Catalytic asymmetric processes

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REVIEW PERKIN 1

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1 Introduction

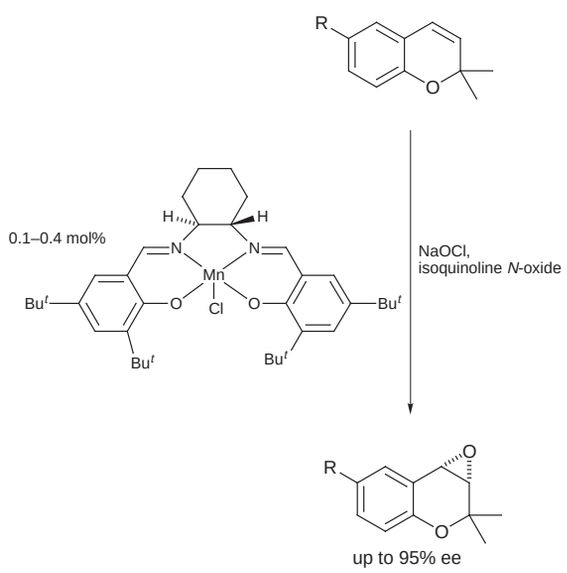
This article covers the literature from April to December 1996, and continues the coverage of corresponding areas in the previous review by A. Regan. A highly selective choice of examples has had to be made from what is a very large, and expanding, field. The emphasis throughout will be on significant improvements and developments of asymmetric catalysis rather than comprehensive coverage of all applications of asymmetric catalysis to synthetic chemistry. Reference to other reviews is limited to those of keynote significance to the field.

2 Synthetic asymmetric catalysts

2.1 Oxidations

2.1.1 Epoxidation and aziridination

As in previous years, the Mn–salen catalysed epoxidation of alkenes (the Jacobsen epoxidation) continues to attract a significant level of interest. Although the mechanism of the reaction is still not fully understood, extensive structural studies have provided a great deal of data about the modes of binding in these[1] and related[2] catalysts. The role of additives and primary oxidant appears to be crucial. Scientists at Merck have established that 4-(3-phenylpropyl)pyrrolidine *N*-oxides are the best of a range of oxidants in this process,[3] giving epoxyindene in up to 88% ee and 90% yield. Other researchers have found that the bleach oxidation gives epoxides from chromenes in up to 95% ee when carried out in the presence of isoquinoline *N*-oxide as an added donor ligand[4] (**Scheme 1**). The additive accelerates the reaction, in which as little as 0.1 mol% of Mn–salen complex need be used, as well as giving good ee values. Racemic indene derivatives may be kinetically resolved to good effect using the Mn–salen system.[5] Epoxidations of enol ethers[6] using the same methodology provides a convenient approach to enantiomerically enriched (80–85% ee) α-hydroxy ketones.



Scheme 1

Contemporary research into asymmetric catalysis has focused in some detail on the immobilisation of catalysts onto a polymer support. The most convenient approach to this in the case of Mn–salen catalysts is through copolymerisation of an alkene substituted derivative with styrene. A number of functional polymers have been prepared by this method, although in general it appears that a long spacer is essential for optimal results.[7] Encasing the catalyst within polydimethylsiloxane membranes also provides a convenient immobilisation method.[8] In a completely different approach, chromenes have been epoxidised in up to 73% ee (although low yield) using an achiral Mn–salen complex (2 mol%) in conjunction with (−)-sparteine (40 mol%).[9]

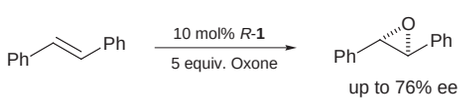
In many respects, aziridination reactions of alkenes represent closely analogous reactions to epoxidations. Using Mn–salen complexes, Katsuki has reported asymmetric inductions of up to 94% ee for this class of reaction.[10] Chiral tetraalkylammonium salts of quinoline alkaloids have been reported to catalyse the reaction to give products of up to 45% ee.[11]

The other very well established asymmetric epoxidation process is of course the Sharpless epoxidation of allylic alcohols. This is now a very mature and well studied reaction which continues to find further applications, both in the synthesis of small molecules such as isostatine[12] and large complex targets such as preswinholide A[13] and FR900482.[14]

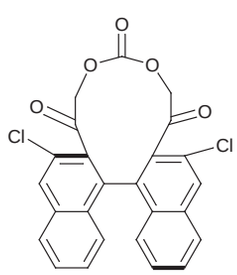
Developments in the synthesis and applications of metalloporphyrins in asymmetric oxidation reactions have been comprehensively reviewed.[15] Although somewhat less effective than Mn–salens and the Sharpless epoxidation, research in this area continues to increase, particularly with Mn porphyrins[16] and

more recently ruthenium complexed analogues. Enantiomeric excesses of up to 57% have been obtained using the latter reagents for the epoxidation of styrene in conjunction with a pyridine oxide as primary oxidant.[17] The same reaction may be achieved using a binuclear iron(III) complex (low yields but 'optical yields' of up to 73%) designed to mimic the methane mono-oxygenase enzyme.[18] An interesting silica supported dioxomolybdenum complex with 4-hydroxyproline has been reported to give moderate enantioselectivity in epoxidations.[19]

A great deal of research has been carried out on the development of *catalytic* dioxirane reagents for asymmetric catalysis. Since many ketones may be readily prepared in enantiomerically pure form, the attraction of the approach is clear. However many attempts have been hindered by the instability of ketones in the reaction, and particularly the propensity for the intermediate dioxiranes to undergo rearrangement to the Baeyer–Villiger product. Ketone **1** is one of the very first reagents which has been demonstrated to be capable of mediating the epoxidation of simple alkenes in catalytic quantities.[20] In the case of stilbene, the epoxide was obtained in up to 76% ee using 10 mol% of **1** and 5 equiv. Oxone (**Scheme 2**). Other substrates gave even better selectivities in the oxidation. The chiral ketone **2** also works effectively, but an excess is required for optimal results (3 equiv. of **2** with 5 equiv. Oxone epoxidises stilbene in up to 95% ee).[21] Further developments in this area are likely to be reported in the next review.



Scheme 2



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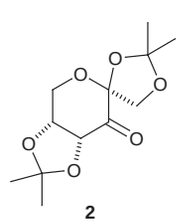


2

Polymeric α-amino acids were found to be effective catalysts for the asymmetric epoxidation of electron-poor alkenes some years ago, however it is only recently that they have emerged as truly valuable synthetic reagents.[22] Of the most recent developments, Roberts has been able to demonstrate the use of polyleucine in the oxidations of a wide range of substrates, affording products such as **3** to **5** in excellent yields and enantiomeric excesses (**Fig. 1**). Polyleucine mediated epoxidation has been applied to the synthesis of enantiomerically enriched dihydroflavanols.[23] In a related process, liposomised MCPBA has been used for the epoxidation of unsaturated esters to give products in a reported 95% ee.[24]

2.1.2 Dihydroxylation

The Sharpless dihydroxylation reaction is one of the foremost asymmetric catalytic processes currently available to the synthetic chemist. The mechanism of the reaction is still a subject

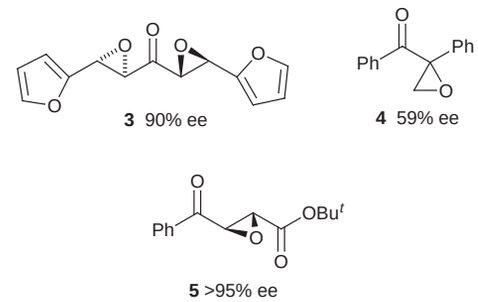
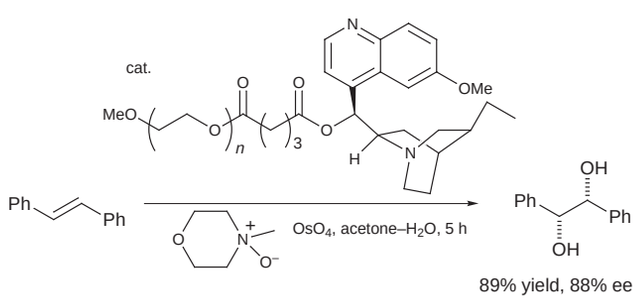


Fig. 1 Products of oxidation with H_2O_2–polyleucine

of some debate, although a comprehensive kinetic and synthetic investigation by Corey,[25] supported by X-ray crystal structures[26] and theoretical calculations[27] appears to favour the longer-established [3+2] cycloaddition mechanism over the alternative [2+2] model forwarded by Sharpless.

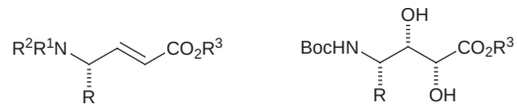
Although a small number of effective alternative ligands have been reported for the asymmetric dihydroxylation reaction,[26,28] Sharpless' own AD-mix method remains dominant. Whilst the use of chemical primary oxidants is normally favoured, an alternative electrochemical method, employing potassium osmate in an undivided cell, has also been reported to give high yields and ee values.[29]

A high profile candidate for modification within a solid support, the dihydroxylation catalysts have been supported on silica gel;[30] however, as in the case of attachment to a polymer chain,[31] the ligand suffers a significant reduction in performance in terms of acceleration and selectivity. In many respects this is perhaps not surprising since ligand-accelerated asymmetric catalysis necessitates a sterically unencumbered ligand system; steric hindrance caused by a nearby polymer chain allows the uncatalysed process to compete. In response to this Janda[31] has described an alternative approach in which a long polyethylene glycol chain is attached to a cinchonidine ligand, thus allowing it to behave as a homogeneous reagent. As a result it performs as well as the free ligand (89% yield of the diol from stilbene in 88% ee) yet may be simply precipitated from the reaction mixture at the end of the reaction by the addition of ether (**Scheme 3**). The recovered catalyst may be reused a number of times without significant loss of activity.



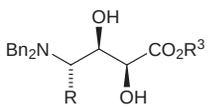
Scheme 3

It is not possible to list here all of the synthetic applications for which the Sharpless dihydroxylation has been employed. It has now become accepted as a widely used versatile and commonplace transformation in which the configuration of the product usually fits that predicted, although there are some exceptions.[32] In some cases it is possible to 'tune' protecting groups to the particular application.[33] An example is provided by the dihydroxylation of compounds **6a** and **6b**, the former of which gives the optimum selectivity with AD-mix-α (product **7**) and the latter of which is optimally protected for the conversion into **8** using AD-mix-β.[33a] In another example, the major enantiomer isolated from the dihydroxylation of 1-phenyl-1-cyclohexylethene proved to be dependent upon the exact bridging group in the alkaloid dimer ligand.[33b]



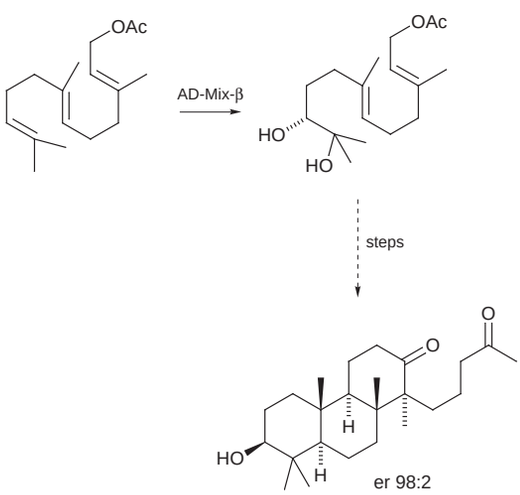
6a (R^1 = H, R^2 = Boc)
6b (R^1 = R^2 = Bn)

7 (97:3 from **6a**) using AD mix–α



8 (97:3 from **6b**) using AD mix-β

Asymmetric dihydroxylation reactions have been carried out in the presence of sulfur containing groups,[34] and in key steps upon furan derivatives to give intermediates in the synthesis of zaragozic acids[35] and multistriatin.[36] A dihydroxylation reaction of a styrene derivative has been employed as a key step in the synthesis of a non-natural amino acid employed in an approach to the total synthesis of vancomycin.[37] The selective dihydroxylation reaction of a polyene has been employed to set up a complex polyene cyclisation for the synthesis of dammarenediol II[38] (**Scheme 4**) and related compounds.[39]



Scheme 4

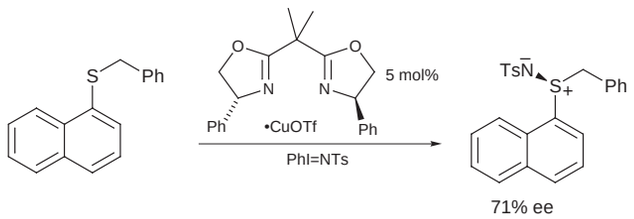
Multiple dihydroxylation reactions, either sequentially or in one concerted process, have proved to be highly effective transformations, providing rapid entries to complex target molecules.[40]

Finally, in this section, readers of the previous review will have noted the introduction of an impressive aminohydroxylation process which works particularly well on unsaturated esters. Subsequently the application of this reaction to the asymmetric synthesis of the side chain of Taxol has been reported.[41]

2.1.3 Sulfoxidations, allylic oxidations and other oxidations

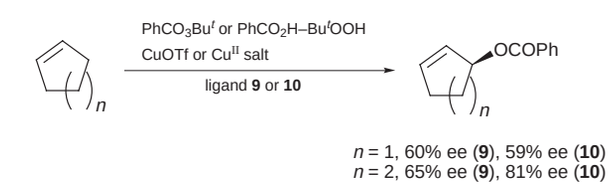
A number of reports have appeared describing the asymmetric synthesis of sulfoxides *via* sulfide oxidation. Perhaps the most widely explored reagent is the titanium–diethyl tartrate system introduced by Kagan.[42,43] This has been studied in depth and has been developed to the point where ees of over 95% may be achieved for certain substrates. A titanium(IV) catalyst containing a C_3-symmetric triol derived ligand[44] and a Mn–salen ligand[45] have also been reported to work well in this application (up to 84 and 94% ee for the optimal substrates in each case).

The synthesis of sulfimides from sulfides represents an analogous process to the sulfoxidation, although it is far less fully developed. The combination of a bis(oxazole) ligand with a Cu^I salt generates a system capable of generation of up to 71% ee for the example shown in **Scheme 5**.[46] Undoubtedly we shall soon see further developments of this interesting reaction.

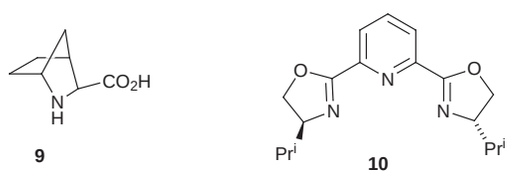


Scheme 5

Another reaction which has generated contemporary interest is the allylic oxidation reaction of cyclic alkenes. Recent reports in this area have concentrated on the use of ligands which are known to be stable to the oxidising conditions (phosphines are unlikely to find an application here). With the ligands **9**[47] and **10**,[48] the transformation shown in **Scheme 6** (n = 1,2) gives products in up to 81% ee, the slightly better result being obtained with **10**. During the study of this reaction with ligand **9**, proline was shown to be rather less effective, however another group have shown that the natural amino acid can give products with an ee of up to 63% when anthraquinone is used as an additive in the reaction.[49] A related asymmetric benzylic oxidation using Mn–salen complexes has been reported.[50] In the latter case the solvent is critical—a 36% ee in acetonitrile increases to 64% ee in chlorobenzene.



Scheme 6



9 **10**

Enzymes have the lead in asymmetric Baeyer–Villiger reaction technology (see a later section), however chemical methods have been reported, with mixed results.[51] Enantioselective decomposition of a racemic peroxide using a Mn–salen complex has been developed as a kinetic resolution process. Under optimised conditions and at 50% conversion, both residual peroxide and derived alcohol (of opposite configuration) are isolated in 45% ee.[52]

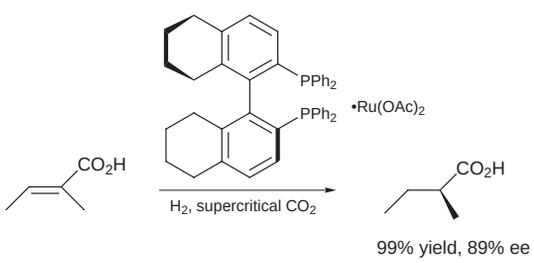
2.2 Reductions

2.2.1 Hydrogenation (C=C double bond reduction)

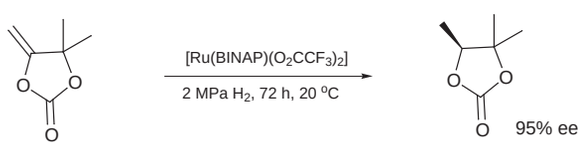
The asymmetric hydrogenation of α-(*N*-acetylamino)acrylic acids and esters using Rh or Ru diphosphine ligands is almost certainly the most widely studied variant of this reaction. Many synthetic transformations, most notably the synthesis of non-natural amino acids, have been achieved using this methodology in conjunction with known ligands[53] and some new ligands have been reported, although they will not be described in detail here. Polymer supported versions which have been reported involve attachment of diphosphines to a polymeric acrylic acid salt (which has the advantage of water solubility),[54] grafting onto Tentagel resin,[55] and attachment to silica.[56] In many cases the supported catalysts perform as well as the free

ligands. Gilbertson has taken the first steps towards the development of an asymmetric hydrogenation system using a combinatorial method.[57] In this work two amino acids bearing diphenylphosphine groups are embedded within a short peptide which is prepared in a multi-well system. The catalysts are tested in parallel in the reduction of α-(acylamino)acrylates. Although the resulting ees are presently low (up to 18%), the method has been demonstrated to be feasible and practical.

The reduction of α-(acylamino)acrylates works well because the amide group coordinates to the metal (usually Rh) in the catalyst, thereby reducing the conformational freedom of the system. α,β-Unsaturated carboxylic acids also behave well in asymmetric hydrogenations for similar reasons, especially in conjunction with ruthenium–BINAP catalyst systems and close analogues thereof.[58] Noyori has this year reported a valuable variant of this process in which a partially hydrogenated BINAP ligand is used in supercritical carbon dioxide. Reduction products from this system are obtained in essentially quantitative yields and ees of up to 89% (**Scheme 7**).[59] Higher selectivities have previously been obtained by Noyori and others[58] in the same reaction under conventional conditions, however the carbon dioxide system provides practical advantages which are of great interest to industry. Asymmetric reduction of unsaturated acids has been achieved in up to 93% ee using a combination of a mixed P–N donor ligand with rhodium.[60] A potentially valuable new transformation is the remarkably selective reduction of cyclic carbonates with Ru–BINAP reagents, which has been the subject of a detailed investigation (**Scheme 8**).[61]

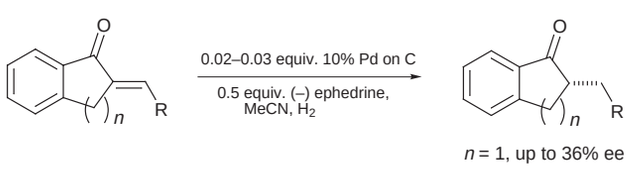


Scheme 7



Scheme 8

Compared to their homogeneous cousins, heterogeneous asymmetric hydrogenations lag considerably in terms of asymmetric induction (although they have potential practical advantages). There are a few notable exceptions which will be highlighted throughout this review. One of these is the combination of cinchonidine with palladium on a titanium oxide support, a complex system in which the ee of reductions increases with conversion, reaching a maximum at a relatively early stage.[62a] Although the latter reactions will require development to become competitive with the homogeneous system, the closely related ephedrine-modified palladium on charcoal reduction of enones (**Scheme 9**) represents a very interesting new development.[62b]

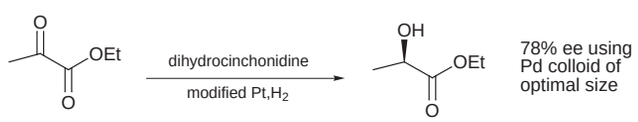


Scheme 9

Asymmetric reduction of isolated double bonds still cannot be achieved using conventional phosphine–metal reagents. It can be achieved however, and with reasonable selectivity, through the use of certain organoyttrium–metallocene reagents. Marks has published a comprehensive paper on this work this year.[63]

Asymmetric hydrogenation provides an excellent method for the asymmetric reduction of ketones to alcohols, indeed many new catalysts which are analogous in structure to BINAP are routinely tested in this application.[58a] The asymmetric hydrogenation of β-keto esters provides a particularly attractive application which is now well established as a standard synthetic method. Refinements and applications of this general transformation are continually being reported,[64a] including the use of supported reagents.[8] β-Keto phosphate esters may also be reduced in high enantioselectivity using this methodology.[64b]

For the reduction of α-keto esters such as pantolactone, amidophosphine phosphinites (*i.e.* derived from amino alcohols) have given good results.[65] However what is perhaps notable about this class of substrate is that it represents one of the few which work well in heterogenous asymmetric hydrogenations. A great deal of work has been carried out on the ethyl pyruvate reduction over cinchonidine-modified Pt (**Scheme 10**).[66–68] The reaction, which requires very low quantities of homochiral modifier and metal, is quite a complex one. In particular the enantioselectivity of the reaction increases with conversion, reaching an optimal level after a relatively short time.[68] Addition of a small amount of enantiomerically pure methyl lactate reduces this 'lag' period, thus strongly suggesting that the product is structurally involved in some way with the catalyst.

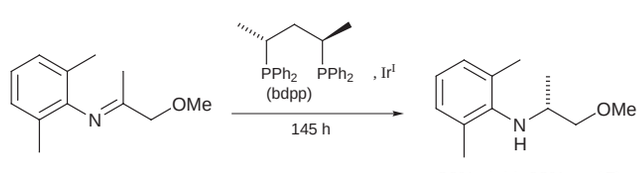


Scheme 10

In a related homogeneous application, a complex of rhodium metal with a chiral diamine was employed to catalyse the asymmetric reduction of methyl phenylglyoxylate in up to 50% enantiomeric excess.[69]

In most of the successful asymmetric hydrogenations of carbonyl groups, it is advantageous for the substrate to contain proximal coordinating groups (*e.g.* hydroxy, ester, halide *etc.*) to assist coordination within the complex. As a result, methods for the asymmetric hydrogenation of simple ketones have, until recently, proved elusive. A number of recent breakthroughs by Noyori and others, which generally rely on the addition of a further phosphine ligand to the reduction system, have provided an effective solution. These developments have been reviewed this year.[70]

Asymmetric hydrogenation of C=N bonds may be achieved by a number of methods. The combination of the diphosphine BINAP with ruthenium(II) generally works well[71] although iridium(I) appears to be a rather more suitable metal for this particular application.[72–74] Again BINAP may be employed as the chiral ligand, promoting reactions of dihydroisoquinolines in up to 88% ee.[72] An alternative ligand which has given good results is the diphosphine bdpp, which is reported by Osborn to be superior to BINAP and DIOP in the application shown in **Scheme 11**.[73] Some interesting results have been obtained in the presence of reverse micelles, in which enhanced reactivity is observed.[74b]

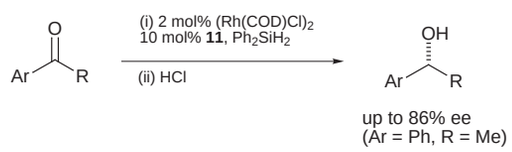


Scheme 11

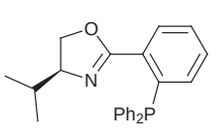
An improved method for the asymmetric reduction of imines, which works particularly well for cyclic substrates, has been reported by Buchwald.[75] In this process a C_2-symmetric titanocene complex is employed at the 5 mol% level for the reduction of cyclic imines in up to 99% enantiomeric excess. This reaction is closely related to the asymmetric hydrosilylation reaction described by the same author, which will be discussed in the next section.

2.2.2 Hydrosilylation

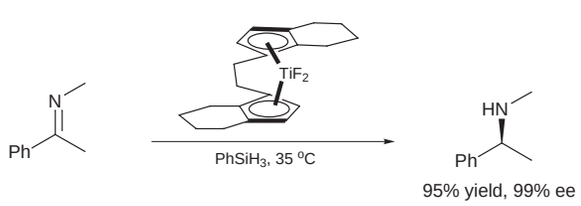
Asymmetric hydrosilylation represents a very attractive alternative to hydrogenation for the reduction of carbonyl groups. Using a combination of (*R*)-BINOL with titanium(IV) tetraisopropoxide gives a catalyst which promotes the hydrosilylation of acetophenone in up to 55% ee.[76] Several groups have reported on the effective use of chiral oxazoline derivatives in combination with either rhodium(I)[77–79] or iridium(I)[80] complexes in asymmetric hydrosilylation reactions. In one of the best of these, reported simultaneously by two research groups, an enantiomeric excess of 86% ee was recorded using the P–N donor ligand **11** in the reaction shown in **Scheme 12**.[77,78] In one of the reports very low levels of ligand were employed (0.4 mol%) and the use of $(CF_3)_2C_6H_3$ group in place of phenyl on the phosphorus atom was found to give an improved ligand.[78] A C_2-symmetric bis(dihydrobenzazaphosphole) ligand has been reported to promote asymmetric hydrosilylation reactions of aryl or alkyl ketones in up to 84% ee.[81]



Scheme 12



Buchwald's asymmetric C=N hydrosilylation reaction using a C_2-symmetric titanocene catalyst is a very powerful process. In many cases as little as 0.02 mol% of the active catalyst is required in order to achieve asymmetric inductions of up to 99% (**Scheme 13**).[82] The reaction is highly versatile and applicable to a wide range of substrates including acyclic, organometallic and alkyl, alkyl substituted imines.

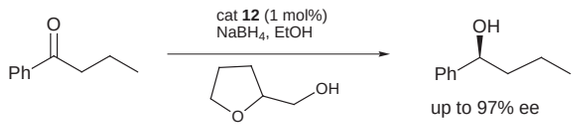


Scheme 13

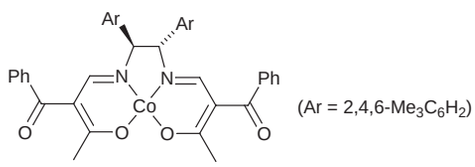
2.2.3 Other reductions

Asymmetric reduction of ketones to secondary alcohols represents a pivotal and fundamental asymmetric transformation (see below). The combination of (*S*)-BINOL with titanium(IV) tetraisopropoxide (10 mol of each) coupled with tributyltin deuteride as the stoichiometric reducing agent is reported to give the labelled product from benzaldehyde in up to 94% ee.[83]

In the sphere of ketone reductions, many new methods have been reported. Cobalt(II)–C_2-symmetric diimine complexes **12** mediate the reduction of ketones with sodium borohydride. This reaction may be dramatically improved by the addition of tetrahydrofurfuryl alcohol as a co-solvent.[84] Both the asymmetric reduction of ketones and the kinetic resolution reactions of racemic ketones are optimised with this additive, the former to the point where products of up to 98% ee may be obtained in sharply reduced reaction times (**Scheme 14**).



Scheme 14



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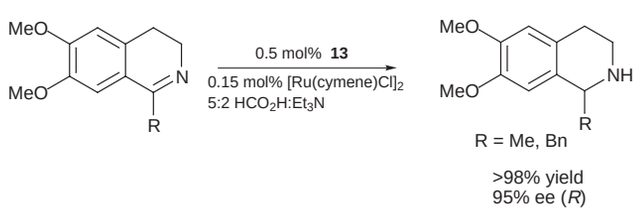
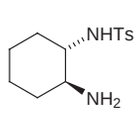
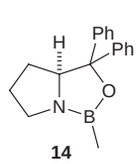
Asymmetric transfer hydrogenation has seen a dramatic increase in recent research interest, largely due to the development of highly active combinations of monotosylated C_2-symmetric diamines **13** with ruthenium(II) complexes (see previous review). New, closely related, ligands have been reported for this reaction,[85] and Noyori has reviewed the area.[86] The methodology has also been extended to an impressive method for the reduction of imines (**Scheme 15**).[87] Diurea ligands have been reported to give enantiomeric excesses of up to 72% when used in conjunction with a rhodium catalyst[88] whilst combinations of ruthenium(II) and BINAP also catalyse the reaction, but in rather moderate selectivity.[89] Meerwein–Ponndorf reductions represent an attractive alternative process and some success has been achieved using aluminium(III) and lanthanide(III) modified reagents in this respect.[90] Lanthanide(III) alkoxy complexes have also been reported to catalyse the reductions of ketones by borane (see below for more details of this), although in modest ee and with a requirement for a relatively large quantity of catalyst.[90a]



Scheme 15



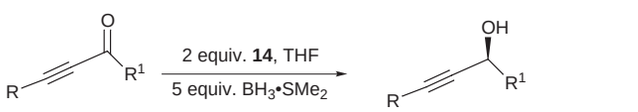


Arguably the most intensely investigated recent breakthrough in asymmetric carbonyl reduction has been the use of oxazaborolidines for catalysis of ketone reductions by borane. Despite the apparant disadvantages of this process (10 mol% catalyst required, use of borane *etc*.) the method has been applied to a very wide spectrum of substrates. Despite the continual development of new oxazaborolidines,[91] Corey's original proline-derived reagent **14** remains the most widely used. In reductions of aryl or alkyl ketones for example, ee values routinely in excess of 95% are obtained.[92]

The mechanism of oxazaborolidine catalysed reductions has been examined in great depth. A modelling study has suggested

that the initial reduction product (a monoalkoxyborane) may compete with borane during the reduction process if there is insufficient time for its dissociation and disproportionation during the reaction.[93] This prediction could account for the improved results obtained when the ketone is added slowly to the reaction mixture, and for certain temperature effects.[94] The addition of triisobutylaluminium to reduction mixtures appears to accelerate the rate of reduction, although the enantioselectivity is largely unchanged.[95]

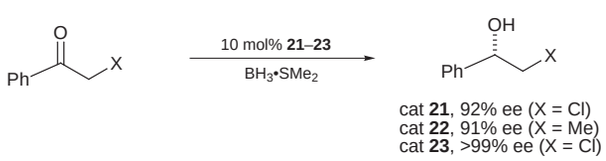
Unsaturated ketones represent challenging substrates for catalytic reductions by borane because the double bond can also participate in reactions. However the highly chemoselective properties of oxazaborolidines make them excellent catalysts for this application.[96] Prop-2-ynyl ketones also make excellent substrates[97–99] although sometimes a rather large quantity of catalyst is required for optimal results of up to 98% ee (**Scheme 16**)![97] A reduction of a prop-2-ynyl ketone with the aid of an oxazaborolidine catalyst was used as a key step in the synthesis of discodermolide by Schreiber and co-workers.[99] The asymmetric reduction of diketones using **14** gives products of extremely high ee (>99%) although at the cost of diastereoselectivity (*threo* : *erythro* 88 : 12 for PhCOCOPh).[100]



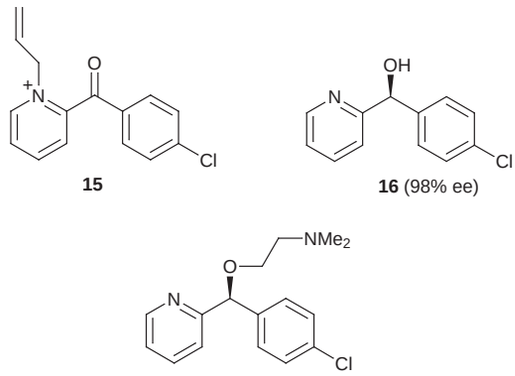
Scheme 16

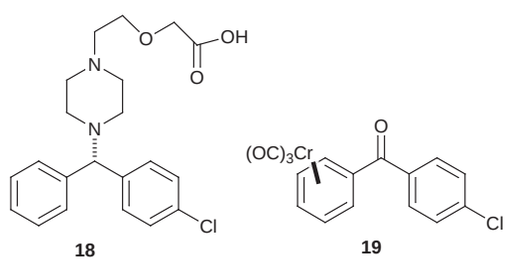
Asymmetric reductions of the pyridinium salt **15** using catalytic quantities of **14** with borane gave a reduction product **16** [a precursor of (*S*)-carbinoxamine **17**] after removal of the allyl group, in 98% ee. The selectivity was much lower when the neutral pyridine was employed as the substrate.[101] A very attractive synthesis of a challenging histidine antagonist (cetirizine hydrochloride) **18** has been achieved *via* the key step of oxazaborolidine catalysed reduction of the chromium tricarbonyl complex **19** to alcohol **20** in 99% yield and 98% ee.[102] The chromium unit serves two roles here; (i) to provide a differentiation between the aromatic rings in the reduction process and (ii) to assist the substitution reaction of the alcohol to give **18**, which proceeds with retention of configuration.

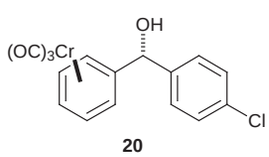
Phosphinamides are a new class of catalyst for the asymmetric reduction of ketones by borane and are a subject on which the author of this review has published.[103,104] Although early versions proved to be rather unselective, it has been found that the incorporation of a proximal hydroxy group into the structure results in a dramatic improvement to the selectivity. Using 10 mol% of **21**[103] or **22**[105] in the reduction of ketones results in high selectivity. **Scheme 17** illustrates some of the optimal results with each catalyst. The related oxazaphospholidine oxide **23**[106] gives even better results (Scheme 17) although it is anticipated that the heterocyclic ring is opened by the action of borane to give a similar intermediate in the reaction to that which is formed from the reaction of **21**. It is therefore likely that they share a common mechanism. Interesting further developments are likely to be reported in this area in the near future.

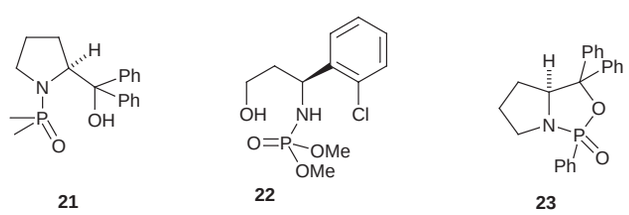


Scheme 17







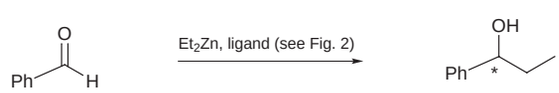


2.3 Carbon–carbon bond forming reactions

Although this section is concerned mainly with the formation of C–C bonds, closely related processes for the formation of C–N bonds will also be described.

2.3.1 Additions of carbon nucleophiles to C=O and C=N bonds

As in previous years, a very large amount of work has been carried out on the asymmetric catalysis of the addition reactions of dialkylzinc reagents to aldehydes (**Scheme 18**). One of the most remarkable features of the amino alcohol accelerated process is the frequent observation of non-linear effects.[107] This is a result of the formation of stable *meso* dimers in the reaction mixture which do not participate in the catalysis process. The result of this process is that a ligand of, say, 15% ee gives a product of 95% ee![108]



Scheme 18

Although limited by space, this review seeks to be comprehensive. **Fig. 2** illustrates some of the new ligands which have been employed within the time frame of this review for the reaction shown in Scheme 18, together with a comparison of their performance.[109–120] Polymeric reagents have also been employed to good effect.[121] Additions of dialkylzincs to C=N

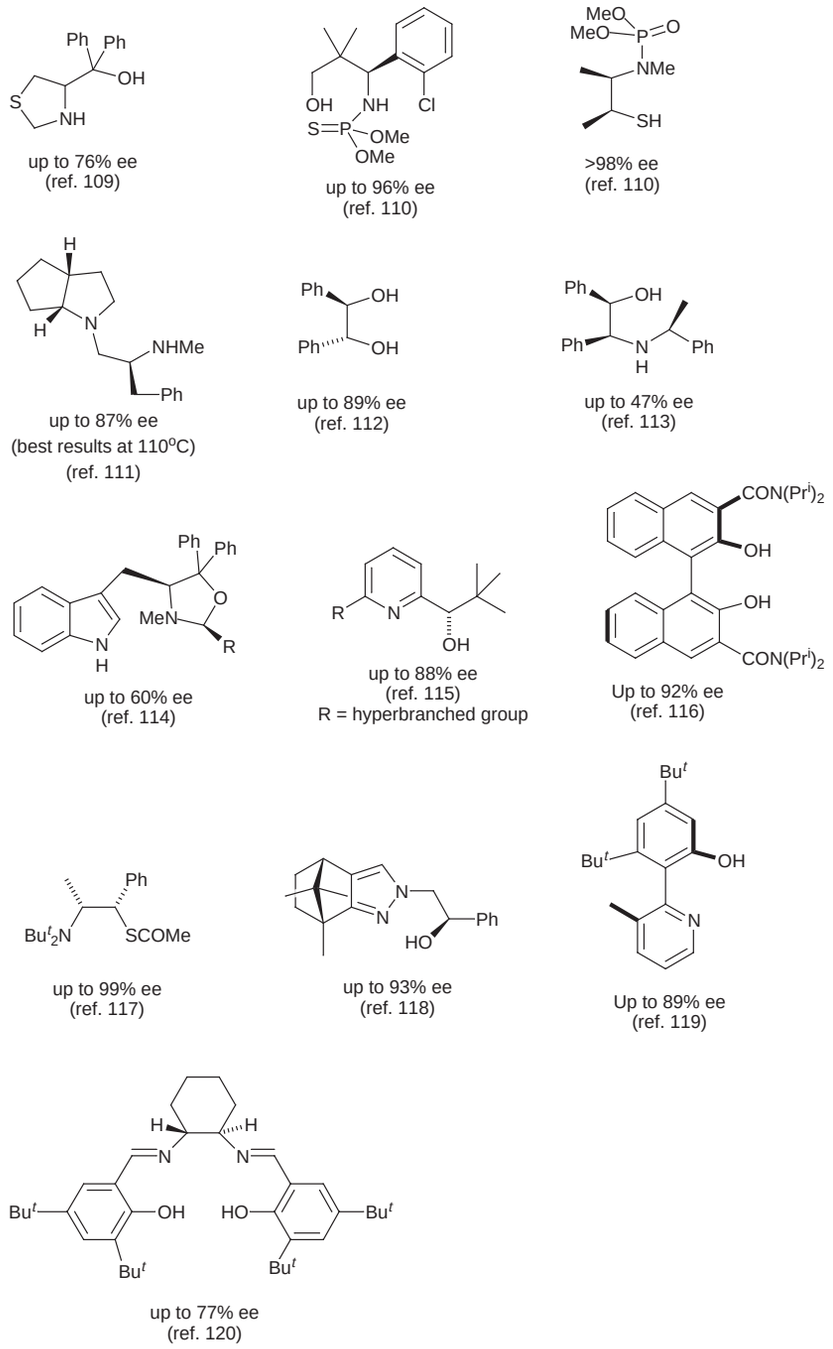
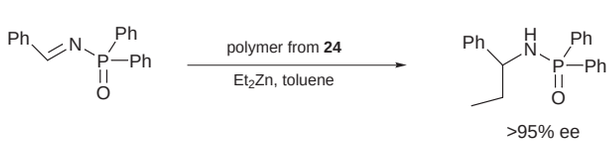


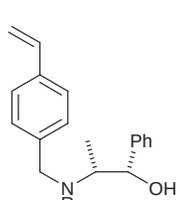
Fig. 2 Ligands used in asymmetric addition of diethylzinc to aldehydes

double bonds work well if the substrates are N-protected by a diphenylphosphino group.[122–124] The copolymer derived from **24** with styrene and vinylstyrene catalyses additions to such imines to give products in as high a selectivity as the homogeneous ligands themselves (**Scheme 19**).[122] Additions of dialkylzincs to symmetrical dialdehydes on iron tricarbonyl complexes shows both regio- and diastereo-selectivity.[125] Although many simple amino alcohols give good results, some researchers have found advantages in the use of titanium(IV) salts with chiral ligands for the asymmetric dialkylzinc addition reaction.[92c,126–128] This method appears to be particularly effective when reactions are carried out on functionalised organozinc reagents, as developed by Knochel and colleagues.

A further interesting feature of diethylzinc chemistry is *autocatalysis*, a phenomenon which results from a situation in which the product of a reaction is also a catalyst for that reaction.[129–131] A typical observation is a rapid increase in the ligand catalysed acceleration which is terminated by exhaustion of reagents. An example of this is the reaction shown in **Scheme 20**, in which catalyst and product are identical![129] In this process the use of 20 mol% of catalyst leads to the formation of the product in 51% yield and of 70.5 % ee.



Scheme 19



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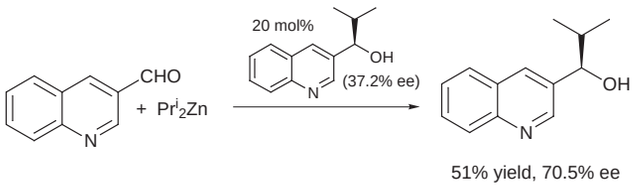
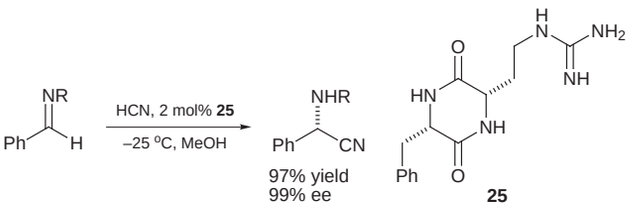


Scheme 20

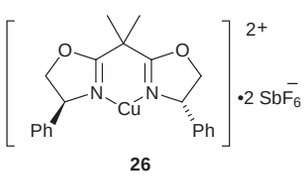
The addition of HCN to imines (an asymmetric Strecker synthesis) is an attractive but elusive target of the synthetic chemist. Using 2 mol% of the cyclic dipeptide **25**, this transformation may be achieved in up to 99% ee and 97% yield (**Scheme 21**).[132,133] Titanium(IV) complexes of chiral salen ligands also work well in this application[134] (87% ee).



Scheme 21

Aldol reaction of nitromethane with aldehydes may be promoted by the addition of a catalytic quantity of a lithium–lanthanide–BINOL combination.[135,136] A quite complex pattern of selectivities is often observed in these reactions, depending on the exact structure of the catalyst and the substrate, however ees of up to 95% may be routinely achieved.

Several examples of catalytic asymmetric aldol reactions of enol ethers with aldehydes have been reported. Some of the best results have been obtained by Evans, who has used chiral copper(II) complexes such as **26** to promote the reaction between a trimethylsilyl ketene acetal and α-benzyloxyacetaldehyde (**Scheme 22**).[137,138] The alkoxy group appears to be important for a chelation interaction in the complex in this reaction, which is also promoted in high selectivity by Cu^{II}• pyridine-2,6-bis(oxazoline) complexes.[138]



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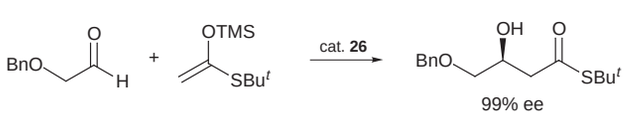
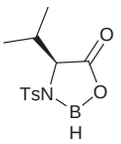


Scheme 22

Trimethylsilyl enol ethers and ketene acetals have been employed in asymmetric titanium(IV)–BINOL catalysed reactions with aldehydes.[139,140] and in conjunction with tin(II)–chiral diamine complexes.[141] Borane-containing heterocycles **27** derived from N-tosylated amino acids are excellent Lewis acid catalysts for catalytic asymmetric aldol reactions, several examples of which have been reported this year.[142–144] The example shown in **Scheme 23** underlines the very powerful directing effect which the catalyst can have in this application.[143] Asymmetric aldol reactions of zinc(II) bromide enolates may be catalysed by an ephedrine-derived amino acid in up to 82% ee.[145]

Lewis-base catalysts are relatively rare in asymmetric synthesis. Apart from the phosphinamide catalysts for ketone



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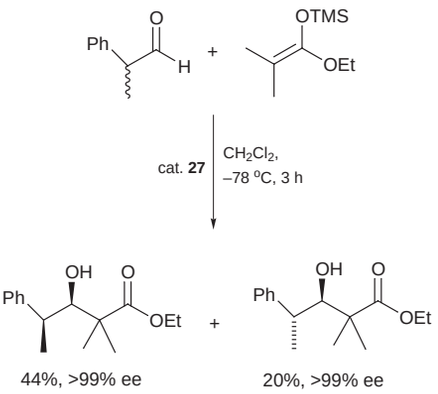
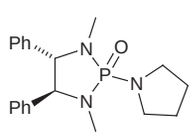


Scheme 23

reduction by borane described in a previous section, the other notable reagents are phosphoramides such as **28**, which are reported by Denmark to catalyse the aldol reaction of trichlorosilyl enol ethers with aldehydes in moderate to good ees (**Scheme 24**).[146] The use of the electron-poor silyl group is essential for coordination of both phosphinamide and aldehyde in the transition state. A related process, in which a phosphoramide catalyses the addition of an allyltrichlorosilane to an aldehyde (which was also developed originally by Denmark) in up to 88% ee, has also been reported this year.[147] The addition of allyltributyltin to aldehydes may be catalysed in excellent ees by Lewis acids derived from titanium–BINOL complexes (up to 97% ee)[148] and with the use of a combination of silver(I) and the diphosphine ligand BINAP[149] (up to 96% ee).



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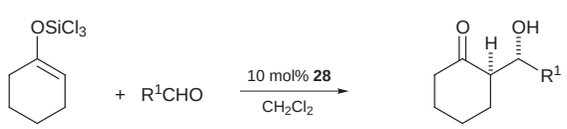
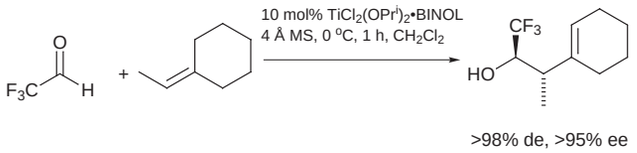


R^1 = Ph, 97% de, 93% ee
R^1 = *E*-(CHCH)Ph, 98% de, 88% ee

Scheme 24

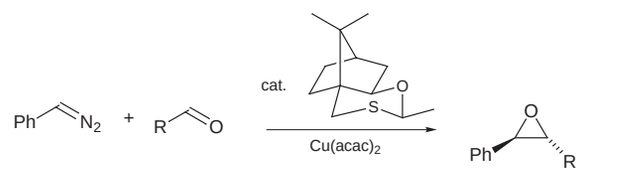
Enantiomerically pure BINOL in conjunction with titanium tetrafluoride forms a highly active catalyst for the asymmetric addition of allyltrimethyl silanes to aldehydes (up to 94% ee).[150] The same chiral diol, within a complex derived from other titanium(IV) complexes, effectively directs the ene reactions of alkenes with aldehydes (**Scheme 25**).[151–155] In an intriguing variation upon this protocol, the use of *racemic* BINOL–Ti^{IV} together with a catalytic amount of enantiomerically pure D-tartrate diester was reported to form a complex capable of generating rather higher asymmetric inductions in the ene reaction than those obtained with enantiomerically pure BINOL alone.[156]

Where exactly to place the very interesting work reported by



Scheme 25

Aggarwal on the asymmetric catalysis of the reaction of sulfur ylides with aldehydes to form enantiomerically enriched epoxides (**Scheme 26**) is not obvious. However since a key step at the end of the sequence of methylene transfers involves a nucleophilic attack on a carbonyl group, it is featured here.[157] The corresponding aziridination reaction, involving an attack on a C=N bond, is also possible using this methdology, although in a slightly lower ee of up to 55%. No doubt this will be improved by optimisation studies.[158]



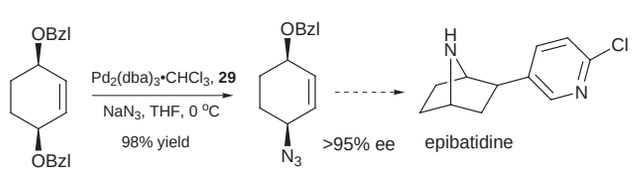
Scheme 26

2.3.2 Palladium-catalysed allylic substitution

In view of the emormous growth in interest in this asymmetric reaction, this reviewer has decided to allocate an entire section to palladium-catalysed allylic substitution reactions.[159,160] One obvious attraction of the reaction is that it is quite easy to perform and generally gives good results, particularly for the prototype reaction of 1,3-diphenyl substituted substrates shown in **Scheme 27**. New ligands for this reaction are featured in **Fig. 3**, together with their optimal inductions.[161–170] It should be noted that the exact conditions for each ligand are likely to vary slightly, however there is not sufficient room for a discussion of this here. Many of the ligands also direct the asymmetric addition of nitrogen nucleophiles in high ee.

Scheme 27

Of the leading researchers in the field, Trost has perhaps been the most industrious over a long and productive term of involvement. He has been instrumental in the development of diphosphines such as **29** with particularly large 'bite angles', which are highly suited to the control of asymmetric inductions with most substrates. Of the many papers published by this author this year[171,172] selected highlights include a concise approach to epibatidine (**Scheme 28**)[171] and a very neat intramolecular cyclisation reaction (**Scheme 29**).[172]



Scheme 28

Other diphosphines,[173,174] most notably BINAP,[175] have been used in allylic substitution reactions, and an X-ray crystal structure of a BINAP–Pd–allyl complex has been reported.[176] The use of rubidium salts was described as critical for optimal

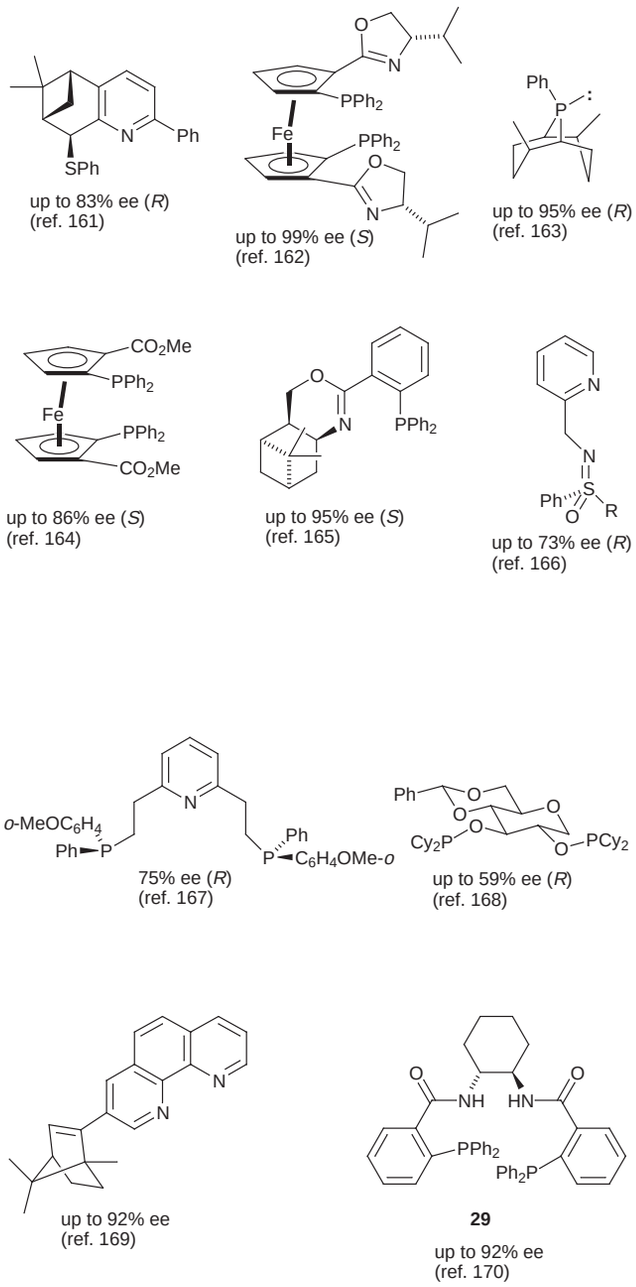
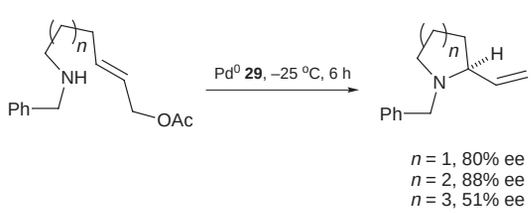


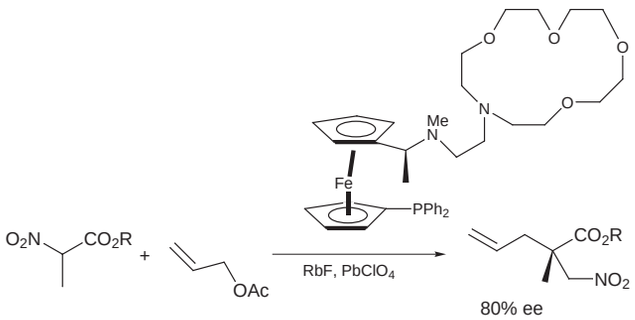
Fig. 3 Ligands used in palladium allyl substitution reactions



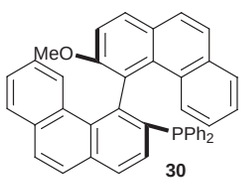
Scheme 29

results in the allylic alkylation reaction shown in **Scheme 30**.[174] Although diphosphines are generally favoured reagents, monophosphines such as MOP-phen **30** sometimes give competitive results.[177] X-Ray crystal structures have clearly demonstrated that **30** binds to palladium only through the phosphorus atom, usually in a 1 : 1 complex (**Scheme 31**).

The second major class of ligands which have worked well in the palladium catalysed allylic substitution reaction are those based on differential atom donors, most commonly P and N. It is generally believed that these ligands work by producing a difference in the level of positive charge density at each end of



Scheme 30



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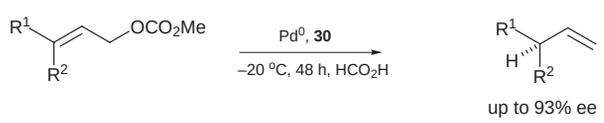
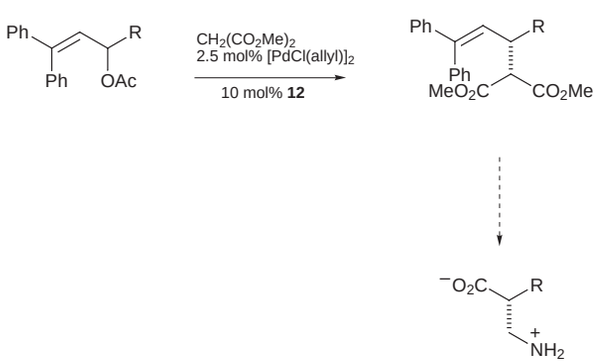


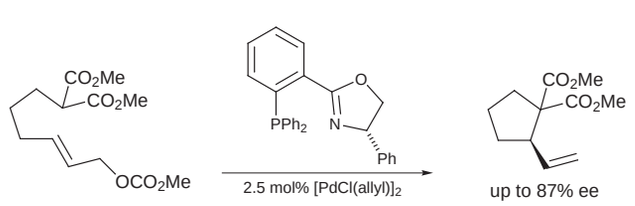
Scheme 31

the allylic ligand, through the well established '*trans*-effect' from the electron-accepting phosphorus atom. Several studies, spectroscopic[178,179] and structural,[180–182] have been reported in support of this effect in both mixed donor and unsymmetric diphosphines.

Using the simple and effective mixed donor ligand **12** (reported previously in a hydrosilylation reaction), and close derivatives thereof, Williams has developed a useful approach to β-amino acids (**Scheme 32**)[183] and Pfaltz has applied the ligand to an intramolecular cyclisation process (**Scheme 33**).[184]



Scheme 32

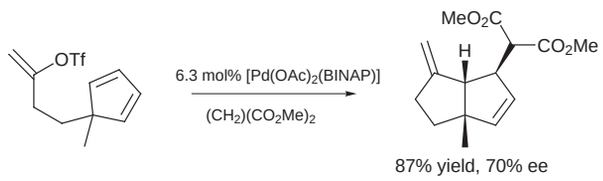


Scheme 33

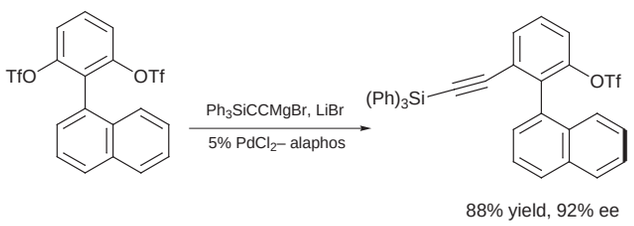
Finally, in this section, we note an asymmetric *elimination* reaction of a racemic carbonate using BINAP–Pd complex which proceeds with an ee of up to 37%.[185]

2.3.3 Heck, hydroformylation and related reactions

A variety of asymmetric Heck reactions have been reported. In the majority of cases the reagent of choice is a combination of palladium with BINAP.[186–188] **Scheme 34** illustrates the key step in a very concise approach to the synthesis of capnellene[188] in which the Heck reaction–allylic alkylation not only established the second ring and the absolute stereochemistry, but also sets up the groups for the cyclisation to the third ring in the product. In contrast, (*S*)-alaphos proved to be the best ligand for the palladium catalysed coupling of an alkynyl Grignard reagent to a prochiral ditriflate precursor (**Scheme 35**).[189]

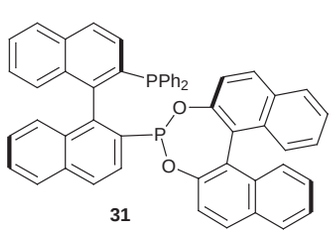


Scheme 34



Scheme 35

Hydroformylation reactions may be catalysed in an asymmetric sense through the use of Pd[190] or Rh[191a] complexes. The mixed phosphine–phosphonite donor **31** appears to work particularly well in this capacity (**Scheme 36**). The related hydrocyanation of alkenes may be carried out using a combination of $Ni(COD)_2$ with a chiral diphosphite in up to 95% ee. The electronic nature of the aryl groups on the phosphine donors is critical for optimal results.[191b]



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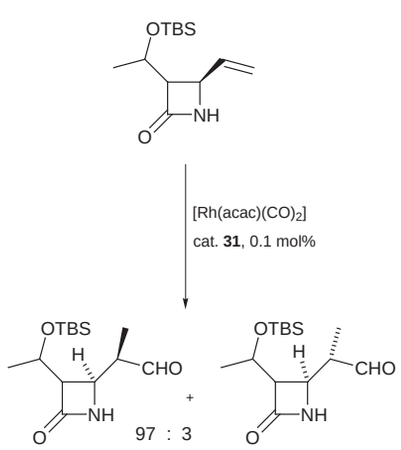
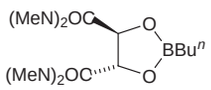


Scheme 36

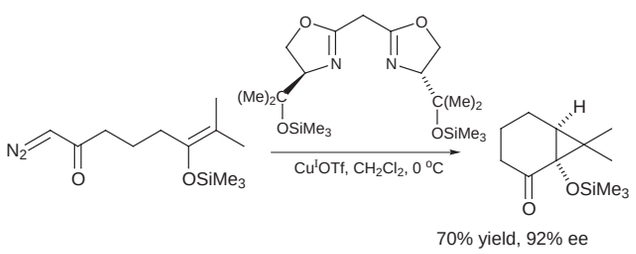
2.3.4 Cyclopropanations

Of the many catalysts reported for asymmetric cyclopropanation reactions, two classes dominate the field; copper(I) complexes, usually of bis(oxazoline), and Rh complexes of chiral amides and esters. A third major class is the borate ester reagent derived from diamide derivatives of tartaric acid *e.g.* **32** which perform particularly well in the cyclopropanation of allylic alcohols.[192–196] Strictly these act as chiral reagents since usually a full equivalent is required, however they are worthy of mention here since the extension to a catalytic version is inevitable. Most notable is their application to the synthesis of the poly(cyclopropane ring) containing natural products FR-900848[195] and U-106305,[192,196] the side chains of which may be prepared by a series of asymmetric cyclopropanation reactions.



32

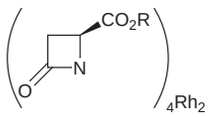
Research into C_2 symmetric bis-oxazolines continues unabated, although very few new reagents match the success achieved by Evans *et al*. some years ago. Several groups have reported the use of large 'bite angle' reagents derived from protected tartrates[197–199] or chiral binaphthyl systems.[200] The particularly attractive feature of this reaction is that the configuration of the chiral backbone may in principle be 'matched' in selectivity to the oxazoline groups. Good results have been obtained in both cases, with ees routinely in excess of 85% being reported for the prototype reaction of diazo acetates with styrene. An analogous reaction on enol ethers has been reported to proceed with high *trans*:*cis* selectivity but moderate enantioselectivities.[201] An intramolecular version has been reported by Shibasaki (**Scheme 37**).[202] Related reagents have been prepared from the pyridine based pybox ligand.[203]



Scheme 37

Dirhodium tetraacetate derivatives of chiral acids and amides, most significantly developed by Doyle, continue to be reported in new applications.[204–208] New β-lactam derived reagents **33** have been reported to be excellent catalysts for the styrene cyclopropanation process (**Scheme 38**).[204] The products are formed in high enantioselectivity, but the *cis*:*trans* ratios are disappointing. Intramolecular variations upon this class of cyclopropanation reaction are frequently highly selective.[206,208] In the example in **Scheme 39**, an intramolecular cycloaddition is followed by a ring expansion to the tremulane natural product skeleton.[208] In this application the substrate containing a *cis*-double bond gives significantly improved results compared to the same reaction on the *trans*- compound (the initial cycloadduct is thermally isomerised to set up the ring-expansion).

Finally in this section we note the use of a titanium(IV)–BINOL complex in the catalysis of an asymmetric cyclopropanation of an enone using 1-trimethylsilyl-2-phenylselanyl ethene. The cycloadduct of the [2+1] addition was formed in up to 47% ee.[209]



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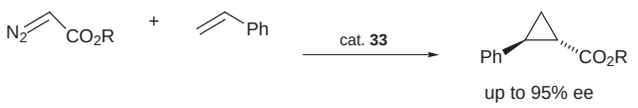
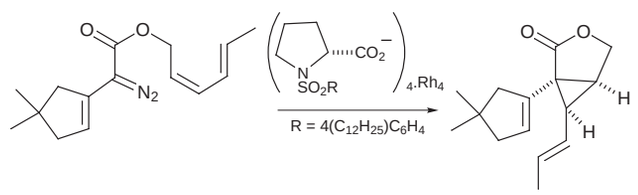


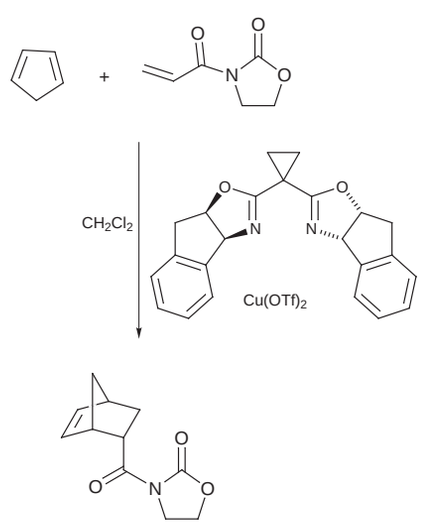
Scheme 38



Scheme 39

2.3.5 Cycloaddition reactions

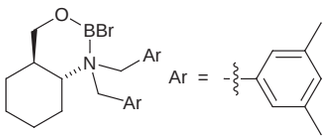
Asymmetric Diels–Alder reactions of cyclopentadiene with acrylamides attached to oxazolidinones may be catalysed effectively by the use of copper complexes of bis-oxazolines[210,211] or pybox ligands.[137] In the example shown in **Scheme 40**, the cyclopropane group in the bridge was considered essential for optimal selectivity—larger rings gave inferior results.[210] In this process the two-point interaction of the dienophile with the metal is essential for control. This interaction, and hence the stereochemical outcome, are often very finely balanced. In the magnesium(II) catalysed variation on this reaction the inclusion of two equivalents of water results in a complete and unexpected inversion of the observed stereochemistry.[212a] The combination of a magnesium(II) salt with a homochiral β-hydroxy sulfoxide has been reported to give a cycloadduct in the reaction shown in Scheme 40 in up to 88% ee.[212b] Hetero Diels–Alder reactions of aldehydes with dienes may also be catalysed by the copper–bisoxazoline system.[213,214]



Scheme 40

N-Tosylated oxazaborolidine systems and related materials[215–218] have been shown to be excellent catalysts for the asymmetric Diels–Alder reaction of α-substituted α,β-unsaturated aldehydes with dienes. In this case, and in contrast to the reagents described in the previous section, a single-point interaction is all that is required to direct the cycloaddition. In one impressive variation a supported reagent contained within

a column of packed material is reported to give products of up to 95% ee.[218] The 'super Lewis acid' catalyst **34** gives particularly good results in this process—up to 98% ee (**Scheme 41**).[216] The same reaction may be catalysed by a rhodium–chiral diphosphine complex, but with rather lower selectivity.[219] Hetero Diels–Alder reactions of imines with cyclopentadiene (in which the latter is the dienophile) can be catalysed in up to 91% with a combination of Yb^{III} and (*R*)-BINOL.[220]



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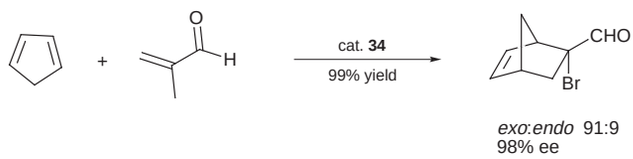
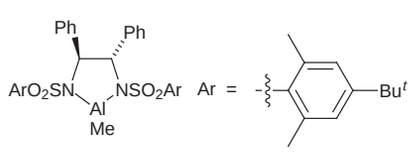


Scheme 41

The [2+2] cycloaddition of ketenes with aldehydes, promoted by the chiral aluminium derivative **35**, provides an impressive entry into β-lactone target molecules, many of which are found in natural products (**Scheme 42**).[221] The related catalytic asymmetric dimerisation of methylketene gives products in up to 98% ee using quinidine as catalysts.[222] In the latter case it is believed that the catalyst actually forms a reactive intermediate upon reaction with one ketene, which then participates in the addition reaction to a second equivalent of ketene.



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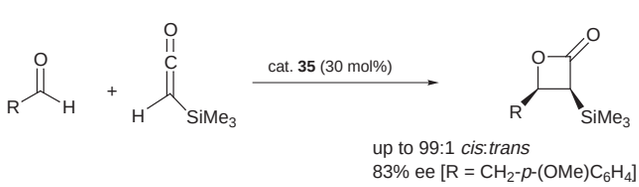


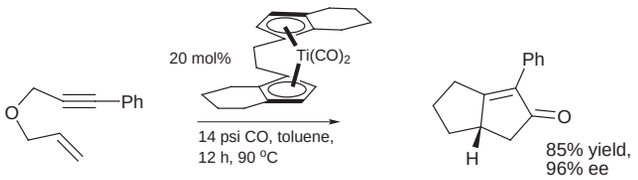
Scheme 42

Metal-catalysed asymmetric 1,3-dipolar cycloaddition reactions have been reported. Effective catalysts for the cycloaddition of nitrones to alkenes include titanium(IV) TADDOLate complexes (in excess of 90% ee)[223] and combinations of silver(I) salts with (*S*)-BINAP–Pd complexes (up to 91% ee[224]). Tartrate-modified diethylzinc reagents moderate the addition of nitrile oxides to allylic alcohols in up to 90% ee.[225]

An impressive and versatile system for the asymmetric catalysis of Pauson–Khand type reactions using a C_2-symmetric titanocene catalyst has been reported by Buchwald (**Scheme 43**).[226] A wide range of examples were described in this paper.

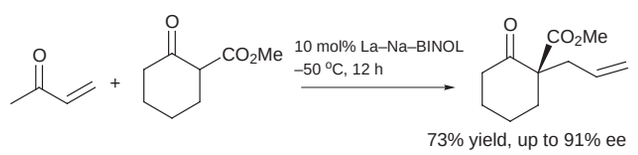
2.3.6 Addition of carbon nucleophiles to C=C bonds

Asymmetric Michael additions have proved elusive, although several asymmetric modifications of cuprate[227–229] and nickel



Scheme 43

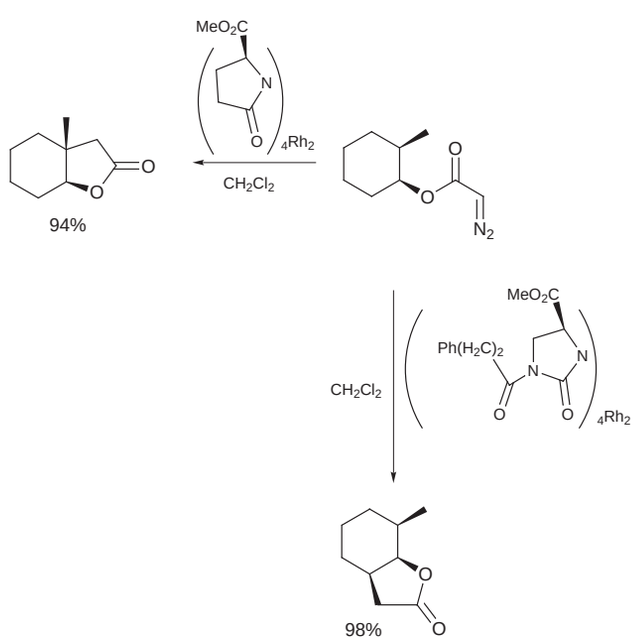
reagents have been tested, with mixed results.[230] Effective promoters include phosphines,[228] bis(oxazolines)[229] and sulfur-containing ligands.[230] In most cases a reasonably large amount of promoter is required for optimal results, suggesting a problem with turnover. Lithium reagents may also be successfully modified in an asymmetric sense with the use of an excess of a suitable C_2-symmetric diether.[231] The use of a *rubidium* salt of proline is effective at directing the asymmetric addition of dimethyl malonate to cyclic enones with good to moderate enantioinductions.[232] Other reagents which have been used in Michael additions include a xylylene-strapped porphyrin,[233] a lanthanide–BINOL combination (**Scheme 44**)[234] and the combination of a silyl enol ether with a stoichiometric quantity of a chiral tetraamide auxiliary.[235] Finally a *radical* mediated reaction of an alkyl iodide with an oxazolidinone-tethered acrylate, mediated by a chiral bis(oxazoline) and zinc(II) Lewis acid is reported to give addition products in up to 82% ee.[236]



Scheme 44

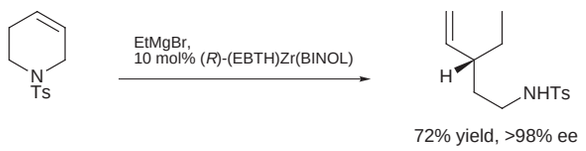
2.3.7 Other carbon–carbon bond forming reactions

The reaction of carbenes to form cyclopropanes has been described. The analogous C–H insertion reactions of carbenes represents a powerful method for the asymmetric formation of C–C bonds, when a suitable catalyst is employed.[237,238] The directing effect of the catalyst can often be very strong, and will override the natural chemoselectivity of the process (**Scheme 45**).[237] Synthetically valuable insertion reactions into N–H and Si–H bonds have also been reported.[239,240]

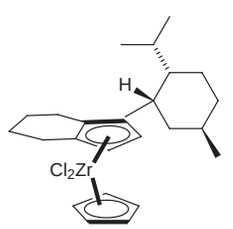


Scheme 45

The combination of a zirconocene catalyst with a Grignard reagent has been shown to be an effective method for the conversion of allylic amines and ethers to the asymmetric products of S_N2' allylic substitution.[241,242] Some impressive examples have been reported this year, in which enantiomeric excesses of up to 98% have been recorded (**Scheme 46**).[242] The same reaction upon racemic substrates provides an effective method for kinetic resolutions.[241] Through the careful consideration of the mechanism of operation and conformation of the zirconium reagents, Whitby has designed and tested the zirconocene **36** in analogous reactions. Some excellent results have been obtained for both asymmetric substitution and kinetic resolution experiments (**Scheme 47**).[243]



Scheme 46



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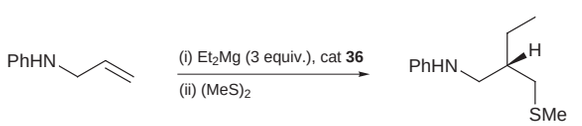
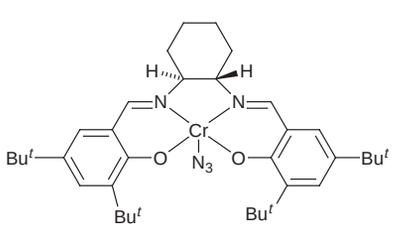


Scheme 47

Selective opening of *meso*-epoxides is a long-established and valuable synthetic method. In a series of papers, Jacobsen has described in detail the use of Cr^{III}–salen complexes **37** for this reaction. Using just 2 mol% of catalyst a product of 96% ee may be obtained from the addition of azide anion to a cyclic epoxide (**Scheme 48**). The product is a carbocyclic nucleoside analogue.[244] Kinetic resolution of racemic epoxides may also be achieved with very high selectivity (97% ee and 98% yield based on the use of 1 equivalent of trimethylsilyl azide with two equivalents of racemic 1-substituted epoxide.[245,246]



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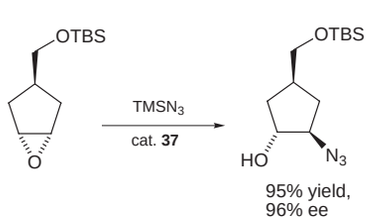
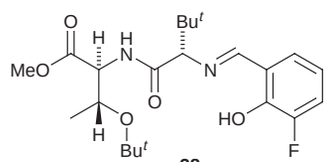


Scheme 48

A combinatorial approach was used by Hoveyda and co-workers in the synthesis of the catalyst **38** for ring opening reaction of cyclohexene oxide by trimethylsilyl cyanide (**Scheme 49**).[247] The optimum catalyst was developed through a process of repetitive iteration in which the final product was 'focused in on' by modification of each part of the catalyst. A different optimum catalyst structure was developed for the corresponding ring-opening of the five membered cyclic epoxide.



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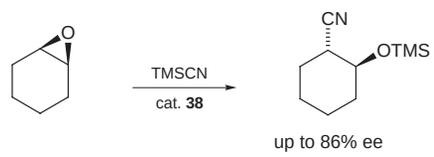
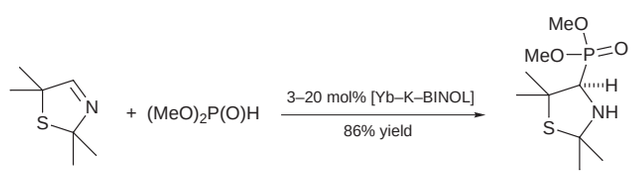


Scheme 49

2.4 Miscellaneous applications of synthetic asymmetric catalysts

α-Hydroxy phosphonate esters may be formed in up to 90% ee through the catalysis of the additions to aldehydes of phosphinate esters by aluminium(III)–BINOL complexes.[248] An analogous reaction upon imines has been applied to the synthesis of α-amino phosphonate esters, in which case the use of 5–20% of the BINOL modified catalyst gives a product of up to 98% ee (**Scheme 50**).[249]

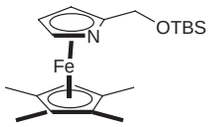


Scheme 50

Asymmetric protonation of prochiral enolates is now a very well established method. However the *catalytic* version (*i.e.* with a sub-stoichiometric quantity of homochiral proton source) of this is quite clearly a far more challenging objective due to the requirement for a delicate balance between the proton-transfer rates from several potential protonating agents. In the first of two recent examples, slow addition of a non-chiral alcohol to a samarium(III) substituted homochiral dialkoxide (15 mol%) results in protonation of a ketene-derived samarium(III) enolate in up to 93% ee.[250] In another example a trimethylsilyl enolate is protonated in up to 82% ee with a combination of a hindered phenol and 2 mol% of a monomethylated BINOL–tin(IV) tetrachloride complex.[251] The latter approach has been successfully applied to the asymmetric synthesis of α-arylpropionic acids such as ibuprofen (93% ee).

As will be described in a later section, the enantioselective acylation of racemic alcohols is performed with extremely high stereoselectivity by enzymes. However recent years have seen the development of quite effective synthetic reagents.[252,253] The design of compound **39** for this application is based on both a face and 'side' differential around the pyrrole ring. Using 10 mol% of **39** the alcohol from the acylation reaction in **Scheme 51** is recovered in 87% ee at 67% conversion.[252]

Some intriguing reactions can be achieved from inclusion compounds of achiral substrates with enantiomerically pure



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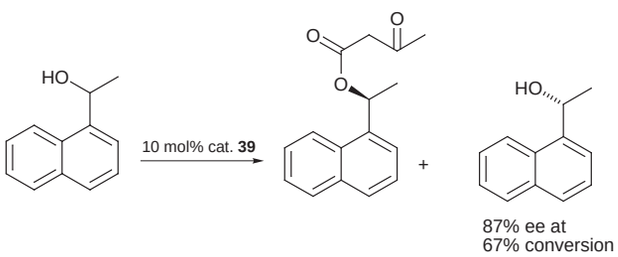
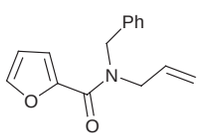


Scheme 51

modifiers.[254,255] In one example the irradiation of a 1 : 1 complex of **40** with diol **41** gave **42** in 98% ee. In contrast the irradiation of a 2 : 1 complex of **41** with **40** resulted in formation of the enantiomer **43**, in 96% ee.[254] Whilst not strictly an asymmetric catalysis in this case, the potential is clear for catalytic modification through development of the process.



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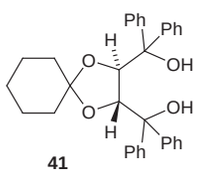

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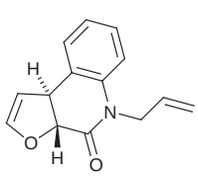

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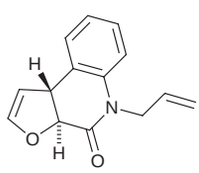
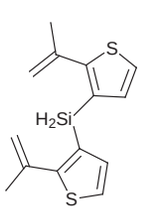


43

Asymmetric hydrosilylation of ketones has been discussed in the section on reductions. The corresponding asymmetric reaction on dienes has been reported to give products in up to 80% ee using the MOP-phen ligand **30** in a complex with palladium.[256] In a remarkable intramolecular reaction, **44** was converted into **45** in up to 99% ee using 0.3–0.5 mol% of a chiral diphosphine–rhodium(I) complex.[257]



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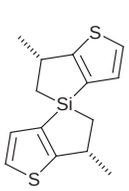

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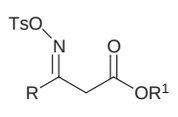
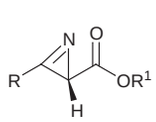


46



47

In the last example in this section, and a very unusual transformation, we note the alkaloid catalysed Neber reaction of **46** to give the heterocycle **47** (which is subsequently converted to the *cis*-aziridine) in up to 82% ee.[258]

3 Enzymes and antibodies

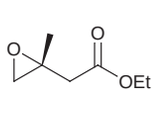
As in past years, reports of the applications of enzymes, either isolated or as part of a whole-cell system, continue to be prolific. For the purposes of this review, the selections are of particularly novel applications and developments, or solutions to difficult problems. Routine applications have not been listed comprehensively. The majority of the work refers to enzymes rather than catalytic antibodies, although the latter has been reviewed.[259]

3.1 Reductions and oxidations

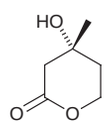
Microbial reduction reactions may be carried out under conditions of high pressure.[260] Using this modification the ee values of products are increased, however yields are reduced. Asymmetric reduction of carbonyl groups with bakers' yeast is a versatile transformation which works well on a range of substrates including 1-acetoxyacetophenone.[261] A detailed study of the reduction of ketones with *Geotricum candidum* served to demonstrate the importance of dilute conditions and control of the oxygen regime.[262] A major drawback in the use of yeast, the need for a large quantity of material for even quite small scale applications, can be overcome through the use of acetone powders, or dried extracts of the cells. Such extracts, to which NADH coenzyme must be re-added, often show modified and/or improved properties over the whole cell system. The reductions of both acetophenone and 1,1,1-trifluoroacetophenone may both be achieved with such an extract with ees of over 98%.[263] Most remarkable, and unexpected, was the observation of a complete reversal of selectivity between each substrate.

Kinetic resolutions may be coupled to asymmetric ketone reduction,[264] however a reaction which is often restricted to 50% yield for the transformation of a racemate may be modified to give 100% potential yield if it is modified to a dynamic version.[265] Such a process is eminently applicable to the reduction of α-substituted β-keto esters, which epimerise at a faster rate than the ketone reduction. Asymmetric reductions of isolated double bonds by bakers' yeast, whilst less common than carbonyl reductions, have been reported.[266] Enantioselective oxidation reactions of racemic alcohols proximal to thiophenol groups can result in recovery of unreacted alcohol of up to 99% ee, although two iterations are required for optimal results.[267]

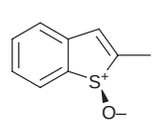
Asymmetric epoxidation reactions may be achieved in good selectivity using chloroperoxidases in conjunction with *tert*-butyl hydroperoxide.[268] The epoxide **48** was prepared in this way and subsequently used as an effective intermediate in the synthesis of (*R*)-(−)-mevalonalactone **49**. Effective epoxidation enzymes also often function well as asymmetric sulfoxidation catalysts.[269] The use of a *Pseudomonas putida* cell system results in formation of the sulfoxide **50** in >98% ee from the corresponding benzothiophene.[270] The same system effectively catalyses the enantioselective (and diastereoselective) synthesis of bifunctional synthetic units *via* a highly versatile benzylic oxidation (**Scheme 52**).[271] Analogous asymmetric hydroxylation of a carboxylic acid provides an entry to α-hydroxy acids in >99% ee.[272]



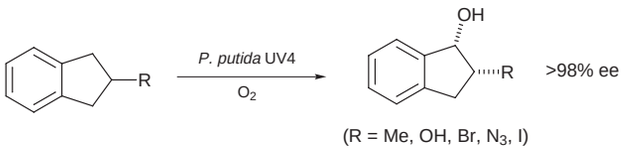
48



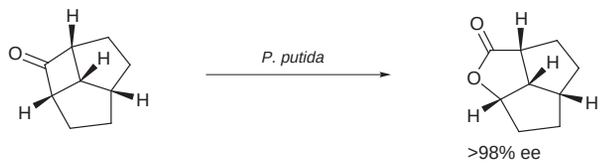
49



50

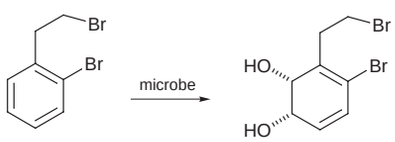


Scheme 52

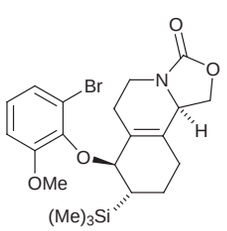


Scheme 54

Asymmetric dihydroxylation of aromatic[273,274] or heterocyclic[275] rings is a powerful method for the introduction of a high degree of functionality in an asymmetric system. The product of the reaction in **Scheme 53** represents a key intermediate in an approach to intermediate **51** and subsequently the morphine skeleton.[273] Asymmetric Baeyer–Villiger oxidation of prochiral, cyclic ketones with the *P. putida* system,[276] cyclohexanone monoxygenase[277] or engineered bakers' yeast[278] has been employed in a variety of applications to good effect. **Scheme 54** illustrates an example in which the substrate has been designed, on the basis of reported results, to be particularly compatible with the enzyme system employed, hence the extremely high enantioselectivity.[276] A detailed proposal for the mechanism of action and origin of stereoselectivity of Baeyer–Villigerases has been published.[279]



Scheme 53



51

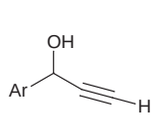
3.2 Lipases

Although one commonly accepts that enzymes tend to give best results at ambient temperature, a report of a study of protease action in frozen aqueous (ice) has been reported to give as good, if not rather better results than those obtained from aqueous–organic systems.[280] The introduction of cross-linked polymer supported enzyme crystal technology has represented a very exciting development in practical enzyme systems for synthetic chemistry. The support of *Candida rugosa* lipase in this manner provides a very effective system for kinetic resolution in hydrolysis reactions of racemic acetates.[281] On substrates related to α-arylpropionic acids, ee values of >99.5% are recorded in one example in contrast to 69% for the crude enzyme.

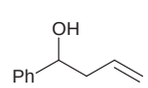
As in past years, a very wide variety of kinetic resolution reactions of racemic secondary alcohols has been reported. **Fig. 4** summarises the results of such a transformation on a representative selection of substrates reported this year.[282–290] In most cases vinyl acetate provides the acetyl source. Alternative acetate donors have been reported, including diketene[291] and an acylated ketene acetal.[292] Dynamic kinetic resolution,[285] of which only one example is featured in Fig. 4, provides a mechanism for quantitative conversions. In a very clever strategy, use has been made of an organometallic complex to perform an *in situ* racemisation of secondary alcohols in conjunction with a *Pseudomonas fluorescens* lipase acylation to furnish products of 98% ee and up to 60% yield (at this conversion the theoretical maximum ee should have been 67%).[293] Although optimisation is still required, there is clearly tremendous potential here.

Enantioselective hydrolysis with a lipase also provides an effective method for the synthesis of enantiomerically pure products. It should be noted that in practice this method can of course be employed for the preparation of either enantiomerically enriched alcohols[294,295] or carboxylic acids[296,297] from the esters which are hydrolysed. Enzymatic hydolysis of racemic six-membered cyclic carbonates provides a method for the formation of chiral diols.[298] Likewise enzymatic formation[299] or cleavage[300] of amides provides an analogous approach to enantiomerically pure products.

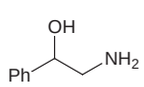
The asymmetric acylation of *meso* diols (the '*meso* trick') provides another solution to the recurring problem of how to get 100% yields from an enzymatic acylation reaction.[301,302] Through the careful choice of enzyme system, the acylation of



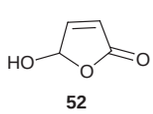
up to 99% ee
(*Pseudomonas* lipase)
(ref. 282)



S-alcohol up to 91% ee
R-acetate upto 98% ee
(Lipase PS)
(ref. 283)

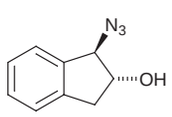


Ester/amide up to 99% ee
(Subtilisin BPN)
(ref. 284)

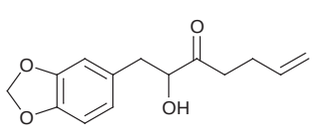


52

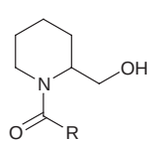
acetate up to 99% ee
(dynamic kinetic resolution)
(ref. 285)



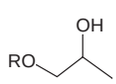
(1*R*,2*R*)-acetate 98% ee
(1*S*,2*S*)-alcohol 99% ee
(Lipase PS)
(ref. 286)



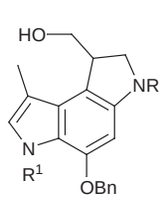
Alcohol >99% ee
(Lipase PS)
(ref. 287)



ester up to 77% ee (*R*)
alcohol up to 99% ee
(ref. 288)



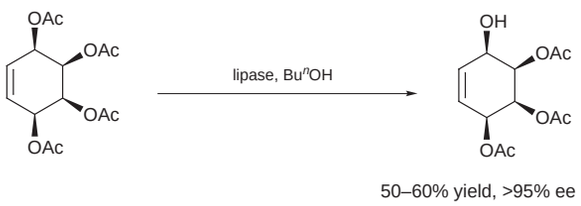
(*C. antarctica*)
(ref. 289)



R-acetate 78% ee
S-alcohol 74% ee
(Lipase PS)
(ref. 290)

Fig. 4 Representative substrates in kinetic resolution of racemic alcohols (vinyl acetate used as coreagent)

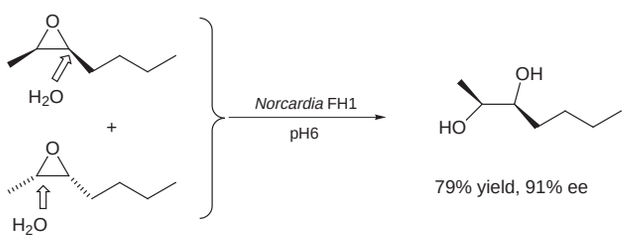
the *cis*-dihydroxylation product of benzene may be achieved in over 98% ee.[301] The solvent dependence of such reactions has been examined in detail.[302] Conventional kinetic resolution reactions of racemic diols have also been reported[303] (one monoacylated and one diacylated product is formed). Likewise, the reverse reaction, of monohydrolysis of a racemic diester, may also be employed to good effect.[304–307] In the example in **Scheme 55**, one of four acetates is stereoselectively hydrolysed in a conduritol desymmetrisation process.[306]



Scheme 55

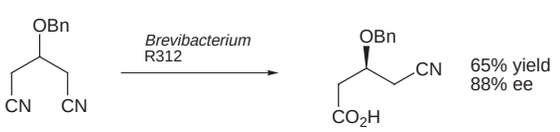
3.3 Miscellaneous biotransformations

Enantioselective ring-opening reactions of racemic epoxides provides an attractive route to enantiomerically enriched diols, if the products are of interest, or epoxides, if recovered substrate is required.[308–311] An interesting enantioconvergent approach (**Scheme 56**) provides an effective route to a single major diol from a racemic epoxide starting material.[308]



Scheme 56

Asymmetric aldol reactions catalysed by aldolases provide a powerful method for the formation of C–C bonds,[213] as does the asymmetric addition of HCN to aldehydes.[313] Selective hydrolysis of a prochiral dinitrile provides a practical and effective desymmetrisation method (**Scheme 57**).[314]



Scheme 57

References

1 P. J. Pospisil, D. H. Carsten and E. N. Jacobsen, *Chem. Eur. J.*, 1996, **2**, 974.
2 R. W. Quan, Z. Li and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 8156.
3 C. H. Senenayake, G. B. Smith, K. M. Ryan, L. E. Fredenburgh, J. Liu, F. E. Roberts, D. L. Hughes, R. D. Larsen, T. R. Verheoven and P. J. Reider, *Tetrahedron Lett.*, 1996, **37**, 3271.
4 D. Bell, M. R. Davies, F. J. L. Finney, G. R. Green, P. M. Kincey and I. S. Mann, *Tetrahedron Lett.*, 1996, **37**, 3895.
5 Y. Noguchi, T. Fukuda, R. Irie and T. Katsuki, *Tetrahedron Lett.*, 1996, **37**, 4533.
6 (*a*) W. Adam, R. T. Fell, C. Mock-Mnoblauch and C. R. Saha-Moller, *Tetrahedron Lett.*, 1996, **37**, 6531; (*b*) T. Fukuda and T. Katsuki, *Tetrahedron Lett.*, 1996, **37**, 4389.
7 (*a*) F. Minutulo, D. Pini, A. Petri and P. Salvadori, *Tetrahedron: Asymmetry*, 1996, **7**, 2293; (*b*) F. Minutolo, D. Pini and P. Salvadori, *Tetrahedron Lett.*, 1996, **37**, 3375.
8 I. F. J. Vankelecom, D. Tas, R. F. Parton, Van de Vyver and P. A. Jacobs, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1346.
9 T. Hashihayata, Y. Ito and T. Katsuki, *Synlett*, 1996, 1079.
10 H. Nishikori and T. Katsuki, *Tetrahedron Lett.*, 1996, **37**, 9245.
11 J. Aires-de-Sousa, A. M. Lobo and S. Prabhakar, *Tetrahedron Lett.*, 1996, **37**, 3183.
12 (*a*) M. Pasto, P. Castejon, A. Moyano, M. A. Pericas and A. Riera, *J. Org. Chem.*, 1996, **61**, 6033; (*b*) G. H. P. Roos and A. R. Donovan, *Synlett*, 1996, 1189.
13 K. Nagasawa, I. Shimizu and T. Nakata, *Tetrahedron Lett.*, 1996, **37**, 6881.
14 S. Terashima, T. Yoshino, Y. Nagata, E. Itoh, M. Hashimoto and T. Katoh, *Tetrahedron Lett.*, 1996, **37**, 3475.
15 L. A. Campbell and T. Kodadek, *J. Mol. Catal. A: Chem.*, 1996, **113**, 293.
16 S. Banfi, A. Manfredi, F. Montanari, G. Pozzi and S. Quici, *J. Mol. Catal. A: Chem.*, 1996, **113**, 77.
17 Z. Gross, S. Ini, M. Kapon and S. Cohen, *Tetrahedron Lett.*, 1996, **37**, 7325.
18 J. F. Wei, X. D. Yu and D. S. Jin, *Chin. Chem. Lett.*, 1996, **7**, 962.
19 A. Corma, A. Fuerte, M. Iglesias and F. Sanchez, *J. Mol. Catal. A: Chem.*, 1996, **107**, 225.
20 D. Yang, X.-C. Wang, M.-K. Wong, Y.-C. Yip and M.-W. Tang, *J. Am. Chem. Soc.*, 1996, **118**, 11 311.
21 Y. Tu, Z.-X. Wang and Y. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 9806.
22 S. M. Roberts, W. Kroutil, P. Mayon, M. E. Lasterra-Sanchez, S. J. Maddrell, S. R. Thornton, C. J. Todd and M. Tuter, *Chem. Commun.*, 1996, 845.
23 D. Ferreira, H. van Rensburg, P. S. van Heerden and B. C. B. Bezuidenhoudt, *Chem. Commun.*, 1996, 2747.
24 A. Kumar and V. Bhakani, *Tetrahedron Lett.*, 1996, **37**, 4751.
25 (*a*) E. J. Corey and M. C. Noe, *J. Am. Chem. Soc.*, 1996, **118**, 11 038; (*b*) E. J. Corey, M. C. Noe and M. J. Grogan, *Tetrahedron Lett.*, 1996, **37**, 4899.
26 E. J. Corey, S. Sarshar, M. D. Azimioara, R. C. Newbold and M. C. Noe, *J. Am. Chem. Soc.*, 1996, **118**, 7851.
27 S. Dapprich, G. Ujaque, F. Maseras, A. Lledos, D. G. Musaev and K. Morokuma, *J. Am. Chem. Soc.*, 1996, **118**, 11 660.
28 C. Rosini, R. Tanturli, P. Pertici and P. Salvadori, *Tetrahedron: Asymmetry*, 1996, **7**, 2971.
29 S. Torii, P. Liu, N. Bhavaneswari, C. Amatore and A. Jutand, *J. Org. Chem.*, 1996, **61**, 3055.
30 B. B. Lohray, E. Nandanan and V. Bhushan, *Tetrahedron: Asymmetry*, 1996, **7**, 2805.
31 H. Han and K. D. Janda, *J. Am. Chem. Soc.*, 1996, **118**, 7632.
32 K. J. Hale and J. Cai, *Tetrahedron Lett.*, 1996, **37**, 4233.
33 (*a*) M. T. Reetz, T. J. Strack, F. Mutulis and R. Goddard, *Tetrahedron Lett.*, 1996, **37**, 9293; (*b*) K. P. M. Vanhessche and K. B. Sharpless, *J. Org. Chem.*, 1996, **61**, 7978.
34 T. Sammakia, T. B. Hurley, D. M. Sammonds, R. S. Smith, S. B. Sobolov and T. R. Oeschger, *Tetrahedron Lett.*, 1996, **37**, 4427.
35 N. Maezaki, H. J. M. Gijsen, C. Q. Sun and L. A. Paquette, *J. Org. Chem.*, 1996, **61**, 6685.
36 T. Taniguchi, H. Ohnishi and K. Ogasawara, *Chem. Commun.*, 1996, 1477.
37 D. L. Boger, R. M. Borzilleri and S. Nukui, *J. Org. Chem.*, 1996, **61**, 3561.
38 E. J. Corey and S. Lin, *J. Am. Chem. Soc.*, 1996, **118**, 8765.
39 A. B. Smith III, T. Kinsho, T. Sunazuka and S. Omura, *Tetrahedron Lett.*, 1996, **37**, 6461.
40 (*a*) S. C. Sinha, A. Sjnha, A. Yazbak and E. Kienan, *J. Org. Chem.*, 1996, **61**, 7640; (*b*) H. Oikawa, T. Kagawa, T. Kobayashi and A. Ichihara, *Tetrahedron Lett.*, 1996, **37**, 6169.
41 G. Li and K. B. Sharpless, *Acta Chem. Scand.*, 1996, **50**, 649.
42 J. M. Brunel and H. B. Kagan, *Bull. Soc. Chim. Fr.*, 1996, **133**, 1109.
43 J. M. Brunel and H. B. Kagan, *Synlett*, 1996, 404.
44 F. DiFurio, G. Licini, G. Modena and R. Motterle, *J. Org. Chem.*, 1996, **61**, 5175.
45 C. Kokubo and T. Katsuki, *Tetrahedron*, 1996, **52**, 13 895.
46 H. Takada, Y. Nishibayachi, K. Ohe and S. Uemura, *Chem. Commun.*, 1996, 931.
47 M. J. Sodergren and P. G. Andersson, *Tetrahedron Lett.*, 1996, **37**, 7577.
48 A. DattaGupta and V. K. Singh, *Tetrahedron Lett.*, 1996, **37**, 2633.
49 C. Zondervan and B. L. Feringa, *Tetrahedron: Asymmetry*, 1996, **7**, 1895.
50 K. Hamachi, R. Irie and T. Katsuki, *Tetrahedron Lett.*, 1996, **37**, 4979.

51 M. Lopp, A. Paju, T. Kanger and T. Pehk, *Tetrahedron Lett.*, 1996, **37**, 7583.
52 H.-J. Hamann and E. Hoft, *Tetrahedron: Asymmetry*, 1996, **7**, 2217.
53 (*a*) A. K. Ghosh and W. Lin, *J. Org. Chem.*, 1996, **61**, 6175; (*b*) M. J. Burk, Y. M. Wang and J. R. Lee, *J. Am. Chem. Soc.*, 1996, **118**, 5142; (*c*) H. J. Kreuzfeld, C. Dobler, U. Schmidt and H. W. Krause, *Amino Acids*, 1996, **11**, 269; (*d*) H. W. Krause, H. J. Kreuzfeld, U. Schmidt, C. H. Dobler, M. Michalik, S. Taudien and C. Fischer, *Chirality*, 1996, **8**, 173; (*e*) H. Brunner and L. Wagenhuber, *J. Organomet. Chem.*, 1996, **525**, 259.
54 T. Malmstrom and C. Andersson, *Chem. Commun.*, 1996, 1135.
55 U. Nagel and J. Leipold, *Chem Ber.*, 1996, **129**, 815.
56 H. N. Flach, I. Grassert, G. Oehme and M. Capka, *Colloid Polymer Sci.*, 1996, **274**, 261.
57 (*a*) S. R. Gilbertson and X. Wang, *Tetrahedron Lett.*, 1996, **37**, 6475; (*b*) S. R. Gilbertson, X. F. Wang, G. S. Hoge, C. A. Klug and J. Schaefer, *Organometallics*, 1996, **15**, 4678.
58 (*a*) T. Benincori, E. Brenna, F. Sannicolo, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin and T. Pilati, *J. Org. Chem.*, 1996, **61**, 6244; (*b*) T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohto, K. Nozaki and H. Takaya, *J. Org. Chem.*, 1996, **61**, 5510.
59 J. Xiao, S. C. A. Nefkens, P. G. Jessop, T. Ikariya and R. Noyori, *Tetrahedron Lett.*, 1996, **37**, 2813.
60 I. Yamada, M. Yamaguchi and T. Yamagishi, *Tetrahedron: Asymmetry*, 1996, **7**, 3339.
61 P. LeGrande, T. Braun, C. Bruneau and P. H. Dixneuf, *J. Org. Chem.*, 1996, **61**, 8453.
62 (*a*) Y. Nitta and K. Kobira, *Chem. Lett.*, 1996, 897; (*b*) C. Thorey, F. Henin and J. Muzart, *Tetrahedron: Asymmetry*, 1996, **7**, 975.
63 C. M. Haar, C. L. Stern and T. J. Marks, *Organometallics*, 1996, **15**, 1765.
64 (*a*) C. Spiro, N. Mayes, H. Desfosses and S. Sotheeswaran, *Tetrahedron Lett.*, 1996, **37**, 6503; (*b*) I. Gautier, V. Ratavelomanana-Vidal, P. Savignac and J.-P. Genet, *Tetrahedron Lett.*, 1996, **37**, 7721.
65 A. Roucoux, L. Thieffry, J. F. Carpentier, M. Devocelle, C. Meliet, F. Agbossou and A. Mortreux, *Organometallics*, 1996, **15**, 2440.
66 R. L. Augustine and S. K. Tanielyan, *J. Mol. Catal. A: Chem.*, 1996, **111**, 93.
67 H. Bonnemann and G. A. Braun, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 1992.
68 J. Wang, Y. Sun, C. LeBlond, R. N. Landau and D. G. Blackmond, *J. Catal.*, 1996, **161**, 752.
69 C. Pinel, N. Gendreau-Diaz, A. Breheret and M. Lemaire, *J. Mol. Catal. A: Chem.*, 1996, **112**, L157.
70 T. Ohkuma and R. Noyori, *J. Synth. Org. Chem. Jpn.*, 1996, **54**, 553.
71 A. B. Charette and A. Giroux, *Tetrahedron Lett.*, 1996, **37**, 6669.
72 T. Morimoto, N. Suzuki and K. Achiwa, *Heterocycles*, 1996, **43**, 2557.
73 R. Sablong and J. A. Osborn, *Tetrahedron: Asymmetry*, 1996, **7**, 3059.
74 (*a*) R. Sablong and J. A. Osborn, *Tetrahedron Lett.*, 1996, **37**, 4937; (*b*) J. M. Buriak and J. A. Osborn, *Organometallics*, 1996, **15**, 3161.
75 B. Chin and S. L. Buchwald, *J. Org. Chem.*, 1996, **61**, 5650.
76 H. Imma, M. Mori and T. Nakai, *Synlett*, 1996, 1229.
77 L. M. Newman, J. M. J. Williams, R. McCague and G. A. Potter, *Tetrahedron: Asymmetry*, 1996, **7**, 1597.
78 T. Langer, J. Janssen and G. Helmchem, *Tetrahedron: Asymmetry*, 1996, **7**, 1599.
79 Y. Imai, W. Zhang, T. Kida, Y. Nakatsuki and I. Ikeya, *Tetrahedron: Asymmetry*, 1996, **7**, 2453.
80 Y. Nishibayashi, K. Segawa, H. Takada, K. Ohe and S. Uemura, *Chem. Commun.*, 1996, 847.
81 G. Brenchley, M. Fedouloff, E. Merifield and M. Wills, *Tetrahedron: Asymmetry*, 1996, **7**, 2809.
82 X. Verdaguer, U. E. W. Lange, M. T. Reding and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 6784.
83 G. E. Keck and D. Krishnamurthy, *J. Org. Chem.*, 1996, **61**, 7638.
84 (*a*) K. D. Sugi, T. Nagata, T. Yamada and T. Mukaiyama, *Chem. Lett.*, 1996, 737; (*b*) T. Nagata, K. D. Sugi, T. Yamamda and T. Mukaiyama, *Synlett*, 1996, 1076.
85 K. Puntener, L. Schwink and P. Knochel, *Tetrahedron Lett.*, 1996, **37**, 8165.
86 S. Hashiguchi, A. Fujii and R. Noyori, *J. Synth. Org. Chem. Jpn.*, 1996, **54**, 818.
87 N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916.
88 P. Gamez, B. Dunjic and M. Lemaire, *J. Org. Chem.*, 1996, **61**, 5196.
89 B. T. Khai and A. Arcelli, *Tetrahedron Lett.*, 1996, **37**, 6599.
90 (*a*) X. M. Hu and R. M. Kellogg, *Recl. Trav. Chim. Pays-Bas*, 1996, **115**, 410; (*b*) F.-Y. Zhang, C.-W. Yip and A. S. C. Chan, *Tetrahedron: Asymmetry*, 1996, **7**, 2463.
91 (*a*) A. S. Demir, I. Mecitoglu, C. Tanyeli and V. Gulbeyaz, *Tetrahedron: Asymmetry*, 1996, **7**, 3359; (*b*) I. Reiners, J. Martens, S. Schwarz and H. Henkel, *Tetrahedron: Asymmetry*, 1996, **7**, 1763; (*c*) L. Xingshu and X. Rugang, *Tetrahedron: Asymmetry*, 1996, **7**, 2779.
92 (*a*) T. S. Kaufman, *Tetrahedron Lett.*, 1996, **37**, 5329; (*b*) R. D. Larsen, E. G. Corley, A. O. King, J. D. Carroll, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang and R. J. Zamboni, *J. Org. Chem.*, 1996, **61**, 3398; (*c*) R. J. Cvetovich, M. Chartrain, F. W. Hartner Jr, C. Roberge, J. S. Amato and E. J. J. Grabowski, *J. Org. Chem.*, 1996, **61**, 6575.
93 A. W. Douglas, D. M. Tschaen, R.A. Reamer and Y.-J. Shi, *Tetrahedron: Asymmetry*, 1996, **7**, 1303.
94 K. R. K. Prasad and N. N. Joshi, *Tetrahedron: Asymmetry*, 1996, **7**, 3147.
95 F.-Y. Zhang, C.-W. Yip and A. S. C. Chan, *Tetrahedron: Asymmetry*, 1996, **7**, 3135.
96 W. Deng, M. S. Jensen, L. E. Overman, R. V. Rucker and J.-P. Vionnet, *J. Org. Chem.*, 1996, **61**, 6760.
97 K. A. Parker and M. W. Ledeboer, *J. Org. Chem.*, 1996, **61**, 3214.
98 J. Bach, R. Berenguer, J. Garcia, T. Loscertales and J. Vilarrasa, *J. Org. Chem.*, 1996, **61**, 9021.
99 D. T. Hung, J. B. Nerenberg and S. L. Schreiber, *J. Am. Chem. Soc.*, 1996, **118**, 11 054.
100 K. R. K. Prasad and N. N. Joshi, *J. Org. Chem.*, 1996, **61**, 3888.
101 E. J. Corey and C. J. Helal, *Tetrahedron Lett.*, 1996, **37**, 5675.
102 E. J. Corey and C. J. Helal, *Tetrahedron Lett.*, 1996, **37**, 4837.
103 M. P. Gamble, J. R. Studley and M. Wills, *Tetrahedron Lett.*, 1996, **37**, 2853.
104 M. P. Gamble, J. R. Studley and M. Wills, *Tetrahedron: Asymmetry*, 1996, **7**, 3071.
105 R. Hulst, H. Heres, N. C. M. W. Peper and R. M. Kellogg, *Tetrahedron: Asymmetry*, 1996, **7**, 1373.
106 V. Peper and J. Martens, *Tetrahedron Lett.*, 1996, **37**, 8351.
107 (*a*) H. B. Kagan, C. Girard, D. Guillaneux, D. Rainford, O. Samuel, S. Y. Zhang and S. H. Zhao, *Acta Chem. Scand.*, 1996, **50**, 345; (*b*) C. Bolm, F. Bienewald and A. Seger, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 1657.
108 M. Kitamura, M. Yamakawa, H. Oka, S. Suga and R. Noyori, *Chem. Eur. J.*, 1996, **2**, 1173.
109 H.-L. Huang, Y.-C. Lin, S.-F. Chen, C.-L. J. Wang and L. T. Liu, *Tetrahedron: Asymmetry*, 1996, **7**, 3067.
110 R. Hulst, H. Heres, K. Fitzpatrick, N. C. M. W. Peper and R. M. Kellogg, *Tetrahedron: Asymmetry*, 1996, **7**, 2755.
111 J. Eilers, J. Wilken and J. Martens, *Tetrahedron: Asymmetry*, 1996, **7**, 2343.
112 K. R. K. Prasad and N. N. Joshi, *Tetrahedron: Asymmetry*, 1996, **7**, 1957.
113 C. Anaya de Parrodi, E. Juaristi, L. Quintera-Cortes and P. Amador, *Tetrahedron: Asymmetry*, 1996, **7**, 1915.
114 W.-M. Dai, H. J. Zhu and X.-J. Hao, *Tetrahedron: Asymmetry*, 1996, **7**, 1245.
115 C. Bolm, N. Derrien and A. Seger, *Synlett*, 1996, 387.
116 H. Kitajima, K. Ito and T. Katsuki, *Chem. Lett.*, 1996, 343.
117 M.-J. Jin, S.-J. Ahn and K.-S. Lee, *Tetrahedron Lett.*, 1996, **37**, 8767.
118 H. Kotsuki, M. Wakao, H. Hayakawa, T. Shimanouchi and M. Shiro, *J. Org. Chem.*, 1996, **61**, 8915.
119 H. Zhang, F. Xue, T. C. W. Mak and K. S. Chan, *J. Org. Chem.*, 1996, **61**, 8002.
120 P. G. Cozzi, A. Papu and A. Umani-Ronchi, *Tetrahedron Lett.*, 1996, **37**, 4613.
121 K. Hosoya, S. Tsuji, K. Yoshizako, K. Kimata, T. Araki and N. Tanaka, *React. Funct. Polym.*, 1996, **29**, 159.
122 T. Suzuki, N. Nurisada, T. Shibata and K. Soai, *Tetrahedron: Asymmetry*, 1996, **7**, 2519.
123 T. Hayase, Y. Inoue, T. Shibata and K. Soai, *Tetrahedron: Asymmetry*, 1996, **7**, 2509.
124 P. G. Andersson, D. Guijarro and D. Tanner, *Synlett*, 1996, 727.
125 Y. Takemoto, Y. Baba, I. Naguchi and C. Iwata, *Tetrahedron Lett.*, 1996, **37**, 3345.
126 S. Vettel, C. Lutz and P. Knochel, *Synlett*, 1996, 731.
127 F. Langer, L. Schwink, A. Devisagayaraj, P.-Y. Chavant and P. Knochel, *J. Org. Chem.*, 1996, **61**, 8229.
128 D. Seebach, R. E. Marti and T. Hintermann, *Helv. Chim. Acta*, 1996, **79**, 1710.
129 T. Shibata, K. Choji, T. Hayase, Y. Aizu and K. Soai, *Chem. Commun.*, 1996, 1235.

130 T. Shibata, H. Morioka, S. Tunji, T. Hayase, Y. Kodaka and K. Soai, *Tetrahedron Lett.*, 1996, **37**, 8783.
131 K. Soai, Y. Inoue, T. Takahashi and T. Shibata, *Tetrahedron*, 1996, **52**, 13 355.
132 M. S. Iyer, K. M. Gigstad, N. D. Namdev and M. Lipton, *J. Am. Chem. Soc.*, 1996, **118**, 4910.
133 M. S. Iyer, K. M. Gigstad, N. D. Namdev and M. Lipton, *Amino Acids*, 1996, **11**, 259.
134 W. Pan, X. Feng, L. Gong, W. Hu, Z. Li, A. Mi and Y. Jiang, *Synlett*, 1996, 337.
135 K. Iseki, S. Oishi, H. Sasai and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 9081.
136 M. Shibasaki and H. Sasai, *Pure Appl. Chem.*, 1996, **68**, 523.
137 D. A. Evans, M. Kozlowski and J. S. Tedrow, *Tetrahedron Lett.*, 1996, **37**, 7481.
138 D. A. Evans, J. A. Murry and M. C. Kozlowski, *J. Am. Chem. Soc.*, 1996, **118**, 5814.
139 K. W. Li, J. Wu, W. Xing and J. A. Simon, *J. Am. Chem. Soc.*, 1996, **118**, 7237.
140 Q.-S. Hu, D. Vitharana, X.-F. Zheng, C. Wu, C. M. S. Kwan and L. Pu, *J. Org. Chem.*, 1996, **61**, 8370.
141 S. Kobayashi, T. Hayashi, S. Iwamoto, T. Furuta and M. Matsumura, *Synlett*, 1996, 672.
142 S.-I. Kiyooka and M. A. Hena, *Tetrahedron: Asymmetry*, 1996, **7**, 2181.
143 S.-I. Kiyooka, H. Kira and M. A. Hema, *Tetrahedron Lett.*, 1996, **37**, 2597.
144 M. Kinugasa, J. Harada and A. Oku, *J. Org. Chem.*, 1996, **61**, 6772.
145 J. M. Andres, M. A. Martinez, R. Pedrosa and A. Perez-Encabo, *Synthesis*, 1996, 1070.
146 S. E. Denmark, S. B. D. Winters, X. Su and K.-T. Wong, *J. Am. Chem. Soc.*, 1996, **118**, 7404.
147 K. Iseki, Y. Kuroki, M. Takahashi and Y. Kobayashi, *Tetrahedron Lett.*, 1996, **37**, 5149.
148 (*a*) C.-M. Yu, H.-S. Choi, W.-H. Jung and S.-S. Lee, *Tetrahedron Lett.*, 1996, **37**, 7095; (*b*) S. Weigand and R. Bruckner, *Chem. Eur. J.*, 1996, **2**, 1077.
149 A. Yanagisawa, H. Nakashima, A. Ishiba and H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 4723.
150 D. R. Gauthier Jr. and E. M. Carreira, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2363.
151 K. Mikami, A. Yoshida and Y. Matsumoto, *Tetrahedron Lett.*, 1996, **37**, 8515.
152 I. Kobayashi, K. Mikami, T. Yajima, M. Terada, S. Kawauchi and Y. Suzuki, *Chem. Lett.*, 1996, 861.
153 K. Mikami, *Pure Appl. Chem.*, 1996, **68**, 639.
154 W. H. Miles, C. L. Berreth and C. A. Anderton, *Tetrahedron Lett.*, 1996, **37**, 7893.
155 K. Mikami, T. Yajima, N. Siree, M. Terada, Y. Suzuki and I. Kobayashi, *Synlett*, 1996, 837.
156 J. W. Faller and X. Liu, *Tetrahedron Lett.*, 1996, **37**, 3449.
157 V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones and M. C. H. Standen, *J. Am. Chem. Soc.*, 1996, **118**, 7004.
158 V. K. Aggarwal, A. Thompson, R. V. H. Jones and M. C. H. Standen, *J. Org. Chem.*, 1996, **61**, 8368.
159 B. M. Trost, *Acc. Chem. Res.*, 1996, **29**, 355.
160 J. M. J. Williams, *Synlett*, 1996, 705,
161 G. Chelucci and M. A. Cabras, *Tetrahedron: Asymmetry*, 1996, **7**, 965.
162 W. Zhang. T. Hirao and I. Ikeda, *Tetrahedron Lett.*, 1996, **37**, 4545.
163 Y. Hamada, N. Seto, H. Ohmori and K. Hatano, *Tetrahedron Lett.*, 1996, **37**, 7565.
164 W. Zhang, T. Kida, Y. Nakatsuji and I. Ikeda, *Tetrahedron Lett.*, 1996, **37**, 7995.
165 P. A. Evans and T. A. Brandt, *Tetrahedron Lett.*, 1996, **37**, 9143.
166 C. Bolm, D. Kaufmann, M. Zehnder and M. Neuburger, *Tetrahedron Lett.*, 1996, **37**, 3985.
167 G. Zhu, M. Terry and X. Zhang, *Tetrahedron Lett.*, 1996, **37**, 4475.
168 N. Nomura, Y. C. Mermet-Bouvier and T. V. Rajanbabu, *Synlett*, 1996, 745.
169 B. Akermark, P. Helquist, E. Penn-Cobrera, P.-O. Norrby, M. Sjogren, A. Vitagliano, V. DeFelice, J. Oslob, S. Ishii and D. O'Neill, *J. Am. Chem. Soc.*, 1996, **118**, 4299.
170 B. M. Trost, A. C. Krueger, R. C. Bunt and J. Zambrano, *J. Am. Chem. Soc.*, 1996, **118**, 6520.
171 B. M. Trost and G. R. Cook, *Tetrahedron Lett.*, 1996, **37**, 7485.
172 (*a*) B. M. Trost, M. J. Krische, R. Radinov and G. Zanoni, *J. Am. Chem. Soc.*, 1996, **118**, 6297; (*b*) B. M. Trost and R. C. Lemoine, *Tetrahedron Lett.*, 1996, **37**, 9161; (*c*) B. M. Trost, R. Madsen, S. G. Guile and A. E. H. Elia, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1569.
173 M. Sawamura, M. Sudoh and Y. Ito, *J. Am. Chem. Soc.*, 1996, **118**, 3309.
174 I. Shimizu, Y. Matsumoto, K. Shoji, T. Ono, A Satake and A. Yamamoto, *Tetrahedron Lett.*, 1996, **37**, 7115.
175 M. Sawamura, Y. Nakayama, W.-M. Tang and Y. Ito, *J. Org. Chem.*, 1996, **61**, 9090.
176 M. Yamaguchi, M. Yabuki, T. Yamagishi, K. Sakai and T. Tsubomura, *Chem. Lett.*, 1996, 241.
177 T. Hayashi, M. Kawatsura, H. Iwamura, Y. Yamaura and Y. Uoizumi, *Chem. Commun.*, 1996, 1767.
178 P. S. Pregosin and R. Salzmann, *Coord. Chem. Rev.*, 1996, **155**, 35.
179 U. Buckhardt, V. Gramlich, P. Hofmann, R. Nesper, P. S. Pregosin, R. Salzmann and A. Togni, *Organometallics*, 1996, **15**, 3496.
180 A. Albinati, P. S. Pregosin and K. Wick, *Organometallics*, 1996, **15**, 2419.
181 T. R. Ward, *Organometallics*, 1996, **15**, 2836.
182 P. E. Blochi and A. Togni, *Organometallics*, 1996, **15**, 4125.
183 J. F. Bower and J. M. J. Williams, *Synlett*, 1996, 685.
184 G. Koch and A. Pfaltz, *Tetrahedron: Asymmetry*, 1996, **7**, 2213.
185 E. B. Koroleva and P. G. Andersson, *Tetrahedron: Asymmetry*, 1996, **7**, 2467.
186 L. F. Tietze and T. Raschke, *Leibigs Ann.*, 1996, 1981.
187 C. Sonesson, M. Larhed, C. Nyquist and A. Hallberg, *J. Org. Chem.*, 1996, **61**, 4756.
188 T. Ohshima, K. Kagechika, A. Adachi, M. Sodeoka and M. Shibasaki, *J. Am. Chem. Soc.*, 1996, **118**, 7108.
189 T. Kamikawa, Y. Uozumi and T. Hayashi, *Tetrahedron Lett.*, 1996, **37**, 3161.
190 A. M. Masdeu-Bulto, A. Orejon, A. Castellanos, S. Castillon and C. Claver, *Tetrahedron: Asymmetry*, 1996, **7**, 1829.
191 (*a*) K. Nozaki, W.-G. Li, T. Horiuchi and H. Takaya, *J. Org. Chem.*, 1996, **61**, 7658; (*b*) T. V. Rajanbabu and A.L. Casalnuovo, *J. Am. Chem. Soc.*, 1996, **118**, 6325.
192 A. G. M. Barrett, D. Hamprecht, A. J. P. White and D. J Williams, *J. Am. Chem. Soc.*, 1996, **118**, 7863.
193 C. K. Zercher, C. R. Theberge and C. A. Verbicky, *J. Org. Chem.*, 1996, **61**, 8792.
194 A. B. Charette, H. Juteau, H. Lebel and D. Deschenes, *Tetrahedron Lett.*, 1996, **37**, 7925.
195 A. G. M. Barrett and K. Kasdorf, *J. Am. Chem. Soc.*, 1996, **118**, 11 030.
196 A. B. Charette and H. Lebel, *J. Am. Chem. Soc.*, 1996, **118**, 10 327.
197 A. M. Harm, J. G. Knight and G. Stemp, *Tetrahedron Lett.*, 1996, **37**, 6189.
198 A. M. Harm, J. G. Knight and G. Stemp, *Synlett*, 1996, 677.
199 A. V. Bedeker and P. G. Andersson, *Tetrahedron Lett.*, 1996, **37**, 4073.
200 Y. Uozumi, H. Kyota, E. Kishi, K. Kitayama and T. Hayashi, *Tetrahedron: Asymmetry*, 1996, **7**, 1603.
201 R. Schumacher and H.-U. Reissig, *Synlett*, 1996, 1121.
202 R. Tokunoh, H. Tomiyama, M. Sodeoka and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 2449.
203 H. Nishiyama, H. Nishiyama, K. Aoki, H. Itoh, T. Iwamura, N. Sakata, O. Kurihara and Y. Motoyama, *Chem. Lett.*, 1996, 1071.
204 M. P. Doyle, Q.-L. Zhou, S. H. Simonsen and V. Lynch, *Synlett*, 1996, 697.
205 M. P. Doyle, Q.-L. Zhou, C. Charnsangasvej, M. A. Longoria, M. A. McKervey and C. F. Garcia, *Tetrahedron Lett.*, 1996, **37**, 4129.
206 M. P. Doyle, C. S. Peterson and D. L. Parker Jr., *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1334.
207 H. M. L. Davies, P. R. Bruzinski and M. J. Fall, *Tetrahedron Lett.*, 1996, **37**, 4133.
208 H. M. L. Davies and B. D. Doan, *Tetrahedron Lett.*, 1996, **37**, 3967.
209 S. Yamazaki, M. Tanaka and S. Yamabe, *J. Org. Chem.*, 1996, **61**, 4046.
210 I. W. Davies, L. Gerena, L. Castonguay, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Chem. Commun.*, 1996, 1753.
211 A. K. Ghosh, P. Mathivanan and J. Cappiello, *Tetrahedron Lett.*, 1996, **37**, 3815.
212 (*a*) G. Desimoni, G. Faita and P. P. Righetti, *Tetrahedron Lett.*, 1996, **37**, 3027; (*b*) M. Ordonez, V. Guerrero de la Rosa, V. Labastida and J. M. Llera, *Tetrahedron: Asymmetry*, 1996, **7**, 2675.
213 A. K. Ghosh, P. Muthivanan, J. Cappiello and K. Krishnan, *Tetrahedron: Asymmetry*, 1996, **7**, 2165.
214 M. Johannsen and K. A. Jorgensen, *Tetrahedron*, 1996, **52**, 7321.
215 T.-P. Loh, R.-B. Wang and K. Y. Sim, *Tetrahedron Lett.*, 1996, **37**, 2989.

216 Y. Hayashi, J. J. Rohde and E. J. Corey, *J. Am. Chem. Soc.*, 1996, **118**, 5502.
217 J. M. Fraile, J. I. Garcia, J. A. Majoral and A. J. Roya, *Tetrahedron: Asymmetry*, 1996, **7**, 2263.
218 K. Komahori, K. Ito and S. Itsuno, *J. Org. Chem.*, 1996, **61**, 8321.
219 D. Carmona, C. Cativiela, R. Garcia-Correas, F. J. Lahoz, M. P. Lamata, J. A. Lopez, M. P. Lopez-Ram de Viu, L. A. Oro, E. San Jose and F. Viguri, *Chem. Commun.*, 1996, 1247.
220 H. Ishitani and S. Kobayashi, *Tetrahedron Lett.*, 1996, **37**, 7357.
221 B. W. Dymock, P. J. Kocienski and J. M. Pons, *Chem. Commun.*, 1996, 1053.
222 M. A. Calter, *J. Org. Chem.*, 1996, **61**, 8006.
223 K. V. Gothelf and K. A. Jorgensen, *Acta Chem. Scand.*, 1996, **50**, 652.
224 K. Hori, H. Kodama, T. Ohta and I. Furukawa, *Tetrahedron Lett.*, 1996, **37**, 5947.
225 M. Shimizu, Y. Ukaji and K. Inomata, *Chem. Lett.*, 1996, 455.
226 F. A. Hicks and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 11 688.
227 Y. Takemoto, S. Kuraoka, N. Hamaue and C. Iwata, *Tetrahedron: Asymmetry*, 1996, **7**, 993.
228 (*a*) Y. Nakagawa, M. Kanai, Y. Nagaoka and K. Tomioka, *Tetrahedron Lett.*, 1996, **37**, 7805; (*b*) M. Kanai, Y. Nakagawa and K. Tomioka, *J. Chem. Soc. Jpn.*, 1996, **54**, 474.
229 A. Bernardi, G. Columbo and C. Scolastico, *Tetrahedron Lett.*, 1996, **37**, 8921.
230 C. L. Gibson, *Tetrahedron: Asymmetry*, 1996, **7**, 3357.
231 D. Amurrio, K. Khan and E. P. Kundig, *J. Org. Chem.*, 1996, **61**, 2258.
232 M. Yamaguchi, T. Shiraishi and M. Hirama, *J. Org. Chem.*, 1996, **61**, 3520.
233 A. Ito, K. Konishi and T. Aida, *Tetrahedron Lett.*, 1996, **37**, 2585.
234 H. Sasai, E. Emori, T. Arai and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 5561.
235 K. Yasuda, M. Shindo and K. Koga, *Tetrahedron Lett.*, 1996, **37**, 6343.
236 M. P. Sibi, J. Ji, J. H. Wu, S. Gurtler and N. A. Porter, *J. Am. Chem. Soc.*, 1996, **118**, 9200.
237 M. P. Doyle, A. V. Kalinin and D. G. Ene, *J. Am. Chem. Soc.*, 1996, **118**, 8837.
238 J. W. Bode, M. P. Doyle, M. N. Protopopova and Q.-L. Zhou, *J. Org. Chem.*, 1996, **61**, 9146.
239 C. F. Garcia, M. A. McKervey and T. Ye, *Chem. Commun.*, 1996, 1465.
240 C. J. Moody, R. T. Buck, M. P. Doyle, M. J. Drysdale, L. Ferris, D. C. Forbes, D. Haigh, N. D. Pearson and Q.-L. Zhou, *Tetrahedron Lett.*, 1996, **37**, 7631.
241 M. S. Visser, J. P. A. Harrity and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1996, **118**, 3779.
242 M. S. Visser, N. M. Heron, M. T. Didiuk, J. F. Sagal and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1996, **118**, 4291.
243 L. Bell, R. J. Whitby, R. V. H. Jones and M. C. H. Standen, *Tetrahedron Lett.*, 1996, **37**, 7139.
244 L. E. Martinez, W. A. Nugent and E. N. Jacobsen, *J. Org. Chem.*, 1996, **61**, 7963.
245 J. F. Larrow, S. E. Schaus and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 7420.
246 S. E. Schaus and E. N. Jacobsen, *Tetrahedron Lett.*, 1996, **37**, 7937.
247 B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper and A. H. Hoveyda, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1668.
248 T. Arai, M. Bougauchi, H. Sasai and M. Shibasaki, *J. Org. Chem.*, 1996, **61**, 2926.
249 H. Groger, Y. Saida, S. Arai, J. Martens, H. Sasai and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 9291.
250 Y. Nakamura, S. Takeuchi, A. Ohira and Y. Ohgo, *Tetrahedron Lett.*, 1996, **37**, 2805.
251 K. Ishihara, S. Nakamura, M. Kaneeda and H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 12 854.
252 J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1996, **61**, 7230.
253 T. Oriyama, Y. Hori, K. Imai and R. Sasaki, *Tetrahedron Lett.*, 1996, **37**, 8543.
254 F. Toda, H. Miyamoto and K. Kanemoto, *J. Org. Chem.*, 1996, **61**, 6490.
255 G. Sundarababu, M. Leibovitch, D. R. Corbin, J. R. Scheffer and V. Ramamurthy, *Chem. Commun.*, 1996, 2159.
256 K. Kitayama, H. Tsuji, Y. Uozumi and T. Hayashi, *Tetrahedron Lett.*, 1996, **37**, 4169.
257 K. Tamao, K. Nakamura, H. Ishii, S. Yamuguchi and M. Shiro, *J. Am. Chem. Soc.*, 1996, **118**, 12469.
258 M. M. H. Verstappen, G. J. A. Ariaans and B. Zwarenburg, *J. Am. Chem. Soc.*, 1996, **118**, 8491.
259 E. Kienan, S. C. Sinha, D. Shabat, H. Itzhaky and J. L. Reymond, *Acta Chem. Scand.*, 1996, **50**, 679.
260 G. Fantin, M. Fogagnolo, M. E. Guerzani, R. Lanciotti, A. Medici, P. Pedrini and D. Rossi, *Tetrahedron: Asymmetry*, 1996, **7**, 2879.
261 M. Utaka, T. Yano, T. Ema and T. Sakai, *Chem. Lett.*, 1996, 1079.
262 K. Nakamura, T. Matsuda and A. Ohno, *Tetrahedron: Asymmetry*, 1996, **7**, 3021.
263 K. Nakamura, T. Matsuda, T. Itoh and A. Ohno, *Tetrahedron Lett.*, 1996, **37**, 5727.
264 P. Righi, G. Fantin, M. Fogagnolo, E. Marotta, A. Medici and P. Pedrini, *Chem. Lett.*, 1996, 511.
265 C. Abalain, D. Buisson and R. Azerad, *Tetrahedron: Asymmetry*, 1996, **7**, 2983.
266 E. Santaniello, P. Ferraboschi, S. R. Elahi, E. Verza and F. M. Rivolta, *Synlett*, 1996, 1176.
267 T. Sugai, Y. Ohtsuka and H. Ohta, *Chem. Lett.*, 1996, 233.
268 F. J. Lakner and L. P. Hagen, *J. Org. Chem.*, 1996, **61**, 3923.
269 S.-I. Ozaki, T. Matsui and J. Watanabe, *J. Am. Chem. Soc.*, 1996, **118**, 9784.
270 D. R. Boyd, N. D. Sharma, S. A. Haughey, J. F. Malone, B. T. McMurray, G. N. Sheldrake, C. C. R. Allen and H. Dalton, *Chem. Commun.*, 1996, 2363.
271 D. R. Boyd, H. Dalton, N. D. Sharma, N. I. Bowers, P. A. Goodrich, M. R. Groocock, A. J. Blacker, D. A. Clarke and T. Howard, *Tetrahedron: Asymmetry*, 1996, **7**, 1559.
272 W. Adam, M. Lazaras, C. R. Saha-Moller and D. Schreier, *Tetrahedron: Asymmetry*, 1996, **7**, 2287.
273 T. Hudlicky, G. Burtora, S. P. Fearnley, A. G. Gum, M. R. Stabile and K. Abboud, *Tetrahedron Lett.*, 1996, **37**, 8155.
274 T. Hudlicky and A. J. Thorpe, *Chem. Commun.*, 1996, 1993,
275 D. R. Boyd, H. Dalton, N. D. Sharma, I. N. Brannigan, S. A. Haughey, J. F. Malone and D. A. Clarke, *Chem. Commun.*, 1996, 2361.
276 D. R. Kelly, S. M. Roberts, C. J. Knowles, J. G. Mahdi, M. A. Wright, I. N. Taylor, P. W. H. Wan, G. Grogan, S. Pedragosa-Moreau and A. Willetts, *Chem. Commun.*, 1996, 2333.
277 C. Ottalina, G. Carrea, S. Colonna and A. Ruckemann, *Tetrahedron: Asymmetry*, 1996, **7**, 1123.
278 M. M. Kayser, J. D. Stewart, K. W. Reed, J. Zhu and G. Chen, *J. Org. Chem.*, 1996, **61**, 7652.
279 D. R. Kelly, *Tetrahedron: Asymmetry*, 1996, **7**, 1149.
280 D. Ullman, F. Bordusa, K. Salchert and H.-D. Jakobte, *Tetrahedron: Asymmetry*, 1996, **7**, 2047.
281 R. A. Persichetti, J. J. Lalonde, C. P. Govardhan, N. K. Khalaf and A. L. Margolin, *Tetrahedron Lett.*, 1996, **37**, 6507.
282 C. Waldinger, M. Schneider, M. Bitto, F. Corelli and V. Summa, *Tetrahedron: Asymmetry*, 1996, **7**, 1485.
283 H. E. Master, R. V. Newudkar, R. A. Rane and A. Kumar, *Tetrahedron Lett.*, 1996, **37**, 9250.
284 S. Takayama, W. T. Moree and C.-H. Wong, *Tetrahedron Lett.*, 1996, **37**, 6287.
285 H. van der Deen, A. D. Cuiper, R. P. Hof, A. van Oeveren, B. L. Feringa and R. M. Kellogg, *J. Am. Chem. Soc.*, 1996, **118**, 3801.
286 M. Takahashi and K. Ogasawara, *Synthesis*, 1996, 954.
287 T. Eicher, M. Ott and A. Speicher, *Synthesis*, 1996, 755.
288 M. Ors, A. Morcuendo, M. I. Jimenez-Vacas, S. Valverde and B. Harradan, *Synlett*, 1996, 449.
289 B. H. Hoff, H. W. Anthonsen and T. Anthonsen, *Tetrahedron: Asymmetry*, 1996, **7**, 3187.
290 L. Ling and J. W. Lown, *Chem. Commun.*, 1996, 1559.
291 K. Suginaka, Y. Hayashi and Y. Yamamoto, *Tetrahedron: Asymmetry*, 1996, **7**, 1153.
292 Y. Kita, Y. Takebe, K. Murata, T. Naka and S. Akai, *Tetrahedron Lett.*, 1996, **37**, 7369.
293 J. M. J. Williams, P. M. Dinh, J. A. Howarth, A. R. Hudnott and W. Harris, *Tetrahedron Lett.*, 1996, **37**, 7623.
294 S. B. Desai, N. P. Argade and K. N. Ganesh, *J. Org. Chem.*, 1996, **61**, 6730.
295 G. Eidenhammer and F. Hammerschmidt, *Synthesis*, 1996, 748.
296 D. T. Chapman, D. H. G. Crout, M. Mahmoudian, D. I. C. Scopes and P. W. Smith, *Chem. Commun.*, 1996, 2415.
297 D. M. Spero and S. R. Kupadia, *J. Org. Chem.*, 1996, **61**, 7398.
298 K. Matsumoto, M. Shimojo, H. Kitajima and M. Hatanaka, *Synlett*, 1996, 1085.

299 Y.-F. Wang, K. Yakovlevsky and A. L. Margolin, *Tetrahedron Lett.*, 1996, **37**, 5317.
300 G. Cardillo, A. Tolomelli and C. Tomasin, *J. Org. Chem.*, 1996, **61**, 8651.
301 A. Patti, C. Sanfilippo, M. Piattelli and G. Nicolosi, *J. Org. Chem.*, 1996, **61**, 6458.
302 T. Ke, C. R. Wescott and A. M. Klimanov, *J. Am. Chem. Soc.*, 1996, **118**, 3366.
303 A. Rosenquist, I. Kvarnstrom, B. Classon and B. Samuelsson, *J. Org. Chem.*, 1996, **61**, 6282.
304 D. A. Griffin and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1996, **118**, 9526.
305 T. F. J. Lampe, H. M. R. Hoffman and V. T. Bornscheuer, *Tetrahedron: Asymmetry*, 1996, **7**, 2889.
306 A. Patti, C. Sanfilippo, M. Piatelli and G. Nicolosi, *Tetrahedron: Asymmetry*, 1996, **7**, 2665.
307 S. Puertas, F. Rebolledo and V. Gotor, *J. Org. Chem.*, 1996, **61**, 6024.
308 K. Faber, W. Kroutil, M. Mischitz and P. Plachota, *Tetrahedron Lett.*, 1996, **37**, 8379.
309 S. Pedragosa-Moreau, A. Archelas and R. Furstoss, *Tetrahedron Lett.*, 1996, **37**, 3319.
310 I. V. J. Archer, D. J. Leak and D. A. Widdowson, *Tetrahedron Lett.*, 1996, **37**, 8819.
311 R. Furstoss, S. Pedragosa-Moreau, C. Morisseau, J. Zlber, A. Archelas and J. Baratti, *J. Org. Chem.*, 1996, **61**, 7402.
312 K. G. Morris, M. E. B. Smith, N. J. Turner, M. D. Lilly, R. K. Mitra and J. M. Woodley, *Tetrahedron: Asymmetry*, 1996, **7**, 2185.
313 E. Kiljunen and L. T. Kanerva, *Tetrahedron: Asymmetry*, 1996, **7**, 1105.
314 N. J. Turner, S. J. Maddrell, A. Kerridge, A. J. Willetts and J. Crosby, *Tetrahedron Lett.*, 1996, **37**, 6001.