Hilman reaction involving the addition of α,β-unsaturated ketones to aldehydes is catalysed in low enantioselectivities by cinchona alkaloids. Using chiral disubstituted DABCO (1,4-diazabicyclo[2.2.2]octane) derivatives this can be improved to 47% ee, but high pressures (5 kbar) are required.[138] The preparation of epoxides which also involves C–C bond formation can be achieved by the reaction of sulfonium ylids with aldehydes; use of catalytic amounts of a chiral camphor-derived sulfide together with formation of the ylid by a rhodium-catalysed reaction with phenyl diazomethane results in epoxides in 23–41% ee.[139]

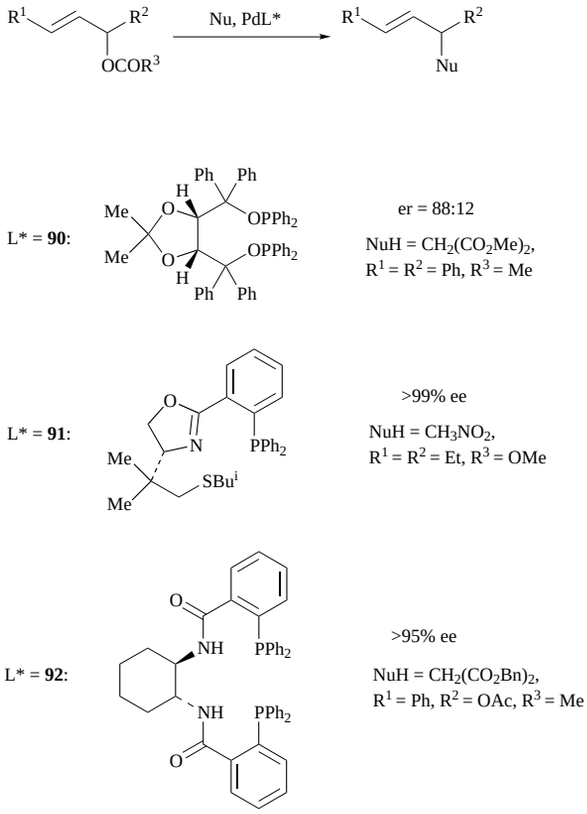
4.3.2 Palladium-catalysed reactions

Several new catalysts and substrates have appeared for the palladium-catalysed substitution of allylic systems. The most studied examples involve the reaction of allylic acetates with malonates as nucleophiles; the terpene-derived phosphinocarboxylic acid ligand **89** gives very high ees with cyclic allylic acetates (**Scheme 40**).[140] A bis(diphenylphosphanyl) ligand **90** based on a tartrate-derived diol gives ers of up to 88 : 12 with acyclic acetates (**Scheme 41**).[141] Nitromethane can serve as the nucleophile as well as the solvent, using allylic carbonates as the substrates.[142] A ligand **91** of the widely used phosphanyldihydrooxazole type is employed, and gives >99% ee. Prochiral *gem*-dicarboxylates react with enantioselective replacement of one carboxylate group in >95% ee using the bis-phosphine ligand **92**.[143] Using a racemic vinyl oxirane as the allylic substrate gives diastereomeric π-allyl palladium intermediates, which interconvert rapidly.[144] Substitution with phthalimide results in conversion of both enantiomers of the oxirane into a protected vinylglycinol in 98% ee.

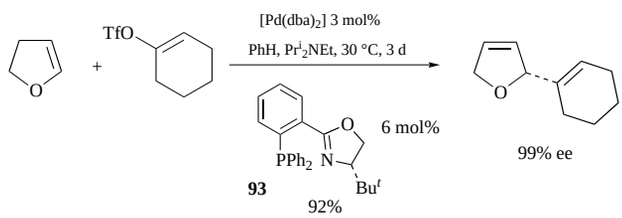


Scheme 40

The phosphanyldihydrooxazole **93**, which has been previously used in allylic substitution reactions, has also been found to be very effective in the palladium-catalysed Heck reaction (**Scheme 42**).[145] Intramolecular asymmetric Heck reactions using BINAP as the ligand have been extended to study the regioselectivity of reaction between two alkene bonds.[146]

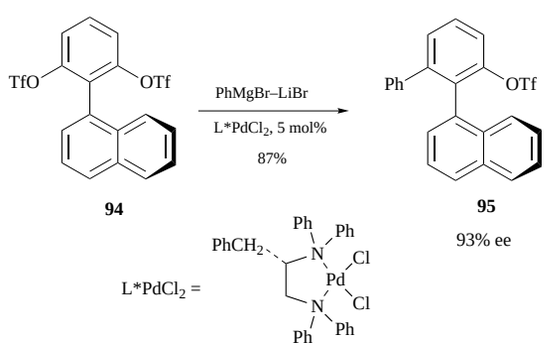


Scheme 41



Scheme 42

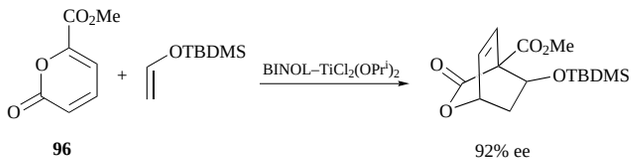
A novel approach to the asymmetric synthesis of biaryl compounds involves the Pd-catalysed cross-coupling of the achiral biaryl **94** with a Grignard reagent (**Scheme 43**).[147] Selective reaction of one of the two enantiotopic triflate groups in **94** gives the chiral biaryl **95** in 93% ee.



Scheme 43

4.3.3 Cycloaddition reactions

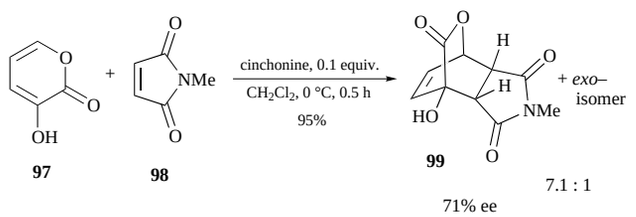
Several examples have appeared of the use of chiral titanium complexes as catalysts in cycloaddition reactions, including Diels–Alder, hetero Diels–Alder and ene reactions. A BINOL–Ti catalyst has been used for 'inverse electron demand' Diels–Alder reactions between the commercial pyrone **96** and electron-rich enol ethers (**Scheme 44**).[148] Details of the preparation of the catalyst are given, which follow the protocol of



Scheme 44

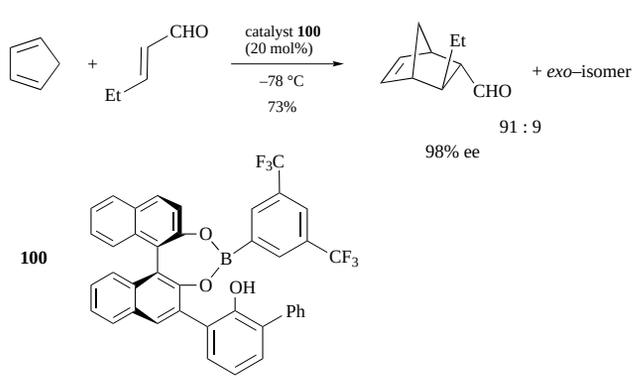
Mikami, but the moisture content of the molecular sieves used to prepare the catalyst, and the temperature of mixing with **96** are crucial for success. Mikami has used a modified catalyst, prepared from 6,6′-dibromo-BINOL to give higher selectivities than the parent BINOL-derived catalyst in hetero Diels–Alder reactions,[149] and also for an ene reaction with isoprene, which gives complete enantioselectivity and very high periselectivity for reaction of one of the two alkene double bonds.[150] A complex prepared from 2:1 BINOL:$Ti(OPr^i)_4$ catalyses the hetero Diels–Alder reaction of Danishefsky's diene with various aldehydes to give dihydropyrans in up to 97% ee.[151]

3-Hydroxypyrone **97** undergoes Diels–Alder reaction with dienophiles, *e.g.* *N*-methylmaleimide **98**, with normal electronic matching (unlike the example with **96** above) (**Scheme 45**). Cinchona alkaloids catalyse the reaction, with cinchonidine and cinchonine giving opposite enantiomers of the product **99** in 77 and 71% ee respectively.[152]



Scheme 45

A Brønsted-acidic catalyst **100**, formed from a BINOL-derived triol and a phenylboronic acid, is a development of a borate catalyst previously described by Ishihara *et al.*, and causes a very large rate acceleration and high enantioselectivity in the Diels–Alder reaction shown in **Scheme 46**.[153]

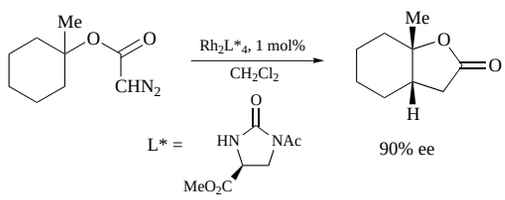


Scheme 46

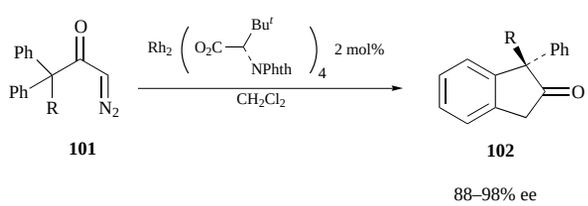
1,3-Dipolar cycloadditions of nitrones have been investigated using Ti catalysts with ligands prepared from tartrate-derived diols (TADDOL–TiX_2).[154] Changing the ligand X from Cl to toluene-*p*-sulfonate remarkably reverses the diastereoselectivity of the reactions from *exo* to *endo*, and also increases the enantioselectivity, often to >90% ee.

4.3.4 Other carbon–carbon bond forming reactions

Various chiral metal complexes can be used to catalyse formation of carbenoid species from α-diazocarbonyl compounds, and both C–H insertion reactions and addition to alkenes to form cyclopropanes can be achieved with high enantioselectivities. Chiral dirhodium(II) carboxamides have been used for intramolecular C–H insertion reactions of diazoacetates, and modification of the catalyst ligand allows insertion into tertiary alkyl ester groups, which have previously given moderate selectivities, in up to 90% ee (**Scheme 47**).[155] Insertion reactions of diazoacetamides of cyclic amines produces bicyclic β-lactams in up to 97% ee, again using chiral dirhodium(II) carboxamide catalysts.[156] An alternative chiral ligand for the dirhodium catalyst is an *N*-protected *tert*-leucine, and selective C–H insertion into one of the two enantiotopic phenyl groups of **101** forms the indanones **102** in 88–98% ee (**Scheme 48**).[157,158] with moderate enantioselectivity, but in a case where rhodium(II) catalysts were unsuccessful. The systematic investigation of different ligand–metal–solvent combinations for C–H insertion reactions has been investigated using the techniques of combinatorial chemistry, with high throughput screening in 96-well plates.[159]

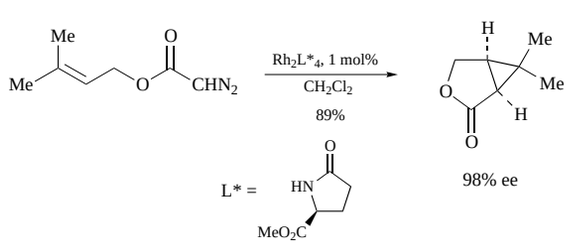


Scheme 47



Scheme 48

The intramolecular cyclopropanation reactions of allylic and homoallylic diazoacetates has been extensively investigated by Doyle[160] using a variety of chiral dirhodium(II) carboxamide catalysts (**Scheme 49**). The allylic substrates give higher enantioselectivities, but these are subject to greater variation with the substitution pattern on the double bond. Racemic secondary allylic diazoacetates undergo kinetic resolution,[161] with the products being formed in 83–95% ee for cycloalkenyl examples, using $Rh_2(MEOX)_4$ (MEOX = methyl 2-oxooxazolidine-4-carboxylate). *N*-Allyl diazoacetamides also undergo intramolecular cyclopropanation with very high enantiocontrol (92–95% ee).[162]

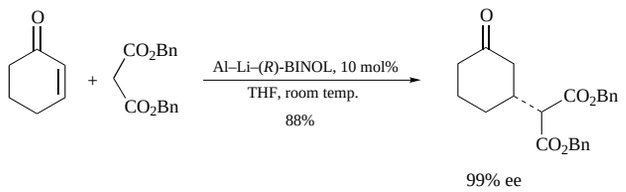


Scheme 49

Chiral semicorrin–copper complexes have been used for the intramolecular cyclopropanation of allylic and homoallylic alkenyl α-diazomethylketones,[163] with the bicyclo[3.1.0]- and bicyclo[4.1.0]-alkanones being formed in up to 85 and 95% ee respectively. Intermolecular cyclopropane formation from α-diazoacetates has been achieved in up to 73% ee using a Co(III)–salen catalyst,[164] and 88% ee using a bis(oxazolinyl)-pyridine Ru(II) complex,[165] with the *trans*-diastereoisomer also being formed selectively in both cases. Cooperative use of a

chiral menthyl α-diazoacetate allows the selectivity in the latter case to be increased to 96% ee.

Shibasaki has reported that Michael additions of malonates to cyclic alkenones occurs with improved enantioselectivities using bimetallic BINOL catalysts containing either lanthanum and sodium,[166] or aluminium and lithium (**Scheme 50**),[167] compared to the previous alkali-metal free BINOL complexes. A very similar lanthanum–potassium–BINOL catalyst is also effective for the addition of dimethyl phosphite to the C=N double bond of *N*-protected imines, to give α-amino phosphonic acids in up to 96% ee.[168]

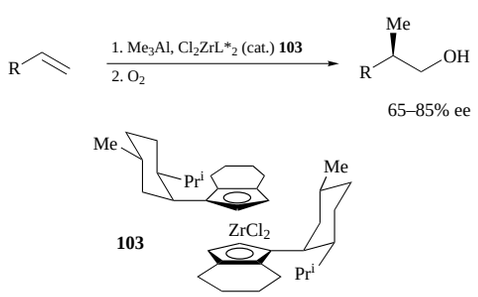


Scheme 50

The asymmetric Michael addition of α-cyano esters to enones and acrolein, catalysed by a bis(phosphinoethyl-ferrocene) ligand, has been extended to the use of an α-cyano Weinreb amide, which allows the chiral products to be transformed into aldehydes and ketones.[169]

Stoichiometric amounts of chiral amidophosphines have previously been used to control the Michael addition of lithium cyanocuprates to cyclic alkenones, and the use of magnesium cuprates has also been found to result in high enantioselectivities, but giving the opposite enantiomer of the product.[170] Use of substoichiometric amounts (0.32 equiv.) of ligand gives good enantioselectivities with alkylmagnesium chlorides and copper iodide, but reducing the amount of ligand to 3 mol% substantially lowers the enantioselectivity.[171]

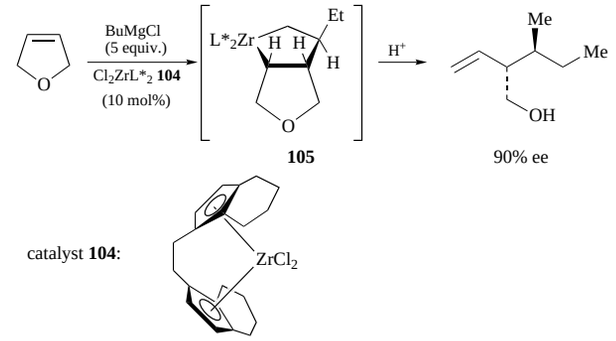
Zirconium-catalysed carbometallation of simple unfunctionalised alkenes is effected by trimethylaluminium and the chiral zirconocene complex **103** in 65–85% ee (**Scheme 51**).[172] In this reaction, the bulky chiral ligand in **103** not only controls the stereochemistry, but also prevents hydride transfer between the methyl-metallated intermediate and the starting alkene. A different chiral zirconocene **104** has been used for asymmetric carbomagnesiation of unsaturated cyclic ethers by Grignard reagents (**Scheme 52**).[173] The reactions proceed in high enantio- and diastereo-selectivity, forming branched alkylated products, consistent with the involvement of intermediate **105**. Addition to unfunctionalised alkenes can also be achieved by iodocarbocyclisation reactions of pentenylmalonates using a chiral titanium catalyst, to give chiral cyclopentanes in up to 94% ee.[174]



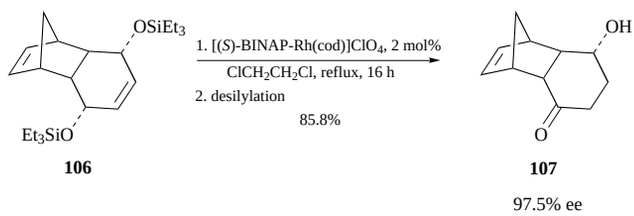
Scheme 51

4.4 Miscellaneous uses of chiral catalysts

Desymmetrisation of *meso*-substrates has been employed in the enantioselective isomerisation of bis(silylated) ene diols *e.g.* **106,** catalysed by a BINAP–rhodium complex, to give the hydroxy ketone **107** in 97.5% ee after desilylation (**Scheme 53**).[175] This reaction has also been extended to the use of a



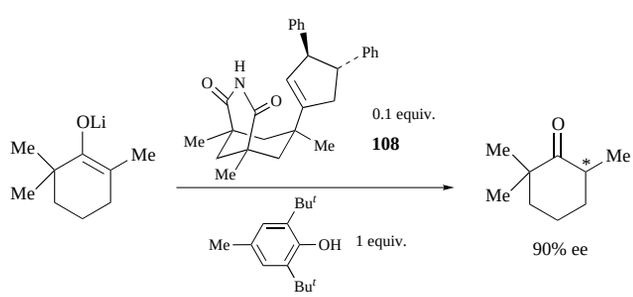
Scheme 52



Scheme 53

monocyclic *meso*-substrate, but in lower enantioselectivity (70% ee).[176] Desymmetrisation of *meso*-epoxides of cyclic alkenes is effected by ring-opening with Me_3SiCN, using a Cr(salen)N_3 catalyst, in 94% ee.[177] Desymmetrisation of *meso*-diols by enantioselective ester formation is generally achieved using enzymic methods; however developments in the use of synthetic catalysts are represented by the acetylation of *cis*-cyclohexane-1,2-diol in 62–67% ee by acetic anhydride in the presence of 5–8 mol% of a chiral phospholane.[178]

Enantioselective protonation of enolates has usually employed stoichiometric amounts of chiral proton donors, however the chiral imide **108**, which has previously been used stoichiometrically, has now been used in catalytic amounts, together with a bulky phenol as an achiral proton source (**Scheme 54**).[179]



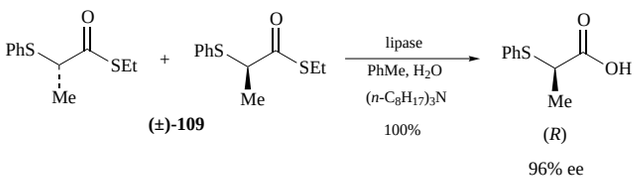
Scheme 54

Rhodium catalysed hydroboration of styrene using a chiral pyrazole-containing phosphinoferrocene ligand is fairly regioselective (2:1) for attachment of boron to the internal carbon atom, and gives 1-phenylethanol in 95% ee after oxidation.[180]

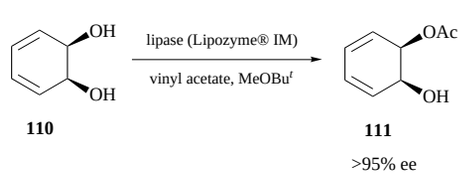
4.5 Enzymes and antibodies

Resolution of racemic esters by enzymic hydrolysis is one of the most widely used applications of enzymes in synthesis. By using the thioester **109** of a carboxylic acid with an α-stereogenic centre, rather than the oxygen analogue, spontaneous racemisation of the substrate occurs in an aqueous–organic biphasic system containing trioctylamine, with lipase-catalysed hydrolysis proceeding to complete conversion in 96% ee (**Scheme 55**).[181] A further advantage is that if the racemisation is fast compared with the hydrolysis, then the substrate never becomes

enriched in the less reactive enantiomer, so the enantioselectivity is independent of the extent of conversion, and remains at the initial (highest) value, unlike the case for a normal kinetic resolution. An alternative approach has been employed in the lipase-catalysed hydrolysis of the acetate esters of some chiral cyclic allylic alcohols, where the racemisation is catalysed by a palladium(II) complex.[182] The reverse reaction, the formation of esters from alcohols, has been applied to the *meso*-diol **110** (derived from the microbial oxidation of benzene) (**Scheme 56**), to give the monoacetate **111**.[183] Substituted analogues of **110** can be formed enantioselectively during the microbial oxidation step, but since the parent compound **110** is achiral, this provides a route to a desymmetrised chiral derivative **111**.

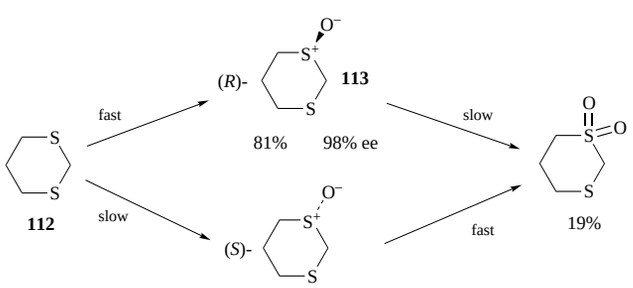


Scheme 55



Scheme 56

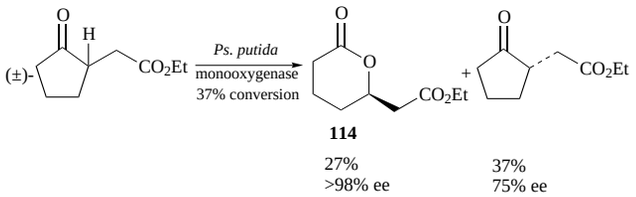
Enantioselective oxidation of sulfides to chiral sulfoxides using enzymes and microorganisms continues to attract considerable attention. The oxidation of methyl *p*-tolyl sulfide can be carried out using bakers' yeast in a procedure which is experimentally simple to perform, and gives the sulfoxide in 92% ee.[184] Cyclohexanone monooxygenase has been used to oxidise 1,3-dithiane **112** (**Scheme 57**);[185] the second oxidation to the sulfone is faster for the minor enantiomer of the sulfoxide **113**, and so a kinetic resolution of the sulfoxide occurs, improving its enantiomeric purity to ⩾98% ee. In contrast, oxidation of **112** by chloroperoxidase or the Kagan method gives **113** in only about 20% ee. Oxidation of 2-substituted dithianes with the same enzyme gives poorer enantioselectivities, except for the 2-benzoyl case, which is oxidised in 90% ee to the *trans*-sulfoxide.[186]



Scheme 57

Enzymatic Baeyer–Villiger reactions using a monooxygenase from *Ps. putida* have been applied to the kinetic resolution of racemic 2-substituted cyclic ketones (**Scheme 58**).[187] By running the reaction to only 37% conversion the product lactone **114** is formed in >98% ee.

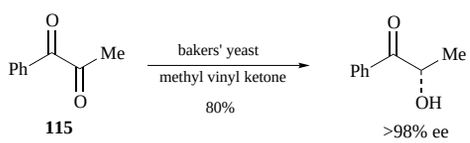
The enantioselectivity of the chloroperoxidase-catalysed epoxidation of simple unfunctionalised alkenes has been examined for a range of different structural types of substrate.[188] Good selectivities are found for a number of disubstituted *cis*-2-alkenes and 3-alkenes, but they are poor for *trans*-disubstituted isomers, and for terminal alkenes and styrene. However, simple



Scheme 58

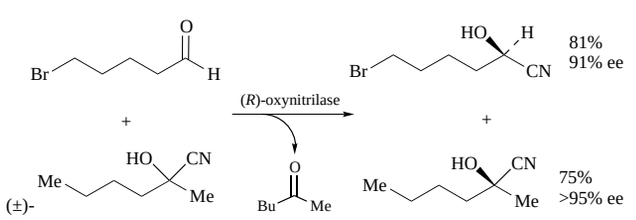
alkyl benzenes undergo side-chain oxidation α to the benzene ring to give benzylic alcohols in high enantioselectivities (88–97% ee). 1,1-Disubstituted terminal alkenes undergo epoxidation with chloroperoxidase with much higher selectivities than the mono-substituted analogues.[189]

The reduction of 1,2-diketones by bakers' yeast normally gives a mixture of the two α-hydroxy ketones and the 1,2-diol, however addition of methyl vinyl ketone as an enzyme inhibitor allows the regio- and enantio-selective reduction of the unsymmetrical diketone **115** (**Scheme 59**).[190]



Scheme 59

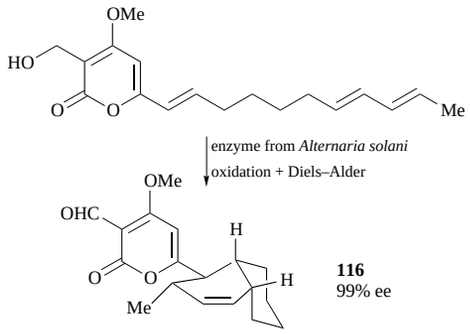
Enantioselective formation of cyanohydrins from aldehydes, catalysed by oxynitrilase from almonds, is a well known enzymatic carbon–carbon bond forming reaction. The reaction also works for methyl and ethyl ketones,[191] with methyl ketones giving higher enantioselectivities in aqueous than in organic media, which is opposite to the case with aldehydes. Using the racemic cyanohydrin of a methyl ketone as the HCN donor, together with an aldehyde as the acceptor, results in both kinetic resolution and enantioselective cyanohydrin formation in the same reaction (**Scheme 60**),[192] allowing both ketone and aldehyde cyanohydrins to be produced in high ee. (*S*)-Selective oxynitrilases can be isolated from plants, but are less accessible than the (*R*)-selective enzyme from almonds. However the gene for the (*S*)-selective oxynitrilase from *Manihot esculenta* has been overexpressed in *E. coli*, with an 80 litre culture giving as much enzyme as 100–200 kg of dried leaves.[193] The (*S*)-cyanohydrins are produced from aldehydes using this recombinant enzyme, mostly in 86–98% ee.



Scheme 60

The isolation of a crude enzyme from *Alternaria solani*, which catalyses Diels–Alder reactions has been reported.[194] In the intramolecular Diels–Alder reaction shown in **Scheme 61** the *exo*-adduct **116** is formed in 99% ee, whereas the spontaneous thermal reaction gives mostly the *endo*-adduct. Antibodies which catalyse the Diels–Alder reaction have been raised using an unusual strategy for the design of the hapten: a flexible ferrocene-containing hapten is employed instead of the more usual rigid bicyclooctane systems,[195] and produces antibodies which give either *exo*- or *endo*-diastereoisomers of the Diels–Alder adduct, in 95% ee in each case.

The first antibody-catalysed enantioselective aldol reaction

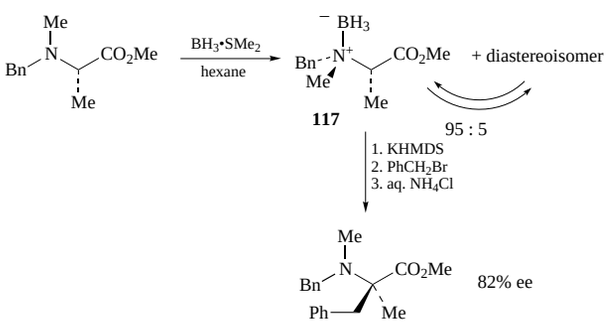


Scheme 61

uses quaternary ammonium salts as the haptens, as analogues of the iminium ion intermediates in the amine-mediated aldol reaction.[196] Selective aldol addition of acetone to the *Si*-face of an aldehyde is observed.

5 Miscellaneous asymmetric processes

The alkylation of enolates of simple α-amino acid derivatives often results in racemisation, however self-regeneration of the stereogenic centre has been achieved by stereoselective formation of a borane adduct **117**, followed by alkylation and simple regeneration of the amino group (**Scheme 62**).[197]



Scheme 62

The asymmetric synthesis of a product with no chiral reagent or catalyst has been achieved by photolysis in the crystalline state.[198] The achiral substrate forms chiral crystals, and can be selectively crystallised in either enantiomeric form by seeding methods. The products are formed in low enantioselectivities (5–20%), but this is an unusual example of crystal-lattice induced stereoselectivity.

Finally, a new method for enantiomeric enrichment exploits differences in density between the crystals of racemic compounds and those of pure enantiomers.[199] Pulverised crystals of an enantiomeric mixture are stirred in a liquid phase whose density is adjusted by mixing bromobenzene and chlorobenzene, and the crystals separate into two layers according to their density. In one case, efficient enrichment was achieved, with phenylalanine of 50% optical purity being separated into two layers of 90 and 13% optical purity respectively.

6 References

1 C. Alvarezibarra, A. G. Csaky, R. Maroto and M. L. Quiroga, *J. Org. Chem.*, 1995, **60**, 7934.
2 A. G. Myers, J. L. Gleason and T. Y. Yoon, *J. Am. Chem. Soc.*, 1995, **117**, 8488.
3 A. G. Myers and T. Yoon, *Tetrahedron Lett.*, 1995, **36**, 9429.
4 M. Kishida, T. Eguchi and K. Kakinuma, *Tetrahedron Lett.*, 1996, **37**, 2061.
5 M. P. Sibi, P. K. Deshpande and J. G. Ji, *Tetrahedron Lett.*, 1995, **36**, 8965.
6 S. M. Sieburth and C. A. Chen, *Synlett*, 1995, 928.
7 P. C. B. Page, M. J. McKenzie and D. R. Buckle, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2673.
8 B. C. Raimundo and C. H. Heathcock, *Synlett*, 1995, 1213.
9 A. K. Ghosh and M. Onishi, *J. Am. Chem. Soc.*, 1996, **118**, 2527.
10 Y. C. Wang, A. W. Hung, C. S. Chang and T. H. Yan, *J. Org. Chem.*, 1996, **61**, 2038.
11 T. H. Yan, A. W. Hung, H. C. Lee, C. S. Hang and W. H. Liu, *J. Org. Chem.*, 1995, **60**, 3301.
12 R. K. Boeckman and B. T. Connell, *J. Am. Chem. Soc.*, 1995, **117**, 12 368.
13 W. Oppolzer, J. Debrabander, E. Walther and G. Bernardinelli, *Tetrahedron Lett.*, 1995, **36**, 4413.
14 D. Enders and U. Reinhold, *Liebigs Ann. Chem.*, 1996, 11.
15 D. Enders, B. B. Lohray, F. Burkamp, V. Bhushan and R. Hett, *Liebigs Ann. Chem.*, 1996, 189.
16 D. Enders, R. Grobner and J. Runsink, *Synthesis*, 1995, 947.
17 D. Enders, T. Berg, G. Raabe and J. Runsink, *Helv. Chim. Acta*, 1996, **79**, 118.
18 D. Enders, M. Knopp, J. Runsink and G. Raabe, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2278.
19 D. Enders and D. Backhaus, *Synlett*, 1995, 631.
20 D. Enders, D. Backhaus and J. Runsink, *Tetrahedron*, 1996, **52**, 1503.
21 K. Tomooka, Y. Nakamura and T. Nakai, *Synlett*, 1995, 321.
22 S. E. Denmark and P. C. Miller, *Tetrahedron Lett.*, 1995, **36**, 6631.
23 M. Guleapurcarescu, E. Aboutjaudet and N. Collignon, *Tetrahedron Lett.*, 1995, **36**, 6635.
24 A. Abiko and S. Masamune, *Tetrahedron Lett.*, 1996, **37**, 1077.
25 D. Enders, J. Kirchhoff, D. Mannes and G. Raabe, *Synthesis*, 1995, 659.
26 A. I. Meyers and B. Santiago, *Tetrahedron Lett.*, 1995, **36**, 5877.
27 C. P. Baird and P. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1995, 893.
28 D. Enders, H. Wahl and K. Papadopoulos, *Liebigs Ann. Chem.*, 1995, 1177.
29 D. Enders, R. Syrig, G. Raabe, R. Fernandez, C. Gasch, J. M. Lassaletta and J. M. Llera, *Synthesis*, 1996, 48.
30 S. Kanemasa, M. Nomura, S. Yoshinaga and H. Yamamoto, *Tetrahedron*, 1995, **51**, 10 463.
31 S. G. Davies and T. D. McCarthy, *Synlett*, 1995, 700.
32 K. Tanaka, Y. Ohta and K. Fuji, *J. Org. Chem.*, 1995, **60**, 8036.
33 S. E. Denmark and J. H. Kim, *J. Org. Chem.*, 1995, **60**, 7535.
34 E. Urban, G. Riehs and G. Knuhl, *Tetrahedron Lett.*, 1995, **36**, 4773.
35 E. Urban, G. Riehs and G. Knuhl, *Tetrahedron*, 1995, **51**, 11 149.
36 E. Urban, G. Knuhl and G. Helmchen, *Tetrahedron*, 1996, **52**, 971.
37 C. J. Andres, P. H. Lee, T. H. Nguyen and A. I. Meyers, *J. Org. Chem.*, 1995, **60**, 3189.
38 J. Barluenga, J. M. Montserrat, J. Florez, S. Garciagranda and E. Martin, *Chem. Eur. J.*, 1995, **1**, 236.
39 K. Utimoto, T. Kodama and S. Matsubara, *Synlett*, 1995, 501.
40 Y. A. Gao and F. Sato, *J. Org. Chem.*, 1995, **60**, 8136.
41 Y. Hashimoto, N. Kobayashi, A. Kai and K. Saigo, *Synlett*, 1995, 961.
42 A. B. Smith, K. M. Yager and C. M. Taylor, *J. Am. Chem. Soc.*, 1995, **117**, 10 879.
43 P. T. Gallagher, A. P. Lightfoot, C. J. Moody and A. M. Z. Slawin, *Synlett*, 1995, 445.
44 Y. Hashimoto, A. Kai and K. Saigo, *Tetrahedron Lett.*, 1995, **36**, 8821.
45 F. A. Davis, P. S. Portonovo, R. E. Reddy and Y. H. Chiu, *J. Org. Chem.*, 1996, **61**, 440.
46 D. Enders, R. Lochtman and G. Raabe, *Synlett*, 1996, 126.
47 A. Alexakis, N. Lensen, J. P. Tranchier, P. Mangeney, J. Feneaudupont and J. P. Declercq, *Synthesis*, 1995, 1038.
48 I. W. Davies, C. H. Senanayake, L. Castonguay, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1995, **36**, 7619.
49 A. K. Ghosh and P. Mathivanan, *Tetrahedron: Asymmetry*, 1996, **7**, 375.
50 M. R. Banks, A. J. Blake, J. I. G. Cadogan, A. A. Doyle, I. Gosney, P. K. G. Hodgson and P. Thorburn, *Tetrahedron*, 1996, **52**, 4079.
51 T. Akiyama, N. Horiguchi, T. Ida and S. Ozaki, *Chem. Lett.*, 1995, 975.
52 V. K. Aggarwal, J. Drabowicz, R. S. Grainger, Z. Gultekin, M. Lightowler and P. L. Spargo, *J. Org. Chem.*, 1995, **60**, 4962.
53 J. Barluenga, M. Tomas, A. Suarezsobrino and L. A. Lopez, *J. Chem. Soc., Chem. Commun.*, 1995, 1785.
54 S. E. Denmark and L. R. Marcin, *J. Org. Chem.*, 1995, **60**, 3221.
55 A. B. Charette, C. Mellon and M. Motamedi, *Tetrahedron Lett.*, 1995, **36**, 8561.
56 A. B. Charette, A. F. Benslimane and C. Mellon, *Tetrahedron Lett.*, 1995, **36**, 8557.
57 D. Basavaiah and P. R. Krishna, *Tetrahedron*, 1995, **51**, 12 169.
58 W. R. Roush and P. T. Grover, *J. Org. Chem.*, 1995, **60**, 3806.

59 L. F. Tietze, K. Schiemann and C. Wegner, *J. Am. Chem. Soc.*, 1995, **117**, 5851.
60 T. Albers, S. C. G. Biagini, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik, M. North, E. Uriarte and G. Zagotto, *Synthesis*, 1996, 393.
61 D. Seebach, G. Jaeschke and Y. M. Wang, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **34**, 2395.
62 H. Fujioka, H. Kitagawa, N. Matsunaga, Y. Nagatomi and Y. Kita, *Tetrahedron Lett.*, 1996, **37**, 2245.
63 M. B. Andrus and S. D. Lepore, *Tetrahedron Lett.*, 1995, **36**, 9149.
64 A. Kubo, M. Takahashi, H. Kubota and K. I. Nunami, *Tetrahedron Lett.*, 1995, **36**, 6251.
65 K. Hiroi, N. Yamaoka, F. Kato and K. Oishi, *Tetrahedron Lett.*, 1995, **36**, 7251.
66 A. G. H. Wee and B. S. Liu, *Tetrahedron Lett.*, 1996, **37**, 145.
67 M. J. Munchhof and A. I. Meyers, *J. Am. Chem. Soc.*, 1995, **117**, 5399.
68 R. J. Butlin, I. D. Linney, M. F. Mahon, H. Tye and M. Wills, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 95.
69 H. Paulsen, C. Graeve and D. Hoppe, *Synthesis*, 1996, 141.
70 I. Hoppe, M. Marsch, K. Harms, G. Boche and D. Hoppe, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **34**, 2158.
71 M. Schlosser and D. Limat, *J. Am. Chem. Soc.*, 1995, **117**, 12 342.
72 D. J. Gallagher, S. D. Wu, N. A. Nikolic and P. Beak, *J. Org. Chem.*, 1995, **60**, 8148.
73 S. D. Wu, S. Lee and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 715.
74 M. Tsukazaki, M. Tinkl, A. Roglans, B. J. Chapell, N. J. Taylor and V. Snieckus, *J. Am. Chem. Soc.*, 1996, **118**, 685.
75 D. Price and N. S. Simpkins, *Tetrahedron Lett.*, 1995, **36**, 6135.
76 A. R. Muci, K. R. Campos and D. A. Evans, *J. Am. Chem. Soc.*, 1995, **117**, 9075.
77 S. Klein, I. Marek, J. F. Poisson and J. F. Normant, *J. Am. Chem. Soc.*, 1995, **117**, 8853.
78 M. Majewski, R. Lazny and P. Nowak, *Tetrahedron Lett.*, 1995, **36**, 5465.
79 K. Fuji, T. Kawabata, A. Kuroda and T. Taga, *J. Org. Chem.*, 1995, **60**, 1914.
80 T. Takahashi, N. Nakao and T. Koizumi, *Chem. Lett.*, 1996, 207.
81 E. Vedejs and X. H. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 1809.
82 R. Hulst, A. Vanbasten, K. Fitzpatrick and R. M. Kellogg, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 2961.
83 K. Hashimoto, J. Kitaguchi, Y. Mizuno, T. Kobayashi and H. Shirahama, *Tetrahedron Lett.*, 1996, **37**, 2275.
84 A. S. Thompson, E. G. Corley, M. F. Huntington and E. J. J. Grabowski, *Tetrahedron Lett.*, 1995, **36**, 8937.
85 M. Braun, A. Vonderhagen and D. Waldmuller, *Liebigs Ann. Chem.*, 1995, 1447.
86 H. Kitajima, Y. Aoki, K. Ito and T. Katsuki, *Chem. Lett.*, 1995, 1113.
87 M. Nishida, H. Hayashi, A. Nishida and N. Kamahara, *Chem. Commun.*, 1996, 579.
88 H. C. Brown, V. K. Mahindroo and U. P. Dhokte, *J. Org. Chem.*, 1996, **61**, 1906.
89 F. Fringuelli, O. Piermatti and F. Pizzo, *J. Org. Chem.*, 1995, **60**, 7006.
90 M. Shimizu, T. Iida and T. Fujisawa, *Chem. Lett.*, 1995, 609.
91 K. Fujita, K. Murata, M. Iwaoka and S. Tomoda, *Tetrahedron Lett.*, 1995, **36**, 5219.
92 H. Suemune, O. Yoshida, J. Uchida, Y. Nomura, M. Tanaka and K. Sakai, *Tetrahedron Lett.*, 1995, **36**, 7259.
93 S. Kobayashi and K. Nishio, *Tetrahedron Lett.*, 1995, **36**, 6729.
94 M. Palucki, G. J. McCormick and E. N. Jacobsen, *Tetrahedron Lett.*, 1995, **36**, 5457.
95 B. D. Brandes and E. N. Jacobsen, *Tetrahedron Lett.*, 1995, **36**, 5123.
96 D. Mikame, T. Hamada, R. Irie and T. Katsuki, *Synlett*, 1995, 827.
97 L. E. Martinez, J. L. Leighton, D. H. Carsten and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5897.
98 C. Bousquet and D. G. Gilheany, *Tetrahedron Lett.*, 1995, **36**, 7739.
99 D. Yang, Y. C. Yip, M. W. Tang, M. K. Wong, J. H. Zheng and K. K. Cheung, *J. Am. Chem. Soc.*, 1996, **118**, 491.
100 V. K. Aggarwal and M. F. Wang, *Chem. Commun.*, 1996, 191.
101 M. E. Lasterra-Sánchez and S. M. Roberts, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 1467.
102 M. E. Lasterra-Sánchez, U. Felfer, P. Mayon, S. M. Roberts, S. R. Thornton and C. J. Todd, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 343.
103 H. Becker, S. B. King, M. Taniguchi, K. P. M. Vanhessche and K. B. Sharpless, *J. Org. Chem.*, 1995, **60**, 3940.
104 H. Becker and K. B. Sharpless, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 448.
105 P. O. Norrby, H. Becker and K. B. Sharpless, *J. Am. Chem. Soc.*, 1996, **118**, 35.
106 G. G. Li, H. T. Chang and K. B. Sharpless, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 451.
107 E. J. Corey, A. Guzmanperez and M. C. Noe, *Tetrahedron Lett.*, 1995, **36**, 3481.
108 E. J. Corey, M. C. Noe and A. Y. Ting, *Tetrahedron Lett.*, 1996, **37**, 1735.
109 M. C. Noe and E. J. Corey, *Tetrahedron Lett.*, 1996, **37**, 1739.
110 J. M. Brunel, P. Diter, M. Duetsch and H. B. Kagan, *J. Org. Chem.*, 1995, **60**, 8086.
111 P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington and D. M. Andrews, *Synlett*, 1995, 773.
112 C. Bolm and F. Bienewald, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **34**, 2640.
113 K. Imagawa, T. Nagata, T. Yamada and T. Mukaiyama, *Chem. Lett.*, 1995, 335.
114 S. D. Rychnovsky, T. L. McLernon and H. Rajapakse, *J. Org. Chem.*, 1996, **61**, 1194.
115 C. Bolm and G. Schlingloff, *J. Chem. Soc.*, *Chem. Commun.*, 1995, 1247.
116 M. B. Andrus, A. B. Argade, X. Chen and M. G. Pamment, *Tetrahedron Lett.*, 1995, **36**, 2945.
117 T. Imamoto, H. Tsuruta, Y. Wada, H. Masuda and K. Yamaguchi, *Tetrahedron Lett.*, 1995, **36**, 8271.
118 S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562.
119 J. Takehara, S. Hashiguchi, A. Fujii, S. Inoue, T. Ikariya and R. Noyori, *Chem. Commun.*, 1996, 233.
120 A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 2521.
121 T. Langer and G. Helmchen, *Tetrahedron Lett.*, 1996, **37**, 1381.
122 J. P. Genet, V. Ratovelomananavidal, M. C. C. Deandrade, X. Pfister, P. Guerreiro and J. Y. Lenoir, *Tetrahedron Lett.*, 1995, **36**, 4801.
123 M. J. Burk, T. G. P. Harper and C. S. Kalberg, *J. Am. Chem. Soc.*, 1995, **117**, 4423.
124 C. Franot, G. B. Stone, P. Engeli, C. Spondlin and E. Waldvogel, *Tetrahedron: Asymmetry*, 1995, **6**, 2755.
125 G. Giffels, C. Dreisbach, U. Kragl, M. Weigerding, H. Waldmann and C. Wandrey, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **34**, 2005.
126 O. Chiodi, F. Fotiadu, M. Sylvestre and G. Buono, *Tetrahedron Lett.*, 1996, **37**, 39.
127 T. Nagata, K. Yorozu, T. Yamada and T. Mukaiyama, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **34**, 2145.
128 J. Y. Kang, J. W. Lee, J. I. Kim and C. Pyun, *Tetrahedron Lett.*, 1995, **36**, 4265.
129 T. Wirth, *Tetrahedron Lett.*, 1995, **36**, 7849.
130 M. Watanabe, *Synlett*, 1995, 1050.
131 T. Shibata, H. Morioka, T. Hayase, K. Choji and K. Soai, *J. Am. Chem. Soc.*, 1996, **118**, 471.
132 M. Kitamura, S. Suga, M. Niwa and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 4832.
133 J. W. Faller, D. W. I. Sams and X. Liu, *J. Am. Chem. Soc.*, 1996, **118**, 1217.
134 P. Bedeschi, S. Casolari, A. L. Costa, E. Tagliavini and A. Umanironchi, *Tetrahedron Lett.*, 1995, **36**, 7897.
135 H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 7388.
136 R. A. Singer and E. M. Carreira, *J. Am. Chem. Soc.*, 1995, **117**, 12 360.
137 M. Hayashi, K. Tanaka and N. Oguni, *Tetrahedron: Asymmetry*, 1995, **6**, 1833.
138 T. Oishi, H. Oguri and M. Hirama, *Tetrahedron: Asymmetry*, 1995, **6**, 1241.
139 V. K. Aggarwal, A. Thompson, R. V. H. Jones and M. Standen, *Tetrahedron: Asymmetry*, 1995, **6**, 2557.
140 G. Knuhl, P. Sennhenn and G. Helmchen, *J. Chem. Soc.*, *Chem. Commun.*, 1995, 1845.
141 D. Seebach, E. Devaquet, A. Ernst, M. Hayakawa, F. N. M. Kuhnle, W. B. Schweizer and B. Weber, *Helv. Chim. Acta*, 1995, **78**, 1636.
142 H. Rieck and G. Helmchen, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **34**, 2687.
143 B. M. Trost, C. B. Lee and J. M. Weiss, *J. Am. Chem. Soc.*, 1995, **117**, 7247.
144 B. M. Trost and R. C. Bunt, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 99.
145 O. Loiseleur, P. Meier and A. Pfaltz, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 200.
146 K. Kondo, M. Sodeoka and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 4322.
147 T. Hayashi, S. Niizuma, T. Kamikawa, N. Suzuki and Y. Uozumi, *J. Am. Chem. Soc.*, 1995, **117**, 9101.

148 G. H. Posner, H. Y. Dai, D. S. Bull, J. K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor and S. Petr, *J. Org. Chem.*, 1996, **61**, 671.
149 Y. Motoyama, M. Terada and K. Mikami, *Synlett*, 1995, 967.
150 M. Terada and K. Mikami, *J. Chem. Soc., Chem. Commun.*, 1995, 2391.
151 G. E. Keck, X. Y. Li and D. Krishnamurthy, *J. Org. Chem.*, 1995, **60**, 5998.
152 H. Okamura, Y. Nakamura, T. Iwagawa and M. Nakatani, *Chem. Lett.*, 1996, 193.
153 K. Ishihara, H. Kurihara and H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 3049.
154 K. V. Gothelf, I. Thomsen and K. A. Jorgensen, *J. Am. Chem. Soc.*, 1996, **118**, 59.
155 M. P. Doyle, Q. L. Zhou, C. E. Raab and G. H. P. Roos, *Tetrahedron Lett.*, 1995, **36**, 4745.
156 M. P. Doyle and A. V. Kalinin, *Synlett*, 1995, 1075.
157 N. Watanabe, T. Ogawa, Y. Ohtake, S. Ikegami and S. Hashimoto, *Synlett*, 1996, 85.
158 H. J. Lim and G. A. Sulikowski, *J. Org. Chem.*, 1995, **60**, 2326.
159 K. Burgess, H. J. Lim, A. M. Porte and G. A. Sulikowski, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 220.
160 M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y. Kwan, S. Liras, C. J. Oalmann, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q. L. Zhou and S. F. Martin, *J. Am. Chem. Soc.*, 1995, **117**, 5763.
161 M. P. Doyle, A. B. Dyatkin, A. V. Kalinin, D. A. Ruppar, S. F. Martin, M. R. Spaller and S. Liras, *J. Am. Chem. Soc.*, 1995, **117**, 11 021.
162 M. P. Doyle and A. V. Kalinin, *J. Org. Chem.*, 1996, **61**, 2179.
163 C. Pique, B. Fahndrich and A. Pfaltz, *Synlett*, 1995, 491.
164 T. Fukuda and T. Katsuki, *Synlett*, 1995, 825.
165 H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki and K. Itoh, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1247.
166 H. Sasai, T. Arai, Y. Satow, K. N. Houk and M. Shibasaki, *J. Am. Chem. Soc.*, 1995, **117**, 6194.
167 T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date and M. Shibasaki, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 104.
168 H. Sasai, S. Arai, Y. Tahara and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 6656.
169 M. Sawamura, H. Hamashima, H. Shinoto and Y. Ito, *Tetrahedron Lett.*, 1995, **36**, 6479.
170 M. Kanai and K. Tomioka, *Tetrahedron Lett.*, 1995, **36**, 4273.
171 M. Kanai and K. Tomioka, *Tetrahedron Lett.*, 1995, **36**, 4275.
172 D. Y. Kondakov and E. Negishi, *J. Am. Chem. Soc.*, 1995, **117**, 10 771.
173 M. T. Didiuk, C. W. Johannes, J. P. Morken and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1995, **117**, 7097.
174 T. Inoue, O. Kitagawa, O. Ochiai, M. Shiro and T. Taguchi, *Tetrahedron Lett.*, 1995, **36**, 9333.
175 K. Hiroya, Y. Kurihara and K. Ogasawara, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2287.
176 K. Hiroya and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1995, 2205.
177 J. L. Leighton and E. N. Jacobsen, *J. Org. Chem.*, 1996, **61**, 389.
178 E. Vedejs, O. Daugulis and S. T. Diver, *J. Org. Chem.*, 1996, **61**, 430.
179 A. Yanagisawa, T. Kikuchi, T. Watanabe, T. Kuribayashi and H. Yamamoto, *Synlett*, 1995, 372.
180 A. Schnyder, L. Hintermann and A. Togni, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 931.
181 D. S. Tan, M. M. Gunter and D. G. Drueckhammer, *J. Am. Chem. Soc.*, 1995, **117**, 9093.
182 J. V. Allen and J. M. J. Williams, *Tetrahedron Lett.*, 1996, **37**, 1859.
183 G. Nicolosi, A. Patti, M. Piattelli and C. Sanfilippo, *Tetrahedron Lett.*, 1995, **36**, 6545.
184 J. Beecher, I. Brackenridge, S. M. Roberts, J. Tang and A. J. Willetts, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1641.
185 S. Colonna, N. Gaggero, A. Bertinotti, G. Carrea, P. Pasta and A. Bernardi, *J. Chem. Soc., Chem. Commun.*, 1995, 1123.
186 S. Colonna, N. Gaggero, G. Carrea and P. Pasta, *Tetrahedron: Asymmetry*, 1996, **7**, 565.
187 B. Adger, M. T. Bes, G. Grogan, R. McCague, S. Pedragosa-moreau, S. M. Roberts, R. Villa, P. W. H. Wan and A. J. Willetts, *J. Chem. Soc., Chem. Commun.*, 1995, 1563.
188 A. Zaks and D. R. Dodds, *J. Am. Chem. Soc.*, 1995, **117**, 10 419.
189 A. F. Dexter, F. J. Lakner, R. A. Campbell and L. P. Hager, *J. Am. Chem. Soc.*, 1995, **117**, 6412.
190 K. Nakamura, S. Kondo, Y. Kawai, K. Hida, K. Kitano and A. Ohno, *Tetrahedron: Asymmetry*, 1996, **7**, 409.
191 F. Effenberger and S. Heid, *Tetrahedron: Asymmetry*, 1995, **6**, 2945.
192 E. Menendez, R. Brieva, F. Rebolledo and V. Gotor, *J. Chem. Soc., Chem. Commun.*, 1995, 989.
193 S. Forster, J. Roos, F. Effenberger, H. Wajant and A. Sprauer, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 437.
194 H. Oikawa, K. Katayama, Y. Suzuki and A. Ichihara, *J. Chem. Soc., Chem. Commun.*, 1995, 1321.
195 J. T. Ylikauhaluoma, J. A. Ashley, C. H. Lo, L. Tucker, M. M. Wolfe and K. D. Janda, *J. Am. Chem. Soc.*, 1995, **117**, 7041.
196 J. L. Reymond and Y. W. Chen, *Tetrahedron Lett.*, 1995, **36**, 2575.
197 V. Ferey, L. Toupet, T. Legall and C. Mioskowski, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 430.
198 M. Sakamoto, M. Takahashi, M. Shimizu, T. Fujita, I. Nishio, I. Iida, K. Yamaguchi and S. Watanabe, *J. Org. Chem.*, 1995, **60**, 7088.
199 D. Kozma, C. Kassai and E. Fogassy, *Tetrahedron Lett.*, 1995, **36**, 3245.