Catalytic asymmetric processes

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REVIEW

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1 Introduction

This review covers developments in catalytic asymmetric processes for the calendar year 1999. In contrast to previous reviews, the section on biotransformations has not been included since this area is covered in more depth elsewhere. As ever, asymmetric catalysis is a burgeoning field and no attempt has been made to be fully comprehensive. Accordingly it has been necessary to focus on significant new developments with the emphasis being placed on synthetic methods rather than structural or mechanistic aspects. Some coverage of solid phase chemistry and high through-put screening has again been included where pertinent but it is by no means all inclusive.

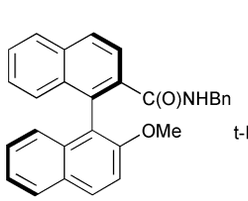
2 Synthetic organic catalysts

2.1 Oxidations

2.1.1 Epoxidation and aziridination

Two variations of the Sharpless epoxidation of allylic alcohols have been reported. The first employs a vanadium complex of binaphthyl ligand **1** to catalyse the reaction of trisubstituted allylic alcohols, resulting in epoxides of up to 94% ee.[1] The second example utilises a silica-supported tantalum complex of diethyl tartrate, giving enantioselectivities of up to 94% ee when prop-2-en-1-ol is used as the substrate.[2]

The epoxidation of unfunctionalised olefins remains an area of interest with Jacobsen-type Salen ligands proving to be most popular. Sheurer and co-workers have reported a tartrate-derived Mn–Salen complex **2** for the epoxidation of cyclic olefin



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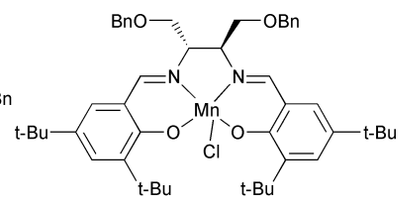

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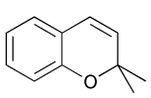

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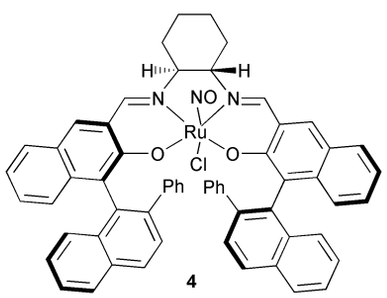

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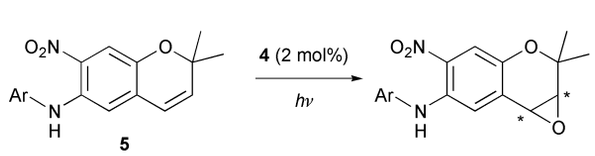
3, resulting in epoxides in up to 76% yield and 69% ee when MCPBA was employed as stoicheiometric oxidant.[3] Katsuki and co-workers have reported two interesting examples of epoxidation using Salen complexes. The first utilised Ru–Salen complex **4** for the epoxidation of olefin **5** (Scheme 1), in which the best results were achieved when the complex was activated using incandescent light, leading to products of up to 98% ee.[4] The second example exploited a combination of an achiral Mn–Salen complex combined with a chiral modifier (Fig. 1) for the epoxidation of **5**, resulting in the formation of epoxides of up to 83% ee.[5] A silica gel supported Mn–Salen complex was reported by Pini and co-workers, giving enantioselectivities of up to 58% for the epoxidation of simple olefins when 5 mol% of the catalyst was employed.[6] An adaptation of Jacobsen's epoxidation system, using tetrabutylammonium monopersulfate as a novel stoicheiometric oxidant, was reported by Pietikainen.[7] The author demonstrated that this oxidant, when used in combination with 7 mol% of Mn–Salen complex, gave high yields and enantioselectivities of up to 93% for a range of olefin substrates. The group of Jacobsen has explored the development of new catalysts for epoxidation of simple olefins by carrying out a screen of metal-binding combinatorial libraries. The group prepared a library of 5760 peptide derivatives on solid phase and these were then screened for metal-binding ability and catalytic activity. The study resulted



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Scheme 1

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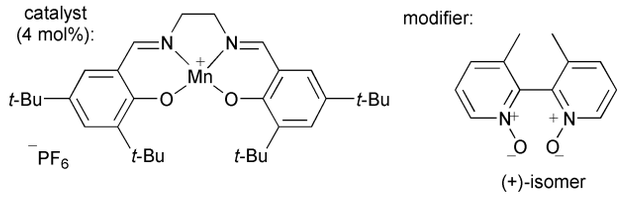
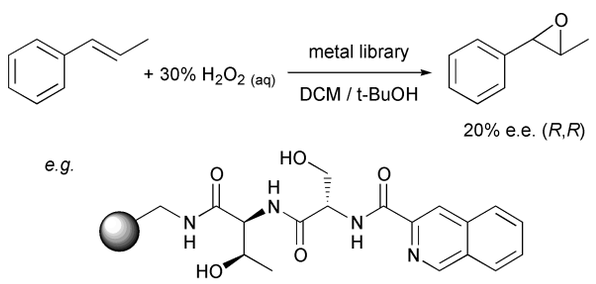


Fig. 1

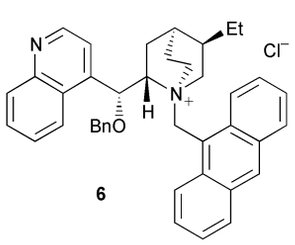
in the identification of three complexes of $FeCl_2$ which catalysed the epoxidation of methylstyrene with high efficiency, giving products of up to 20% ee (Scheme 2).[8]



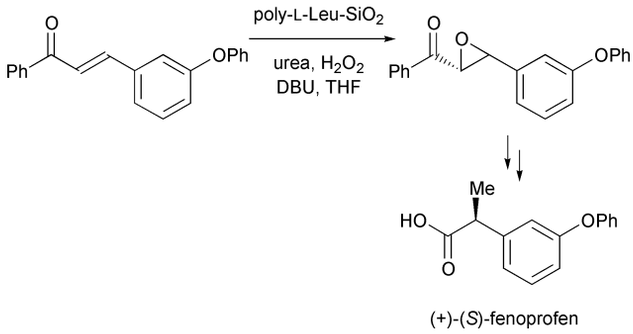
Scheme 2

Other types of epoxidation catalyst that have been reported include chiral porphyrin derivatives. Collman and co-workers have described an Fe–porphyrin complex for the epoxidation of terminal olefins, giving products of up to 90% ee in some cases, using only 0.1 mol% of catalyst.[9] A ruthenium–porphyrin complex was reported to act as an effective catalyst for the epoxidation of (*E*)-olefins (up to 50% ee) when employed in conjunction with a pyridine *N*-oxide derivative as stoicheiometric oxidant.[10]

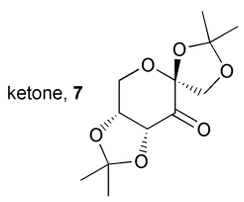
The nucleophilic epoxidation of α,β-unsaturated ketones employing quaternary ammonium salts as chiral phase transfer catalysts has been reported independently by Corey and by Lygo.[11,12] In both cases the Cinchona alkaloid derivative **6** proved to be the most effective catalyst, giving enantioselectivities in the range of 77–98% depending on the substrate. The group of Roberts and co-workers has continued to exploit polyleucine as a phase transfer catalyst in the epoxidation of α,β-unsaturated ketones. A modification of their original procedure by employing sodium percarbonate as base and oxidant has enabled the catalyst loading to be reduced without significant erosion of yield or enantioselectivity.[13] An alternative means for reducing the amount of catalyst required for effective epoxidation was the immobilisation of polyleucine onto silica prior to its use in the reaction.[14] Roberts and co-workers have also demonstrated the utility of polyleucine catalysed epoxidation by applying this method to the synthesis of enantiomerically pure (+)-(*S*)-fenoprofen (Scheme 3).[15]



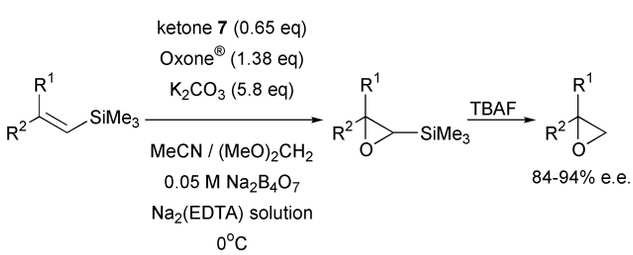
Epoxidation utilising chiral dioxiranes has been further exploited by Shi and co-workers. The use of a hydrogen peroxide–acetonitrile mixture as the primary oxidant proved to be simpler than, and as effective as, using Oxone® giving enantioselectivities of up to 95% for simple olefin substrates.[16] The more conventional Oxone®-mediated epoxidation method, using ketone **7**, has been extended to novel substrates including



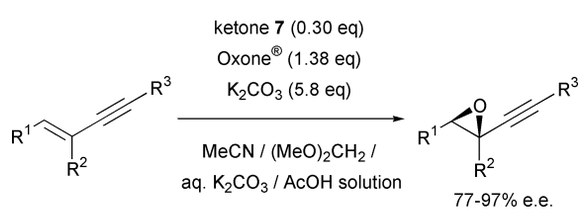
Scheme 3



vinyl silane derivatives and enynes (Schemes 4 and 5 respectively).[17,18] A related epoxidation method employing a chiral oxaziridine as catalyst, and again employing Oxone® as the primary oxidant, was reported by Bohe and co-workers, although the enantioselectivities achieved using this method were only modest (up to 35% ee).[19]



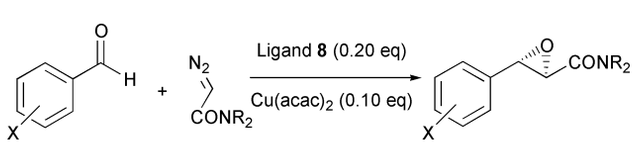
Scheme 4



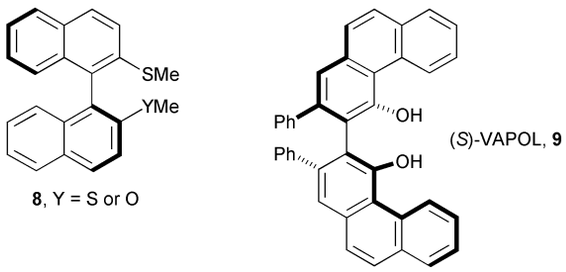
Scheme 5

A further method which has been explored for the asymmetric synthesis of epoxides is a Darzens type condensation reaction. Imashiro and co-workers have employed a binaphthyl thioether **8** as a catalyst for the reaction between diazo amides and aldehydes (Scheme 6). The reaction is reported to proceed *via* a chiral sulfur ylide giving epoxides of up to 64% ee.[20] A similar Darzens condensation catalysed by a glucose-derived crown ether has also been reported to give α-keto epoxides of up to 71% ee.[21] Finally, Arai and co-workers have employed a Cinchona alkaloid derivative as a phase transfer catalyst for the Darzens condensation between α-chloro ketones and aldehydes.[22,23]

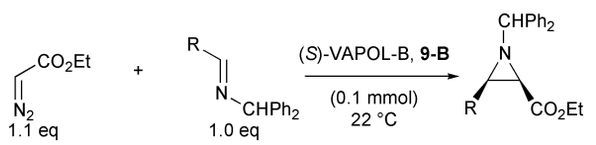
In contrast to epoxidation, there are few examples of catalytic asymmetric aziridine synthesis. An example of the



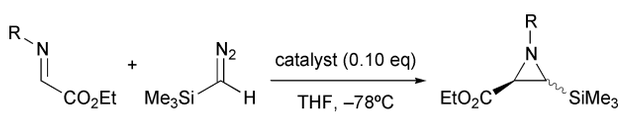
Scheme 6



reaction between an imine and a diazoacetate has been reported by Antilla and Wulff.[24] The active catalyst in this case was a boron complex of (*S*)-VAPOL **9** leading to the formation of aziridines with a *cis–trans* ratio of >50 : 1 and enantioselectivities of up to 97% ee for the *cis* isomer (Scheme 7). A similar transformation, involving the use of diazosilanes in combination with glyoxylate derived imines, was reported by Jørgensen and co-workers. A screen of suitable Lewis acids revealed that a Cu–BINAP complex was the most effective catalyst giving up to 72% ee of the *cis*-aziridine in some cases (Scheme 8).[25] Finally, the reaction of styrene, with the iminoiodane PhI=NTs as a nitrene source, has been described using a ferrocene-derived C_2-symmetric diamine as the ligand in the presence of CuOTf.[26]



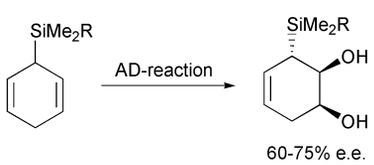
Scheme 7



Scheme 8

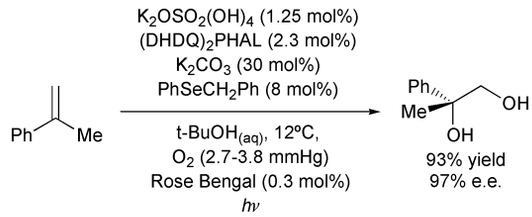
2.1.2 Dihydroxylation and aminohydroxylation

Reports relating to the Sharpless asymmetric dihydroxylation reaction (AD) focus mainly on the application of this reaction to novel substrates and slight modifications to the reaction conditions. The dihydroxylation of ketene acetals has been shown to give α-hydroxy esters in good yield and with excellent levels of enantioselectivity (up to 99.9% ee).[27] Angelaud and co-workers have utilised the AD reaction for the synthesis of conduritols and inositols *via* a desymmetrisation of dienylsilanes. High levels of diastereofacial selectivity were achieved along with moderate to good enantioselectivity (Scheme 9).[28]



Scheme 9

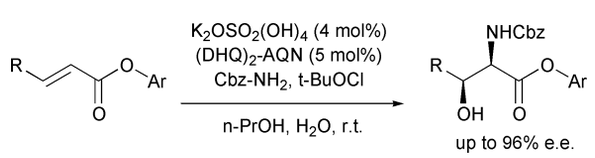
An alternative stoicheiometric oxidant for the AD reaction in the form of molecular oxygen has been reported by two groups. Dobler and co-workers demonstrated the use of 1 bar of molecular O_2 as oxidant under strictly buffered conditions (pH 10.4) for the AD reaction of styrene giving moderate yields and good levels of enantioselectivity (52% and 90% respectively).[29] The use of $^1O_2$ as the oxidant under photolytic conditions using a catalytic quantity of an aryl selenide as the oxygen carrier was also reported for use in the AD reaction of simple olefins (see Scheme 10).[30] Under these modified conditions excellent



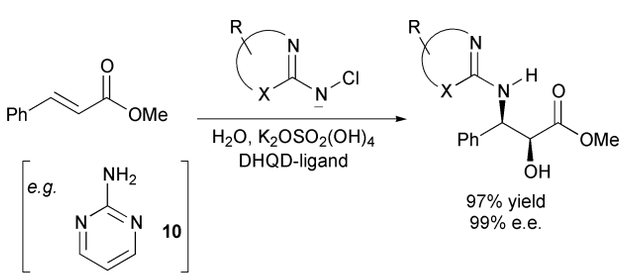
Scheme 10

yields and enantioselectivities, comparable to conventional AD reactions, were achieved.

The aminohydroxylation reaction (AA) has also seen some advances during the period under review. Morgan and co-workers have presented a study on the effect of substituents on the regioselectivity of the AA reaction carried out using Sharpless's modified $(DHQ)_2$-AQN ligand. Reaction of α,β-unsaturated aryl esters gave varying levels of regiochemical control depending on the nature of the aryl substituent (Scheme 11). In all cases high levels of enantioselectivity were achieved.[31] In all cases the regiochemical outcome in the case of the aryl esters was opposite to that achieved when using ethyl esters as substrates. Sharpless has reported the extension of the AA reaction to unsaturated phosphonates as substrates. A number of substrates and nitrogen sources were studied giving yields ranging from 20–53% and enantioselectivities ranging from 32–98%.[32] A new and "biologically relevant" nitrogen source for the AA reaction has also been described by Sharpless. Amino-substituted heterocycles such as 2-aminopyrimidine **10**, added to the reactions as the corresponding *N*-chloro anions (as illustrated in Scheme 12), gave excellent yields of up to 97% and enantioselectivities of up to 99% in the AA reaction of unsaturated esters (see Scheme 12).[33]



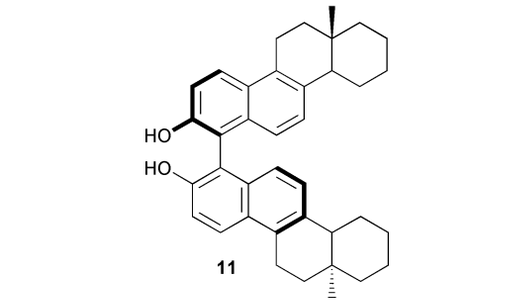
Scheme 11



Scheme 12

2.1.3 Sulfoxidation, allylic oxidation and other oxidations

Bolm and Dabard have reported a new ligand for use in the oxidation of aryl alkyl sulfides.[34] Their steroid-derived BINOL analogue **11** when used in conjunction with titanium tetraisopropoxide gave enantioselectivities of up to 90% for the oxidation of methyl phenyl sulfide. The best results were achieved when up to one equivalent of water was added to the reaction mixture which is in keeping with observations made for similar oxidation reactions in the past. A related BINOL-derived catalyst was reported by Capozzi and co-workers to give excellent levels of enantioselectivity (>98%) in the oxidation of α-thiophosphonate derivatives **12** (Scheme 13).[35] The double oxidation of disulfides to give C_2-symmetric bis(sulfoxides) has been achieved using a vanadium complex of half-Salen ligand **13** (Scheme 14).[36] The best results were realised when a two-carbon tether separated the sulfides, giving



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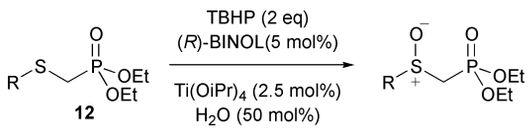

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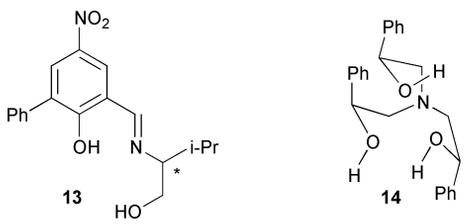
Scheme 13



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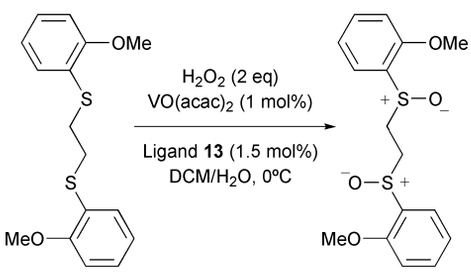
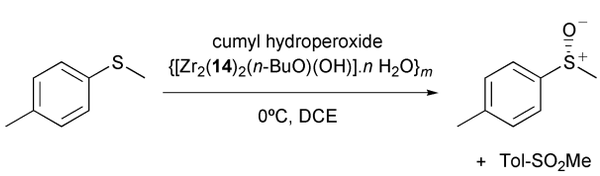


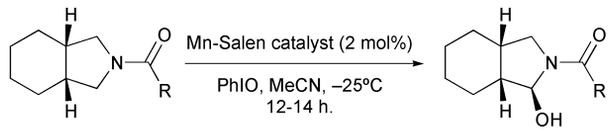
Scheme 14

a yield of 95% as an 83 : 17 mixture of C_2–*meso* isomers and >95% ee for the C_2 isomer. A novel Zr(IV)-derived catalyst containing a C_3-symmetric triol ligand **14** has been reported for the oxidation of sulfides using cumyl hydroperoxide as the stoicheiometric oxidant. At moderate levels of catalyst loading (10 mol%) up to 86% ee was achieved, however the yield of sulfoxide was low (35%) owing to a competing over-oxidation reaction. The over-oxidation to give the sulfone product could be avoided by using a low catalyst loading (0.5 mol%), however, enantioselectivity dropped to only 9% under these conditions (Scheme 15).[37]

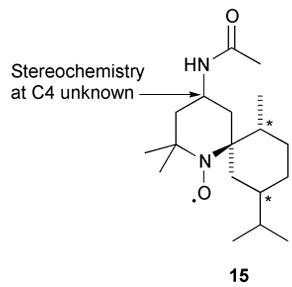


Scheme 15

Benzylic oxidation using an Ru–porphyrin complex in combination with a pyridine *N*-oxide as stoicheiometric oxidant has been reported to give arylmethyl alcohols with enantioselectivities of >50% in most cases.[38] Katsuki and Punniyamurthy have reported an unusual oxidative desymmetrisation of a *meso*-amide using a modified Mn–Salen complex.[39] Only 2 mol% of catalyst was required to give the α-hydroxy amide product of up to 76% ee (Scheme 16). A rather unusual oxidation, employing electrolysis in the presence of chiral aminoxyl radical **15**, for the resolution of racemic arylmethyl alcohols has been described.[40] Using this process chiral alcohols were prepared in 36–49% yield and 50–70% ee (see Scheme 17).



Scheme 16



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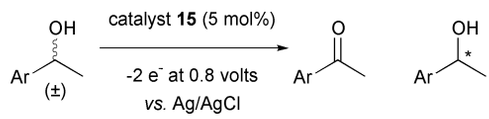
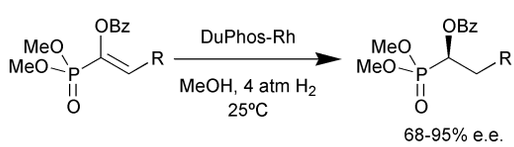


Scheme 17

2.2 Reductions

2.2.1 Hydrogenation

As in recent years, the preparation of novel ligands for rhodium-catalysed, asymmetric hydrogenation of enamides and dehydro amino acids has continued apace.[41–53] A selection of such ligands is depicted in Fig. 2. The extension of hydrogenation methods to use with novel substrates has also been an area of continued interest. Burk and co-workers have reported the application of the Duphos ligand in the rhodium-catalysed hydrogenation of α-hydroxy and α-amino phosphonates possessing α,β-unsaturation (Scheme 18).[54] The same group has also utilised this catalytic system for the production of β-amino alcohols and 1,2-diamines from their corresponding unsaturated precursors.[55] The preparation of β-amino acid derivatives utilising a Duphos-derived catalyst has also been described.[56] Enantioselectivities of up to 99.6% have been achieved for some cases.



Scheme 18

The asymmetric hydrogenation of enol acetates has been reported by Jiang and co-workers (Scheme 19).[57] In this case use of the Me-PennPhos ligand led to the formation of cyclic acetates of up to 99% ee, the best results being achieved when methanol was employed as solvent. A related hydrogenation of an acyclic enol acetate was reported by Knochel and co-workers using the FERRIPHOS ligand (Scheme 20).[58] Several groups have developed novel catalysts for the hydrogenation of α,β-unsaturated carboxylic esters or acids.[59–61] Of particular note is an example of a BINAP-derived soluble polymer which has been successfully utilised as a ligand in the ruthenium-catalysed hydrogenation of α,β-unsaturated acids giving up to 88% ee when a catalyst loading of only 0.5 mol% was employed.[61]

The use of rhodium- and, to a lesser extent, ruthenium-derived catalysts for C=C bond hydrogenation still predominates. However, a couple of notable examples employing other transition metals have been reported during 1999. Pfaltz and Hilgraf have demonstrated the use of an iridium catalyst for the hydrogenation of olefins, leading to the formation of

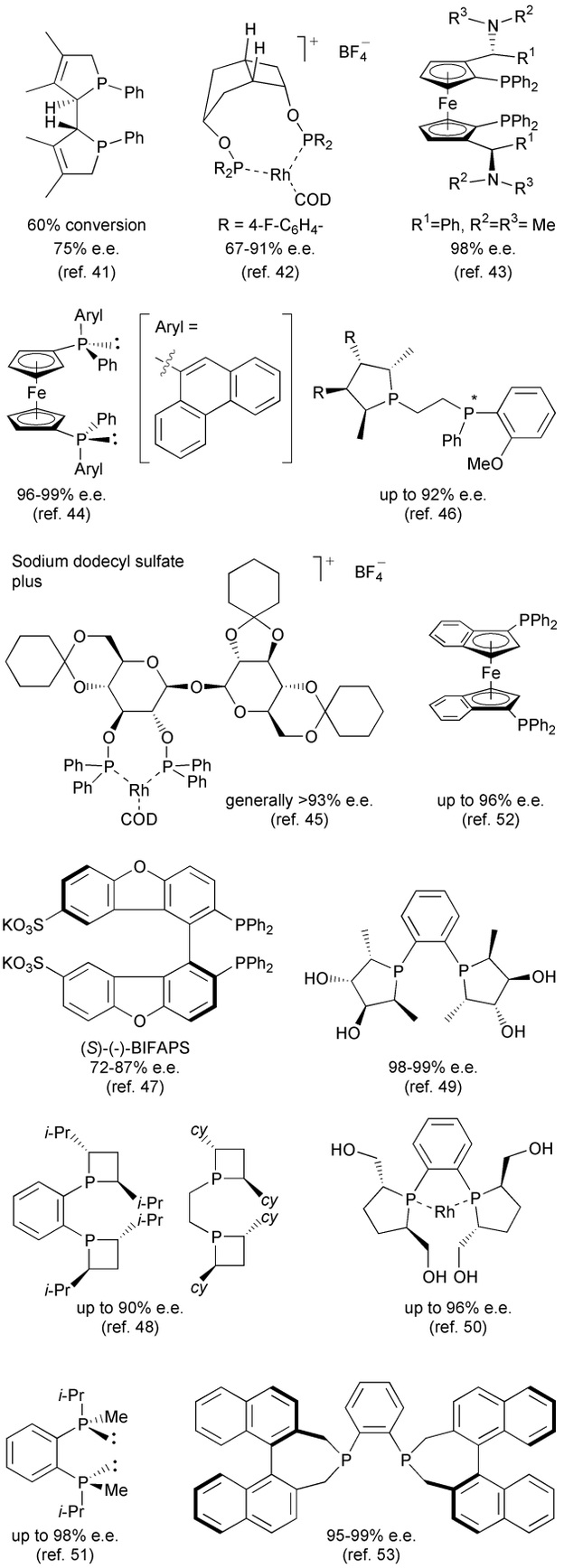
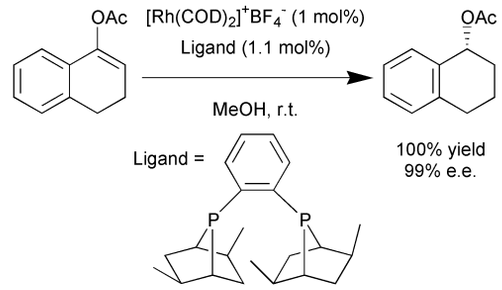
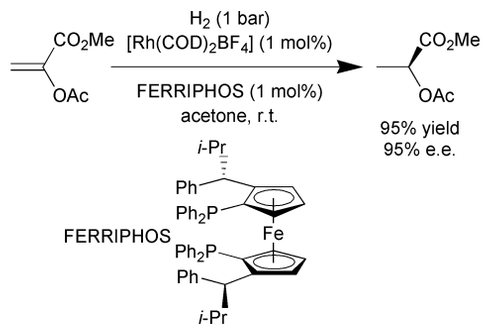


Fig. 2

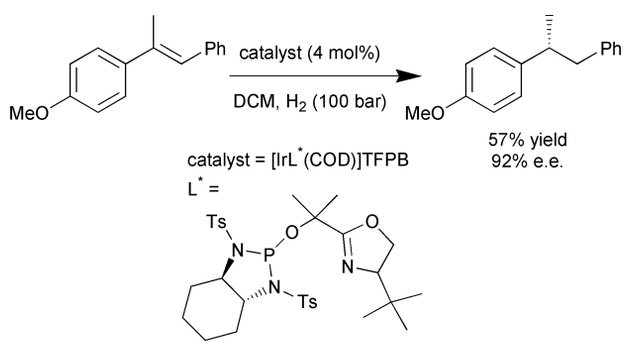
products of up to 92% ee (see Scheme 21).[62] Buchwald and co-workers have demonstrated the utility of a Zr–ethylene bis(tetrahydroindenyl) (EBTHI) catalyst for the hydrogenation of a range of unfunctionalised olefins, with enantioselectivities ranging from 84 to 98%.[63]



Scheme 19

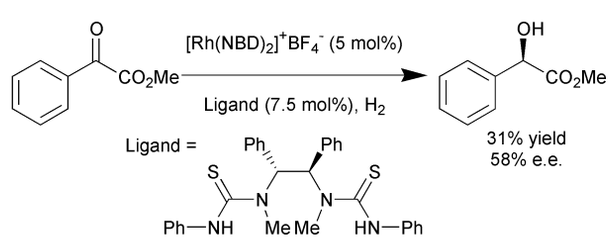


Scheme 20

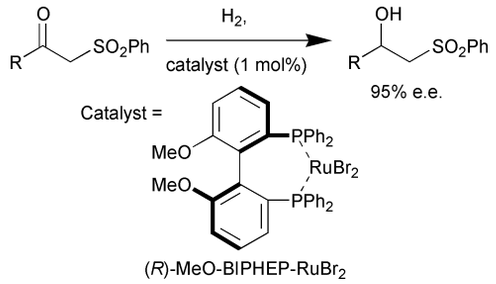


Scheme 21

The hydrogenation of C=O bonds using catalytic asymmetric methods remains an area of interest. Lemaire and co-workers have reported an interesting example involving the use of an Rh–diamide catalyst for the hydrogenation of α-keto esters (Scheme 22).[64] Although the enantioselectivities achieved are only modest, this represents an interesting departure from the more traditional phosphine-based ligands. The related hydrogenation of β-keto esters using novel ruthenium diphosphine catalysts has also been described.[65,66] Another class of substrate which has attracted some interest during 1999 is that of β-keto sulfones and sulfonates. A catalyst derived from Ru(II) and the axially chiral BIPHEP ligand has been successfully employed in the hydrogenation of β-keto sulfones giving the corresponding hydroxysulfones in up to 95% ee (Scheme 23).[67,68] Noyori and co-workers have employed a Ru–BINAP catalyst in the hydrogenation of β-keto sulfonates in excellent yield and with high levels of enantioselectivity (up to 97% ee).[69]

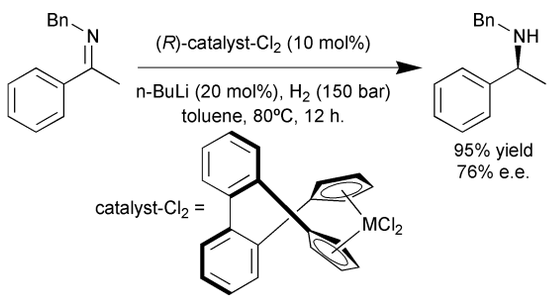


Scheme 22



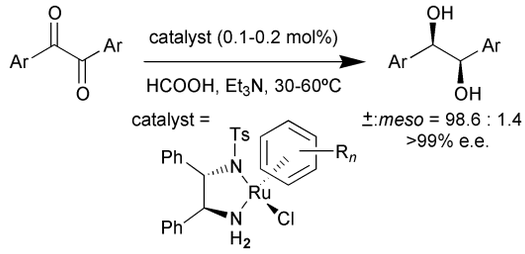
Scheme 23

The hydrogenation of C=N bonds continues to present a significant challenge to catalytic, asymmetric methods. Ringwald and co-workers have reported a novel, axially chiral complex for the asymmetric hydrogenation of both cyclic and acyclic imines, giving the corresponding amines in 76–98% ee (Scheme 24).[70] Pfaltz and co-workers have extended the application of their Ir–oxazoline–phosphine catalyst to the hydrogenation of imines in supercritical CO_2.[71] The results achieved were variable (26–81% ee) depending on the precise catalyst and reaction conditions employed.

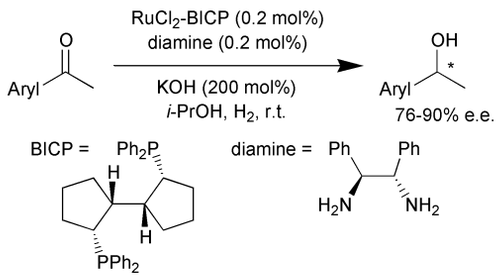


Scheme 24

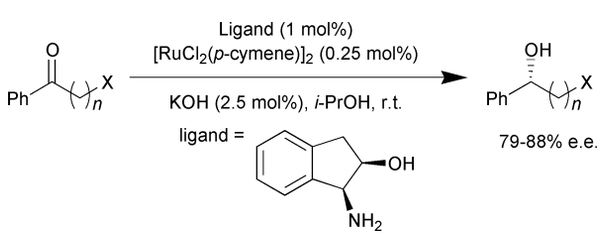
Over the review period there has been a significant increase in the number of examples of catalytic, asymmetric transfer hydrogenations. Given the range of ligand types and reaction conditions which have been employed it is difficult to categorise the examples in a logical fashion. An attempt has been made to group the examples according to ligand type. Noyori and co-workers have continued to develop the use of chiral diamines in the Rh- or Ir-catalysed transfer hydrogenation of aryl alkyl ketones.[72] Frost and Mendonca have also reported a related study on the effect of varying the nature of the *N*-substituent of the diamine ligand upon enantioselectivity in the transfer hydrogenation of acetophenone.[73] Noyori and co-workers have further extended the application of Ru–DPEN-catalysed transfer hydrogenation to 1,2-diketones giving diols with a (±) : *meso* ratio of 99 : 1 and enantioselectivities of up to 99% when as little as 0.1–0.2 mol% of catalyst was employed (Scheme 25).[74] Cao and Zhang have reported the use of a ruthenium catalyst which comprises a diamine and a diphosphine as ligands (Scheme 26).[75] A number of aryl alkyl ketones were employed as substrates in this study, giving enantioselectivities in the range of 76–90%. Other ligand types which have been employed for Ru-catalysed transfer hydrogenation include β-amino phosphine oxides[76] and ephedrine derivatives.[77,78] Wills and co-workers have demonstrated the utility of aminoindanol as a ligand for the transfer hydrogenation of α-hetero-substituted ketones.[79] The group noted that careful choice of *O*- or *N*-substituent is required to achieve good yields and enantioselectivity (Scheme 27). Finally, Mao and Baker have reported the application of Noyori's DPEN ligand for the Rh-catalysed transfer hydrogenation of imines. The reaction is reported to be rapid (10 min) and highly stereoselective (up to 97% ee) even at catalyst loadings as low as 0.5 mol%.[80]



Scheme 25



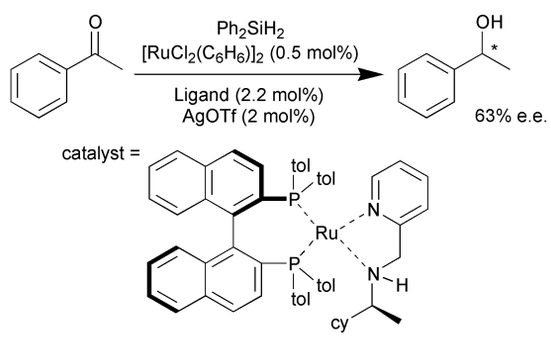
Scheme 26



Scheme 27

2.2.2 Hydrosilylation

Comparatively few examples of hydrosilylation reactions have appeared in 1999. The use of Rh–diphosphine complexes as catalysts in the presence of diarylsilanes as the stoicheiometric reducing agent for the hydrosilylation of C=O bonds remains an area of interest.[81–83] A ruthenium complex, comprising a BINAP unit and a pyridylamine, proved to be an effective catalyst for the hydrosilylation of ketones in the presence of a catalytic quantity of AgOTf (Scheme 28).[84] Seebach and Heldmann reported a mixed donor P–N ligand derived from α,α,α′,α′-tetraaryldioxolane dimethanol (TADDOL) and an oxazoline unit for use in the hydrosilylation of ketones.[85] Best results were achieved when the chirality of the TADDOL was matched with that of the oxazoline (up to 86% ee product). Two examples of the use of transition metals other than Rh or Ru for hydrosilylation have been reported. Bandini and co-workers have described a Ti–bis(oxazoline) catalyst for the hydrosilylation of ketones giving alcohols in 18–72% ee depending on the choice of counterion and silyl source.[86] Buchwald and Yun have extended the use of the EBTHI ligand for the zirconium-catalysed hydrosilylation of ketones.[87]



Scheme 28

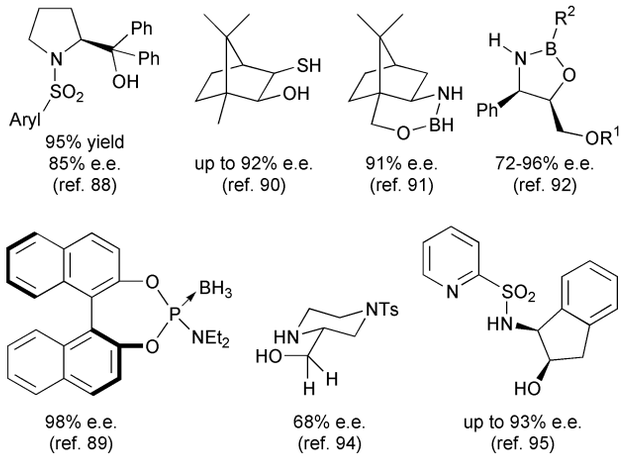


Fig. 3

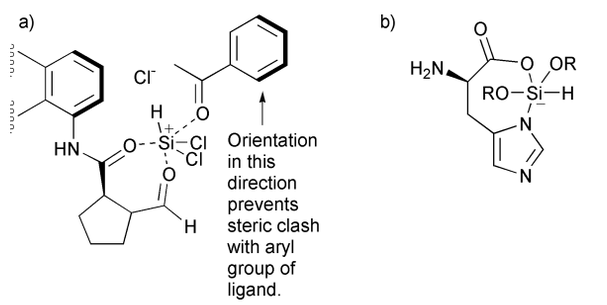
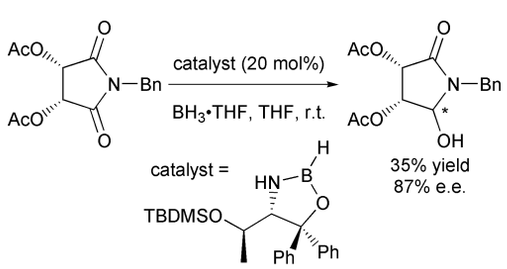


Fig. 4

2.2.3 Other reductions

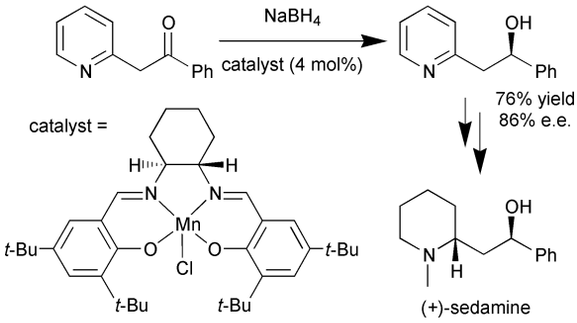
The borane-mediated reduction of aryl alkyl ketones continues to attract attention and a number of new ligands have been described for this purpose (Fig. 3).[88–95] The use of an oxazaborolidine catalyst for the desymmetrisation of *meso*-imides has been demonstrated by Shimizu and co-workers (Scheme 29).[96] The group went on to use this methodology in the synthesis of (+)-deoxybiotin in 98% ee. The borane-mediated reduction of α-keto acetals using a range of oxazaborolidine catalysts has been described by Cho and Chun.[97] Woodward and Ford have reported a Ga–monothiobinaphthol complex, similar to BINAL-H, which can be employed in the catecholborane-mediated reduction of ketones in 89–91% ee.[98]



Scheme 29

The use of silanes as a hydride source for the reduction of carbonyl compounds has been reported by two groups. In both cases 10 mol% of a chiral activator was employed, giving silicate complexes as the active catalysts, leading to alcohols with 43 and 70% ee respectively [Fig. 4(a) and (b)].[99,100]

Enantiomerically pure sedamines and related alkaloids have been prepared using a reductive application of Jacobsen's Mn–Salen complex.[101] The use of only 4 mol% of the Mn(III) complex in the presence of sodium borohydride as the stoicheiometric reductant resulted in the reduction of a pyridyl methyl ketone in 86% ee (Scheme 30). Buchwald and co-workers have reported the asymmetric, conjugate reduction of



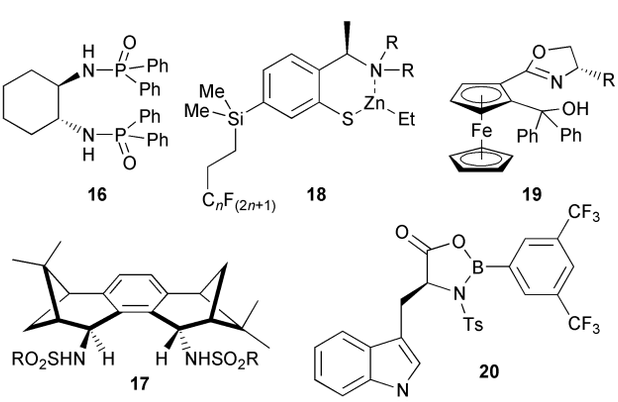
Scheme 30

α,β-unsaturated esters using a combination of a Cu(I)–BINAP catalysts and polymethylhydroxysilane as reducing agent.[102] Exclusive 1,4-addition of hydride was observed giving esters in 80–92% ee.

2.3 Carbon–carbon bond forming reactions

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

The now well established addition of diethylzinc to aldehydes in the presence of a chiral ligand has continued to attract a significant amount of attention. A comprehensive discussion of this topic is beyond the scope of this review. Articles describing the preparation and use of novel ligands for this transformation are cited here.[103–120] Papers which introduce significant modifications to existing methodology will be discussed in more detail. The titanium-catalysed addition of diethylzinc to aldehydes has received somewhat less attention. Two groups have reported novel ligands for use in this reaction. Shi and Sui have described a C_2-symmetric bis(phosphinamide) **16** and Paquette and Zhou have employed a bis(sulfonamide) **17** derived from verbenone.[121,122] A related reaction employing a Co(II)–Salen type complex prepared from a novel, axially chiral diamine was reported to give enantioselectivities of up to 80%.[123]

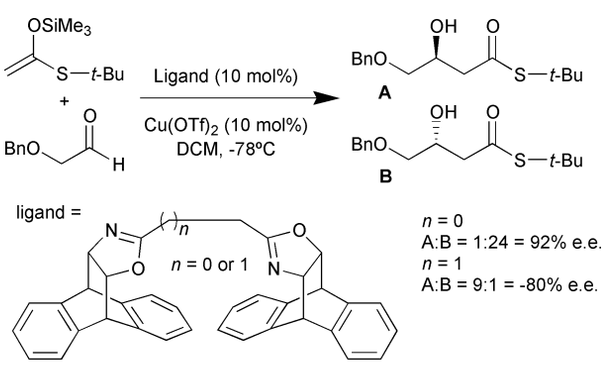


Several reports of the application of polymer-bound ligands for the diethylzinc addition reaction have appeared during 1999. Sung and co-workers have described a polystyrene-bound 3-*exo*-(dimethylamino)isoborneol (DAIB) derivative which gave excellent levels of stereoinduction (up to 97% ee at 5 mol% catalyst loading) and which could be re-used without erosion of selectivity or conversion.[124,125] A similar polymer-bound amino alcohol ligand was described by Zwanenberg and co-workers.[126] Seebach has reported the application of dendritic TADDOL ligands for the Ti-catalysed addition of diethylzinc to aldehydes. Results showed that the rate of reaction and the degree of enantioselectivity achieved using first- and second-generation dendrimers were comparable to those for TADDOL itself. The group went on to co-polymerise the dendritic TADDOLs with styrene to produce a reusable macroporous polymer which could be effectively employed in up to 20 consecutive iterations

of the Ti-catalysed reaction.[127,128] An alternative to immobilisation of ligands on a solid support is to employ a biphasic system in which the catalyst remains in one phase and the reaction proceeds in the other. This approach has been demonstrated by van Koten and co-workers using a perfluorous biphase system.[129] The catalyst **18** has a perfluorinated side chain which renders it soluble in perfluoromethylcyclohexane, the reactants and product are insoluble in the fluorous phase but dissolve readily in octane. The group has demonstrated the utility of this system for diethylzinc addition to benzaldehyde giving up to 92% ee (unfortunately some erosion of selectivity is observed upon repeated use of the ligand).

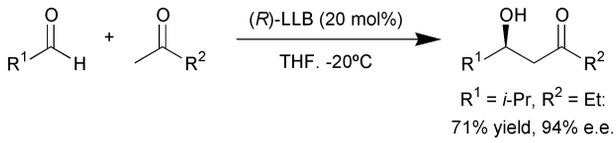
Alternative zinc reagents have been employed in additions to aldehydes. Huang and Pu[130] have reported a BINOL-derived ligand for use in the addition of diphenylzinc to aromatic aldehydes (up to 94% ee) and Bolm and Muniz have reported the use of an oxazolinyl alcohol **19** in an analogous transformation (up to 90% ee).[131] The use of alkynylzincs (generated *in situ*) as nucleophiles for addition to aldehydes has been reported to proceed in up to 85% ee in the presence of 10 mol% of an amino alcohol ligand.[132]

Advances continue to be made in the area of catalytic, asymmetric aldol chemistry. Ishihara and co-workers have reported a highly diastereo- and enantioselective (98% de, 99% ee) aldol reaction, catalysed by an extremely active oxazaborolidine **20** derived from tryptophan.[133] The use of a sterically congested bis(oxazoline) for the Cu(II)-catalysed addition of ketene silyl acetals to aldehydes has been demonstrated to give a reversal in the sense of stereoinduction depending on the length of the tether between the oxazoline units (Scheme 31).[134] This phenomenon is thought to be due to a difference in the coordination sphere of the copper in the two complexes. Corey and co-workers have demonstrated the utility of a cinchonidine-derived ammonium fluoride salt as a phase transfer catalyst for aldol and nitroaldol reactions enabling the highly stereoselective synthesis of β-hydroxy amino acids and the anti HIV drug amprenavir respectively.[135,136]



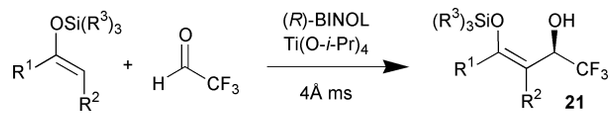
Scheme 31

Shibasaki and co-workers have presented a breakthrough in the area of aldol chemistry by reporting the first effective example of a direct aldol reaction between a ketone and an aldehyde catalysed by an LLB (lithium lanthanum binaphthoxide) complex under anhydrous conditions giving aldol products in up to 94% ee (Scheme 32).[137] An unusual aldol reaction has been reported by Yamamoto and co-workers who employed a Ag–BINAP complex in combination with a trialkyltin methoxide in order to catalyse the reaction between an enol trichloroacetate and benzaldehyde.[138] The reaction proceeded in good yield with *anti* : *syn* ratios of up to 94 : 6 and enantioselectivities of up to 96% for the *anti*-isomer. An aldol reaction using a ketone as the electrophile has been reported by Jørgensen and co-workers.[139] The group have described the Cu(II)-bis(oxazoline)-catalysed reaction of diethyl ketomalonate with a range of silyl enol ethers giving aldol products in up to 93% ee when the reaction was performed at −78 °C.



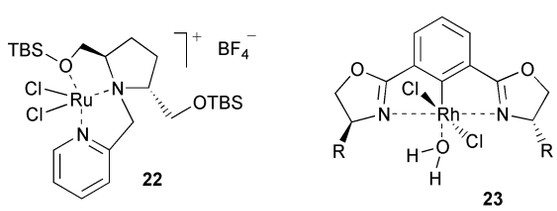
Scheme 32

Finally, on the subject of aldol reactions, the group of Mikami has presented a Mukaiyama aldol reaction which appears to proceed *via* a Friedel–Crafts type mechanism in the first step (Scheme 33).[140] The Ti–BINOL-catalysed reaction between a silyl enol ether and trifluoroacetaldehyde gave rise to an isolable intermediate **21** in 98% ee which could be transformed to the normal aldol adduct on treatment with TBAF. This result clearly prompts the question, "Do all Mukaiyama aldol reactions proceed *via* the same mechanism?"

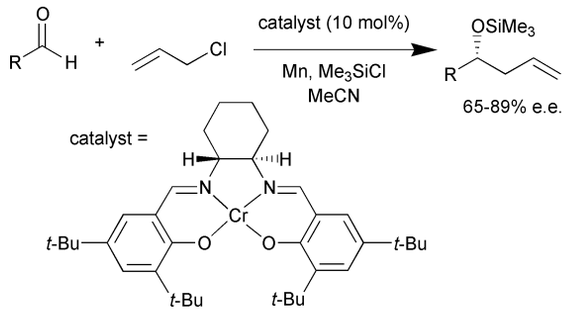


Scheme 33

Asymmetric allylation of aldehydes using allyltin reagents can be catalysed by Ru or Rh complexes. Shi and co-workers described the use of a pyridylpyrrolidine-derived Ru complex **22** which gave up to 50% ee in an allylation reaction.[141] Motoyama and co-workers reported a similar transformation in which the use of a Rh–bis(oxazoline) complex **23** was effective as catalyst giving allyl alcohols in up to 61% ee.[142] A related transformation employing allenyltin as the nucleophile was found to be effectively catalysed (91–98% ee, 53–81% yield of dienyl alcohols) by 10 mol% of a Ti–BINOL complex.[143] The use of an indium–(−)-cinchonidine complex for the allylation of aldehydes using allyl bromides was reported to give up to 90% ee and 99% conversion when 30 mol% of the complex was used.[144] Bandini and co-workers have reported the first example of a catalytic enantioselective Nozaki–Hiyama reaction.[145] The group employed a Cr(II)–Salen complex in conjunction with Mn [to recycle Cr(III) to Cr(II)] and Me_3SiCl (to ensure turnover). As little as 10 mol% of the catalyst was required to achieve enantioselectivities of 65–89% with moderate yields of 40–60% (Scheme 34). The allylation of ketones to give tertiary alcohols has been reported by Casolari and co-workers.[146] The combination of BINOL, $Cl_2Ti(OiPr)_2$ and tetraallyltin led to the formation of a catalytic complex which could be used in sub-stoicheiometric quantities (40 mol%) for the allylation of a range of ketones, giving up to 80% ee (Scheme 35).



Several groups have reported examples of the addition of cyanide to C=O bonds. Aspinall and co-workers have described an ytterbium-bis(oxazoline) catalyst,[147] Shibasaki has described an aluminium–BINOL–bisphosphine oxide complex[148] and Buono has reported a titanium–diazaphospholidine oxide catalyst.[149] All three examples give excellent levels of enantioselectivity (89% ee or greater) for the addition of Me_3SiCN to aryl aldehydes. Belokon and co-workers have extended the application of their previously reported titanium–Salen catalyst to use in the reaction of Me_3SiCN with ketones.[150] Use of as little as 0.5 mol% of the catalytic complex



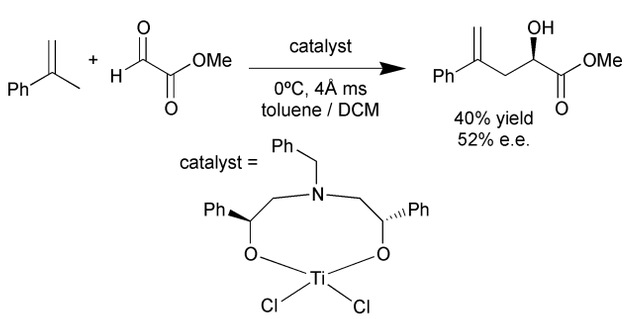
Scheme 34

Scheme 35

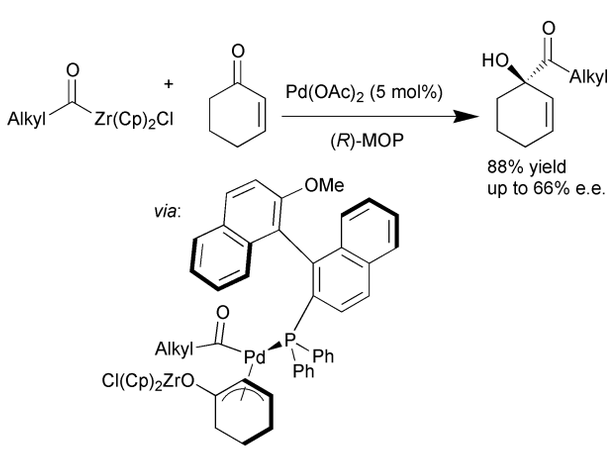
gave up to 66% ee when acetophenone was employed as the substrate.

Finally, on the subject of additions to C=O bonds, a few examples of more unusual transformations have appeared in the literature during 1999. An intermolecular carbonyl ene reaction between 1-methylstyrene and methyl glyoxylate was reported to give 52% ee of product in 40% yield (Scheme 36).[151] A similar reaction between cyclopentene and ethyl glyoxylate in the presence of a Cu–bis(oxazoline) catalyst has been described by Jørgensen.[152] Hanazawa and co-workers have described the 1,2-addition of an acylzirconocene chloride to cyclohexenone under Pd-catalysed conditions in the presence of Hayashi's MOP ligand.[153] The reaction is thought to proceed *via* a transmetallation of the acyl group from Zr to Pd (Scheme 37). An asymmetric Baylis–Hillman reaction has been reported using a quinidine-derived catalyst.[154] The reaction was carried out at −55 °C and gave 58% yield and 91% ee when a fluorinated acrylate was employed as substrate.

Addition of carbon nucleophiles to C=N bonds has become an increasingly popular area of synthetic endeavour. Kobayashi

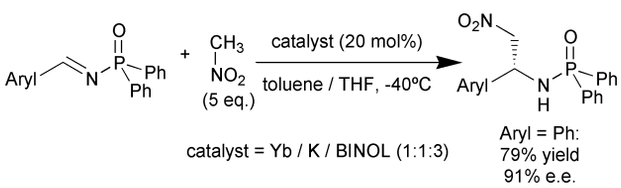


Scheme 36



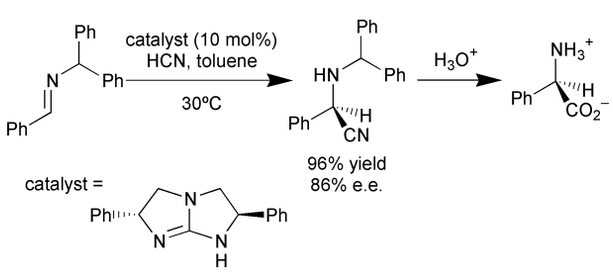
Scheme 37

and co-workers have employed a novel Zr–bis(BINOL)methane complex in the addition of ketene silyl acetals to imines. The ligand, which was designed to be preorganised, proved to be more effective (enantioselectivities up to 95%) than using two equivalents of BINOL to form the catalytic complex.[155] Shibasaki and co-workers have reported the first catalytic, asymmetric nitro-Mannich reaction promoted by a novel heterobimetallic complex (Scheme 38).[156] Use of 20 mol% of catalyst (Yb–K–BINOL = 1 : 1 : 3) resulted in the formation of β-nitro amine derivatives in up to 91% ee. Other Mannich-type reactions reported include a Ti–BINOL-catalysed addition of silyloxyfurans to imines and the Cu(I)–BINAP-catalysed addition of indoles to iminoglyoxylates.[157,158] A modification to the Mannich reaction in which the imine is formed *in situ* from an aminal derivative has been described by Ferraris and co-workers.[159] The use of a Cu(I)–BINAP catalyst developed by this group for standard Mannich reactions resulted in excellent levels of stereoinduction (89–95% ee) for a range of substrates.



Scheme 38

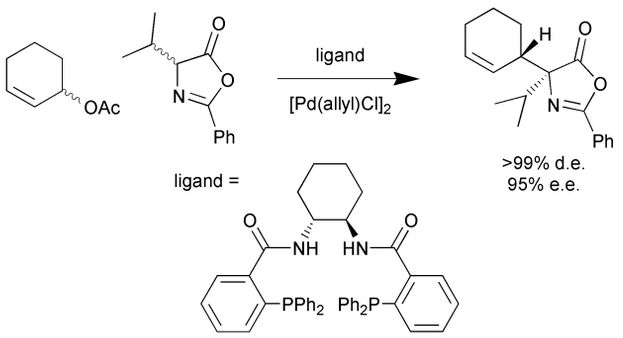
The addition of diethylzinc to a phosphinamide-protected imine has been carried out in the presence of a chiral amino alcohol.[160] The addition of a silyl chloride to the reaction mixture was required to give accelerated reaction rates and only moderate levels of enantioselectivity (72% ee) were achieved when sub-stoicheiometric amounts (20 mol%) of the ligand were employed. Nakamura and co-workers[161] reported the addition of allylsilanes to imines using 5 mol% of an allyl–Pd complex in the presence of TBAF resulting in the formation of allylic amines in up to 84% ee. Corey and Grogan have reported a novel Strecker reaction catalysed by a chiral bicyclic guanidine derived from phenylglycine (Scheme 39).[162] Reaction of a benzaldimine derivative with HCN led to the formation of a phenylglycine precursor in up to 86% ee.



Scheme 39

2.3.2 Transition metal catalysed allylic substitution

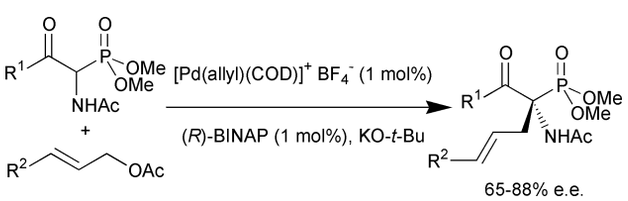
The main thrust of research in this area remains the development of novel ligands for the Pd-catalysed allylic substitution of allylic acetates.[81,163–192] There is not scope within this review to discuss novel ligands in detail and instead emphasis will be placed on novel applications of allylic substitution methodology. Moberg and co-workers have reported enhanced reactivity of Pd–ligand complexes when reactions are carried out in the presence of microwave radiation.[193] Reaction times were reduced from 1 hour to 1.5 minutes, in the case of a Pd–pyridyloxazoline catalyst, without significant erosion of enantioselectivity. Trost and Azira have developed a new application of the bis(2-diphenylphosphinobenzamide) ligand, in which a racemic azlactone and racemic allylic acetate react together to give a quaternary amino acid derivative in 99% de



Scheme 40

and 95% ee (Scheme 40).[194] Trost and co-workers have also applied this ligand to the synthesis of anatoxin,[195] aflatoxin-B,[196] a fragment of vitamin E[197] and in the allylation of tin enolates derived from cyclic ketones.[198] Dynamic kinetic transformations of racemic, vinylic epoxides have also been demonstrated using this ligand, giving vinylic diols of up to 97% ee and in 91% yield.[199] A dynamic kinetic resolution of cyclic allylic acetates using an amine nucleophile has been reported by Mori and co-workers who utilised 1 mol% of a Pd–BINAPO (BINAPO = BINAP monooxide) complex, resulting in 73% yield of product and up to 83% ee.[200]

α-Acetamido-β-keto carboxylates and phosphonates have been utilised as nucleophiles in allylic substitution reactions catalysed by a Pd–BINAP complex.[201,202] The latter case represents the first example of a catalytic, enantioselective synthesis of α-amino phosphonates possessing a quaternary carbon centre (Scheme 41). Helmchen and Flubacher have demonstrated the use of a Pd–oxazoline–phosphine catalyst in a domino Heck–allylic amination reaction.[203] The allylic amination step proceeded in up to 81% ee.

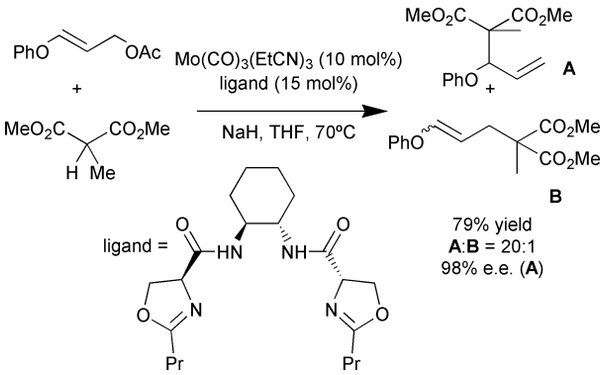


Scheme 41

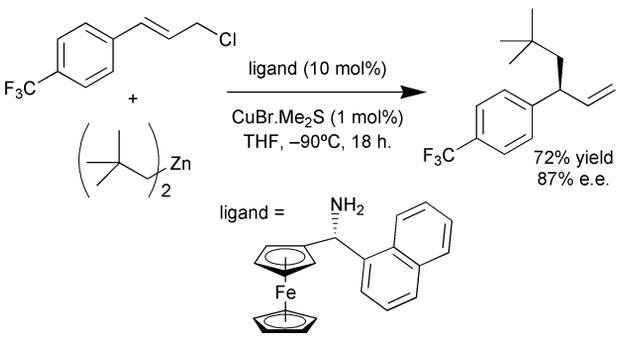
A number of examples of allylic substitution reactions, catalysed by metals other than Pd, have appeared during 1999. Williams and co-workers have utilised a Pt–oxazoline–phosphine in the reaction of allylic acetates with dimethyl malonate.[204] Enantioselectivities achieved using this catalyst are generally lower than for the comparable Pd-catalysed reactions, giving up to 84% ee at 81% conversion. Two groups have reported Ir–phosphine catalysts for use in allylic substitution reactions using dimethyl malonate as the nucleophile.[205,206] Enantioselectivities ranged from 8–93% depending on the substrate and catalyst chosen. Pfaltz and Glorius have reported a novel molybdenum catalyst for the substitution of terminal allylic acetates with dimethyl malonate.[207] Good levels of regioselectivity (20 : 1 in favour of branched product) and enantioselectivity (98%) were achieved (Scheme 42). Trost has employed an Mo–bis(2-diphenylphosphinobenzamide) complex in a similar transformation employing terminal allylic acetates with extended conjugation as substrate.[208] Finally, Knochel and Dubner have developed a novel Cu(I)-catalysed substitution of allylic chlorides employing diorganozinc compounds as the nucleophile (Scheme 43).[209] The use of 10 mol% of a chiral ferrocene-derived ligand led to the formation of branched allylic products in up to 87% ee.

2.3.3 Hydroformylation, Heck and related reactions

There have been comparatively few examples of reactions over

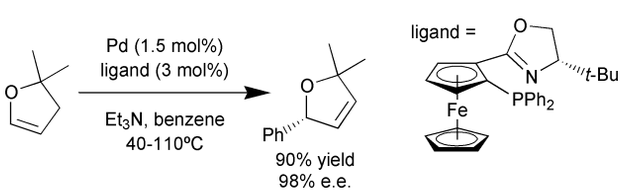


Scheme 42



Scheme 43

the period under review which fit into this category. Hennessy and co-workers have described the use of 2,2-dimethyl-2,3-dihydrofuran as a novel substrate for asymmetric Heck reactions.[210] The use of this substrate in a Heck reaction with aryl triflate catalysed by a Pd–oxazoline–phosphine complex was reported to give a single product in 90% yield and 98% ee (Scheme 44). Use of an asymmetric Heck reaction has proved to be highly effective in the synthesis of an epibatidine derivative which was prepared in 81% ee when a Pd–BINAP complex was employed as the catalyst.[211]

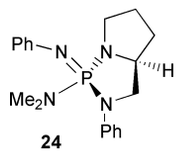


Scheme 44

A water-soluble diphosphine catalyst has been employed in the hydroformylation of styrene under aqueous conditions.[212] The catalyst was demonstrated to be reusable, however regioselectivity was poor (1 : 1 ratio of linear to branched products) and enantioselectivities of the branched isomers reached a maximum of 43%. Hydroformylation of styrene in supercritical CO_2 using an Rh–phosphine–phosphite catalyst led to somewhat better results, with higher selectivity for the branched isomer in up to 90% ee being reported.[213]

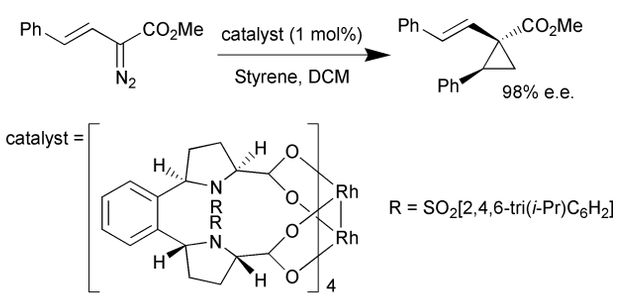
2.3.4 Cyclopropanations

The preferred method for achieving asymmetric cyclopropanation is the reaction between a diazoacetate and an olefin, catalysed by a transition metal complex. Use of a Cu(I) complex of diazaphospholidine ligand **24** gave excellent *trans–cis* selectivity (98 : 2) and high enantioselectivity (92% ee) for the *trans*-isomer in the reaction between ethyl diazoacetate and styrene.[214] The application of a ferrocene-derived C_2-symmetric diamine ligand in an analogous reaction resulted in a *trans* : *cis* ratio of 63 : 37 giving the *trans* isomer in 87% ee.[26] An intramolecular cyclopropanation, catalysed by a Ru–

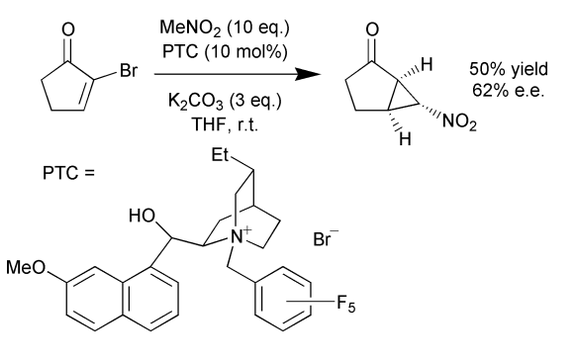


24

oxazoline–phosphine complex, has been reported by Park and co-workers.[215] The resultant 3,5-fused cyclic ketone was formed in 91% yield and 75% ee. The group of Katsuki has presented some intriguing results in which a Ru–Salen complex catalyses the cyclopropanation reaction between styrene and *tert*-butyl diazoacetate, giving differing levels of reactivity and stereoselectivity in the presence or absence of light.[216,217] When an incandescent light source was employed 53% conversion was achieved [*cis* : *trans* ratio of 80 : 20 and ee (*cis*-isomer) of 81%], whereas when the reaction was carried out in the dark, only 6% conversion was observed [*cis* : *trans* ratio of 44 : 56 and ee (*cis* isomer) of 71%]. Davies and Panaro have reported the use of a D_2-symmetric dirhodium prolinate complex for vinyl carbenoid cyclopropanations giving up to 98% ee (Scheme 45).[218] An unusual approach to cyclopropanation has been described by Satake and co-workers, in which a Pd-catalysed reaction between an allylic acetate and a ketene silyl acetal gave rise to a cyclopropane adduct in 54% ee.[219] Finally Arai and co-workers have reported a cyclopropanation resulting from a successive Michael addition, proton transfer, intramolecular alkylation process (Scheme 46).[220] Up to 62% ee could be achieved in the presence of 10 mol% of a quinidine-derived phase transfer catalyst.



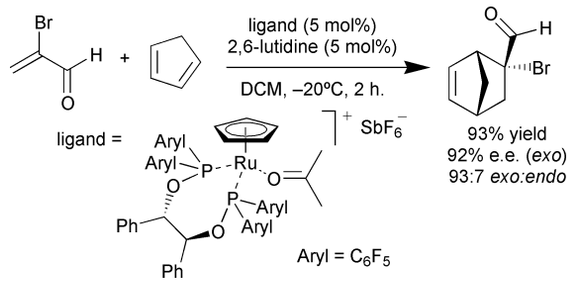
Scheme 45



Scheme 46

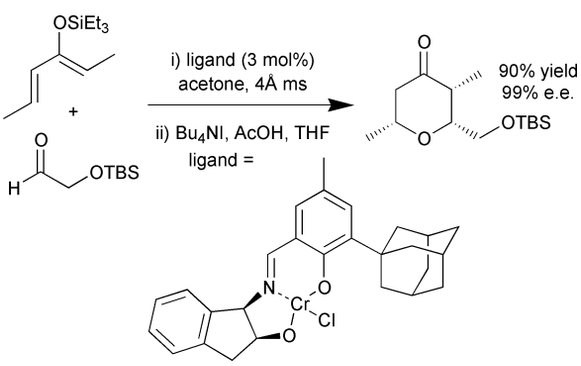
2.3.5 Cycloaddition reactions

The Diels–Alder reaction between cyclopentadiene and an oxazolidinone-derived dienophile has long been a proving ground for novel Lewis acid catalysts. Several groups have reported examples of novel catalysts for this transformation during the review period.[151,221–223] Of particular note is the use of Pd(II)– or Pt(II)–BINAP complexes for which there is a marked counterion effect on the rate of the reaction and the stereoselectivity.[222] In the cases where a palladium perchlorate salt was employed an *endo–exo* ratio of 97 : 3 and ee (*endo*) of 99% was recorded. Kundig and co-workers have reported a stable, recoverable Ru-Lewis acid which was employed in the Diels–Alder reaction between cyclopentadiene and 2-bromoacrolein, giving a marked preference for the *exo* product (*exo–endo* ratio of 93 : 7) in 92% ee (Scheme 47).[224]

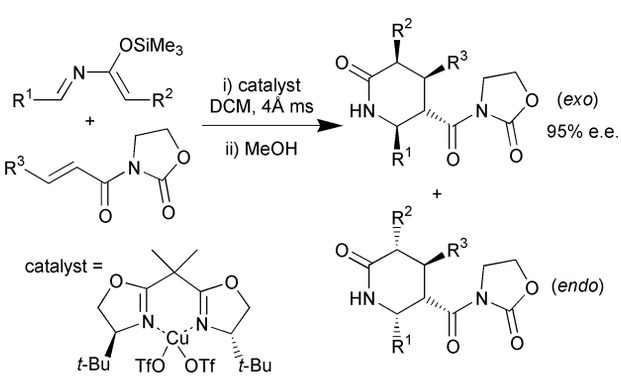


Scheme 47

Jacobsen has reported a hetero-Diels–Alder reaction catalysed by a novel Cr(III) complex derived from 1-aminoindan-2-ol (Scheme 48).[225] The cyclic ether product was formed in 90% yield and 99% ee. Similar hetero-Diels–Alder reactions between dienes and glyoxylate derivatives have been reported by Johannsen and by Oi.[226,227] Kobayashi has reported an aza-Diels–Alder reaction between an imine and Danishefsky's diene catalysed by a Zr–BINOL complex.[228] The reaction proceeded in high yield (93%) and excellent ee (91%). The use of an imine-derived diene has been demonstrated by Ghosez and Jnoff in which the Cu(II)–bis(oxazoline)-catalysed reaction of an oxazolidinone-derived dienophile led to the formation of the *exo* product in 95% ee when the reaction was carried out at −45 °C (Scheme 49).[229] A similar transformation, also catalysed by a Cu(II)–bis(oxazoline) complex, involving a thioketone-derived diene, was reported by Saito and co-workers.[230]



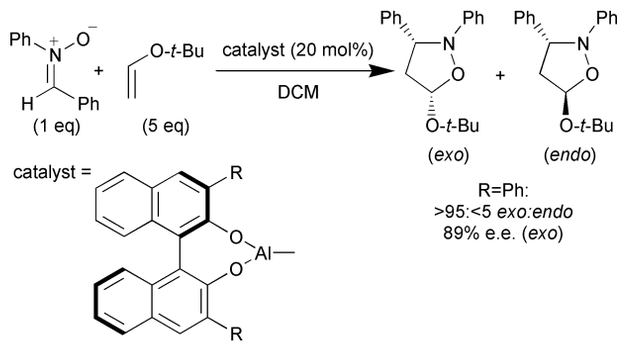
Scheme 48



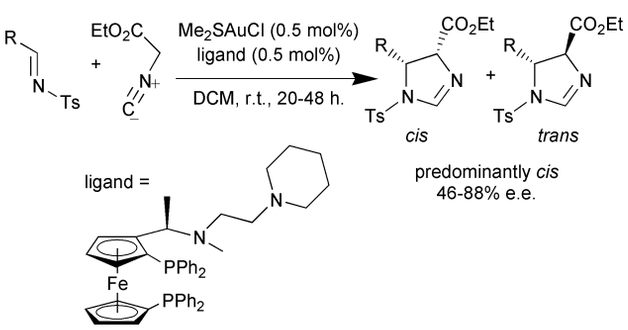
Scheme 49

A variety of 1,3-dipolar cycloaddition reactions have been described during 1999 with nitrones proving to be the most popular type of dipole under investigation. Desimoni and co-workers have reported the use of an Mg–bis(oxazoline) complex in the reaction between a nitrone and an oxazolidinone-derived dipolarophile, giving the *endo*-C_4-adduct as the major

product in 86% ee.[231] A very similar transformation catalysed by a Pd(II)–BINAP complex, was reported by Hori and co-workers.[232] Jørgensen and co-workers have made an extensive study of an inverse electron demand 1,3-dipolar cycloaddition reaction.[233–235] Best results were achieved by employing an Al–BINOL complex as catalyst resulting in the formation of the *exo*-adduct as the major product (>90%) in 89% ee (Scheme 50). A somewhat unusual dipolar cycloaddition reaction between an imine and a nitrile ylide precursor has been described by Zhou and co-workers (Scheme 51).[236] The Au–diphosphine-catalysed reaction gave predominantly the *cis*-adduct in enantioselectivities ranging from 46–88% depending on the substrates employed.

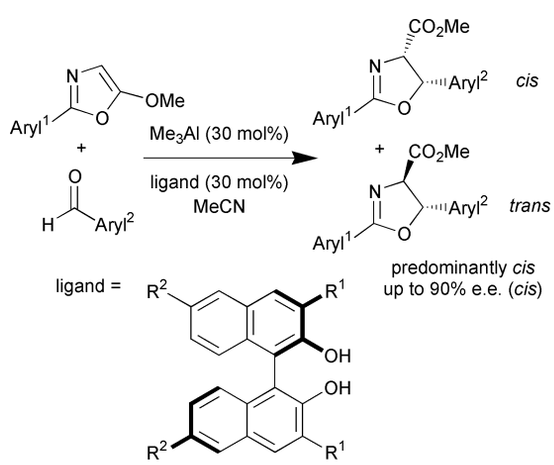


Scheme 50



Scheme 51

A formal [3+2] cycloaddition reaction, catalysed by an Al–BINOL complex, has been reported by Suga and co-workers (Scheme 52).[237] The oxazoline adducts were formed in good yield, with a marked preference for the *cis*-isomer (*cis*–*trans* ratio of 87 : 13) in up to 90% ee. The [4+1] cycloaddition of carbon monoxide with vinylallenes, catalysed by a Rh–Duphos complex, leading to the formation of substituted cyclopentenones in up to 78% ee, has been described by Ito and co-workers.[238]

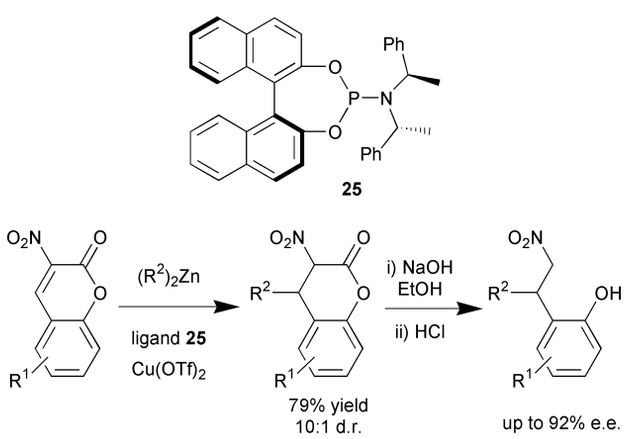


Scheme 52

2.3.6 Addition of carbon nucleophiles to C=C bonds

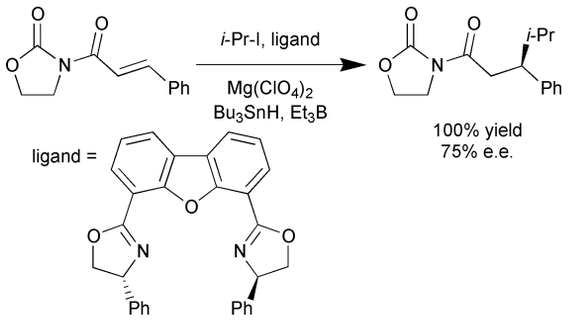
This section is predominantly concerned with the Michael addition of various carbon nucleophiles to α,β-unsaturated carbonyl compounds. Reactions have been subdivided according to nucleophile type as far as possible.

There remains a significant amount of interest in the Cu-catalysed addition of organometallics (normally diethylzinc) to enone substrates. Some new diphosphite ligands have been reported to give good to excellent levels of enantioselectivity (53–90%) in the addition of diethylzinc to cyclohexenone.[239–241] A binaphthyl-derived N–P-containing ligand has been described by Hu and co-workers to give excellent enantioselectivities (>90%) in the Cu-catalysed addition of diethylzinc to cyclohexenone and (*E*)-chalcone.[242] Feringa and co-workers have extended the use of the phosphoramidite ligand **25** with more complex substrates.[243] Scheme 53 shows the reaction of α,β-unsaturated nitroacetates with diethylzinc in the presence of 1.2 mol% $Cu(OTf)_2$ and 2.4 mol% ligand **25** giving products in up to 92% ee and 10 : 1 dr.[244] A further application of ligand **25** has been in the desymmetrisation of *meso*-dienones utilising the Cu-catalysed reaction with diethylzinc, giving unsymmetrical enone products in up to 99% ee.[245] A similar BINOL-derived phosphite ligand has been employed by the group of Alexakis for the synthesis of (−)-muscone in 79% ee *via* a Michael addition reaction.[246] Woodward and co-workers have investigated the use of binaphthyl-derived ligands bearing OH, SH or thioamide groups in the Cu-catalysed addition of a range of organometallics to enone substrates.[247,248]

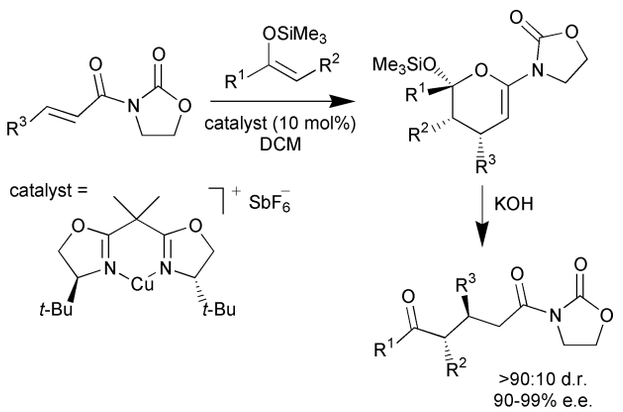


Scheme 53

The 1,4-addition of a radical species has been demonstrated by Curran and co-workers to proceed with high enantioselectivity (75%) when carried out in the presence of a dibenzofuran-derived bis(oxazoline) (Scheme 54).[249] Sato has reported a nickel–oxazoline-catalysed tandem carbometallation–conjugate addition reaction in which a vinylzinc species reacts with an enone, giving products of up to 88% ee.[250] Hayashi and co-workers have further developed the Michael addition of aryl nucleophiles to enones, α,β-unsaturated esters and α,β-unsaturated phosphonate esters using a Rh(I)–BINAP catalyst.[251–253] In all cases the use of aryl borates (generated *in situ*) gave the best yields and levels of enantioselectivity (up to 99% ee). Evans and co-workers have explored the Michael addition of enol ethers and ketene acetals to oxazolidinone-derived enamides or α,β-unsaturated esters using a Cu(II)–bis(oxazoline) complex as catalyst. The expected products were formed in high yield (89–99%) and enantioselectivity (86–99%) *via* an unexpected reaction pathway.[254,255] *In situ* IR analysis demonstrated the presence of a cyclic intermediate, indicating that the reaction was proceeding *via* a cycloaddition pathway (Scheme 55). The breakdown of this intermediate was dependent on the presence of an alcohol in the reaction mixture which was also required to achieve turnover of the catalyst.



Scheme 54



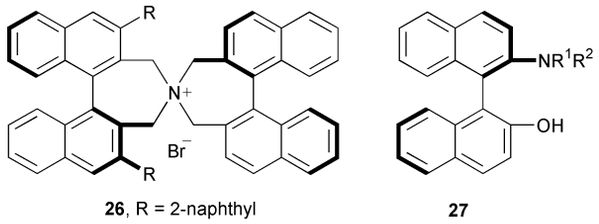
Scheme 55

Several reports of Michael addition of malonate- or β-keto ester-derived nucleophiles to enones have appeared, however, most give only poor to moderate levels of enantioselectivity.[256–258] A notable exception has been described by Alvarez and co-workers who employed a polymer-supported Cinchona alkaloid-derived ligand, giving up to 87% ee at 30 mol% catalyst loading.[259] Ji and co-workers have described the Mg–bis(oxazoline)-catalysed addition of malonate nucleophiles to nitro olefins, giving enantioselectivities of up to 97%.[260] Finally, Normant and co-workers have reported an unusual addition of alkyllithiums to a range of alkenes in the presence of catalytic quantitites of sparteine. Enantioselectivities ranged from 70–92% depending on the nature of the substrate and the quantity (0.05–0.1 mol%) of sparteine employed.[261]

2.3.7 Other C–C bond forming reactions

This section can be divided into two main areas, the first being phase transfer catalysed alkylation of enolates and the second being carbenoid insertion reactions, both of which have received considerable attention during 1999. The discussion here will commence with alkylation reactions.

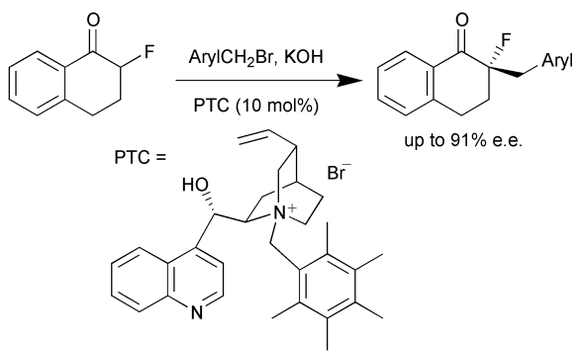
Maruoka and co-workers have employed a novel quaternary ammonium salt **26** as a catalyst for the preparation of α-amino acid derivatives with high levels of enantioselectivity (90–96%) using 1 mol% of the catalyst.[262] Belokon and co-workers have reported a similar alkylation reaction in which the use of 10 mol% of BINOL derivative (NOBIN), **27**, gave rise to amino acid derivatives of up to 68% ee.[263] The groups of Belokon and North have also demonstrated the application of a Cu–Salen complex as a phase transfer catalyst in the formation of α,α-disubstituted amino acid derivatives of up to 96% ee.[264] A similar transformation has been reported by Lygo and co-workers using a Cinchona alkaloid-derived catalyst.[265] The same group has also applied this methodology to the preparation of a range of bis(α-amino ester)s in up to 95% ee.[266,267] The α-alkylation of a number of cyclic enolates using chiral phase transfer catalysts has been reported.[268–270] Arai and co-workers have described the alkylation of α-fluorotetralone (2-fluoro-3,4-



R^1 = H, Me

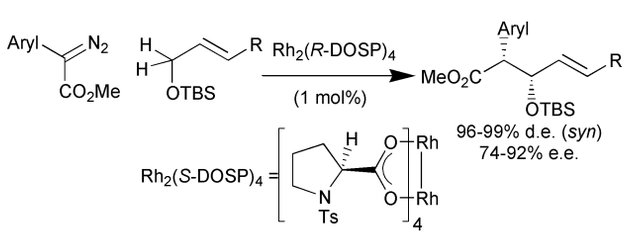
R^2 = H, Me, i-Pr, Cy, Ad, Ph, -$(CH_2)_2$-OH

dihydronaphthalen-1(2*H*)-one), giving up to 91% ee of product using 10 mol% of a Cinchona derived-catalyst (Scheme 56).[269] Koga and co-workers have reported the alkylation of tetralone-derived silyl enol ethers in the presence of a C_2-symmetric tetraamine catalyst, forming quaternary carbon centres in up to 88% ee using 10 mol% of ligand.[270]

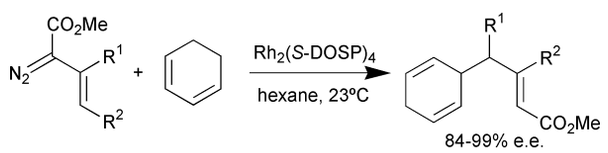


Scheme 56

The second major area of interest, carbenoid insertion reactions, has mainly seen advances in the range of insertion reactions which can be carried out asymmetrically rather than in novel catalyst development. Davies and co-workers have shown that the reaction between a diazoacetate and an allylic silyl ether can be tuned in favour of carbenoid insertion, rather than cyclopropanation, leading to products in 96–99% de and 74–92% ee (Scheme 57).[271] The same group has again demonstrated a high level of chemoselectivity in the Rh_2[(*S*)-DOSP]$_4$-catalysed reaction between an unsaturated diazoacetate and cyclohexa-1,3-diene described formally as a C–H insertion–Cope rearrangement (Scheme 58).[272] Davies and co-workers have also employed the same catalyst system in the disubstitution of *N*-Boc-pyrrolidine *via* C–H insertion of a carbenoid species derived from diazoacetates, giving C_2-symmetric amines of up to 99% ee.[273]



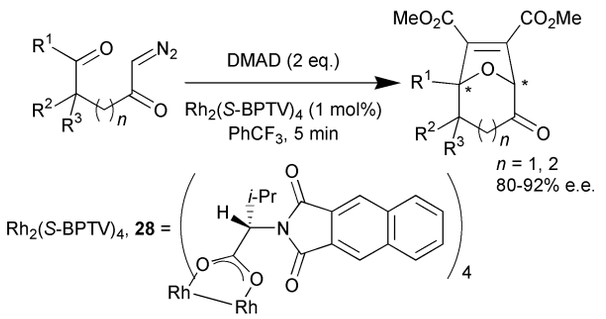
Scheme 57



Scheme 58

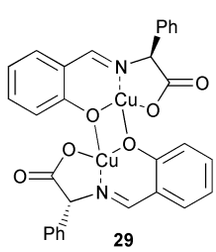
An intramolecular carbenoid insertion reaction, leading to a cyclopropyl intermediate which rearranges *in situ* (*via* a Cope

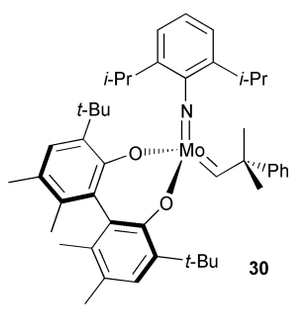
mechanism) to give a bicyclic lactone, has been described by Davies and Doan using $Rh_2[(S)\text{-DOSP}]_4$ as catalyst.[274] Two groups have reported examples of carbenoid insertion reactions resulting in the formation of oxonium ylides which subsequently go on to react with dipolarophiles. Kitagaki and co-workers have demonstrated the use of catalyst **28** in the reaction shown in Scheme 59, giving bicyclic lactones in >80% ee.[275] Hodgson and co-workers have described a similar intramolecular reaction involving addition of the oxonium ylide to a tethered dipolarophile[276] leading to tricyclic products of up to 90% ee.



Scheme 59

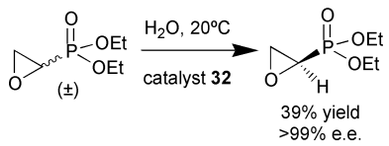
A number of other interesting C–C bond forming reactions have appeared in the literature during 1999. Hayashi and Kamikawa have described an asymmetric Kharasch reaction in which an achiral ditriflate is converted into an axially chiral monotriflate by Pd-catalysed reaction with a Grignard reagent, with enantioselectivities of up to 90%.[277] Buchwald and Sturla have reported an asymmetric Pauson–Khand reaction catalysed by a chiral titanocene. The resultant bicyclic enones were formed in up to 94% yield and 94% ee.[278] A similar carbonylation reaction catalysed by a Pd–diphosphine complex, employing allylic alcohols as substrates, has been reported by Zhang and Cao. The lactone products were prepared in enantioselectivities of typically >90%.[279] Muller and Nury have described the desymmetrisation of *meso*-aziridines using Grignard reagents as nucleophiles, in the presence of Cu complex **29**.[280] The resultant amines were formed in up to 91% ee when 30 mol% of the catalyst was used. Finally, Hoveyda and co-workers have reported a ring-opening metathesis reaction between a norbornene (bicyclo[2.2.1]hept-2-ene) derivative and styrene, catalysed by 5 mol% of Mo complex **30**.[281] Yields for the transformation were typically 50–95% and enantioselectivities were >98%.





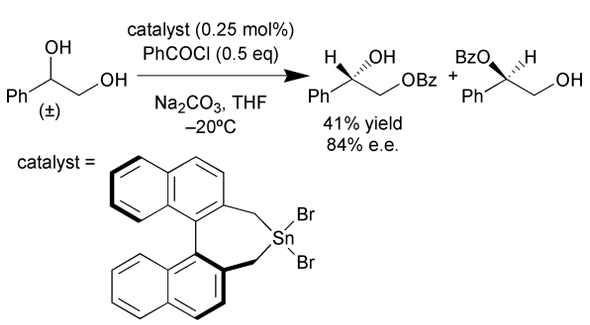
2.4 Miscellaneous applications of synthetic asymmetric catalysts

The kinetic resolution of racemic substrates using synthetic asymmetric catalysts is an area which is gaining increasing interest. Jacobsen and co-workers have reported the Co(III)–Salen-catalysed resolution of terminal epoxy alcohols giving cyclic and bicyclic ethers in up to 46% yield and 95% ee. Unreacted epoxides were recovered in 50% yield and up to 93% ee.[282] A very similar transformation, in which phenol derivatives react with racemic terminal epoxides, was also reported to be effectively catalysed by a Co–Salen complex.[283] Jacobsen and Lebel have also demonstrated the kinetic resolution of 2,2-disubstituted epoxides using a Cr(III)–Salen catalysed addition of Me_3SiN_3.[284] The enantiomeric excess of both product and unreacted starting material at 50% conversion was in the range of 80–99%. Wyatt and Blakskjaer have demonstrated the use of a Co–Salen complex as catalyst for the hydrolytic kinetic resolution of racemic oxiranyl phosphonates, leading to the recovery of unreacted substrate in 39% yield as a single enantiomer (Scheme 60).[285] The Ti–BINOL-catalysed kinetic resolution of enol ester epoxides to give α-keto benzoates in high enantioselectivity has been reported by Feng and co-workers.[286] The extension of this methodology to give greater than 50% yield of product in up to 97% ee was also discussed.

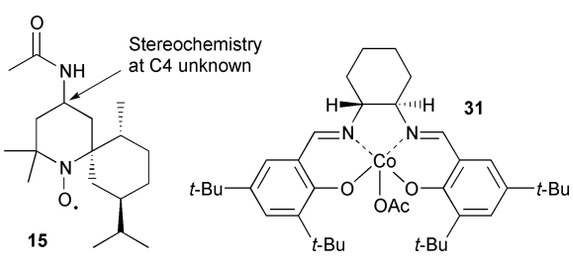


Scheme 60

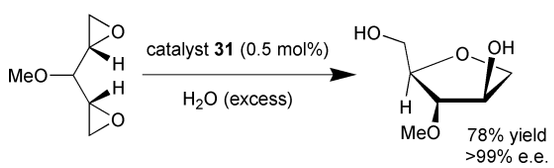
The non-enzymatic kinetic resolution of 1,2-diols has been achieved using a binaphthyl-derived organotin catalyst.[287] Reaction of the racemic diol with benzoyl chloride in the presence of 0.25 mol% catalyst, and a small quantity of water, led to the formation of the 1-benzoyloxy product in 41% yield and 84% ee (Scheme 61). Kashiwagi and co-workers have reported the use of a chiral aminoxyl radical **15** as a catalyst for the electrolytic kinetic resolution of racemic secondary amines.[288] Unreacted amine could be isolated in 40–45% yield and up to 78% ee when as little as 5 mol% of catalyst was employed. A dynamic kinetic resolution of racemic azlactones using a Ti–TADDOL complex has been reported by Seebach and Gottwald.[289] α-Amino acid derivatives could be isolated in quantitative yield and in up to 68% ee, however, 70 mol% of catalyst was required to achieve enantioselectivity at this level. The oxidative resolution of racemic alkenes, using a perester to effect allylic oxidation, in the presence of a Cu–tris(oxazoline) catalyst, has been described by Kohmura and Katsuki.[290] The reaction was observed to give only modest levels of regiocontrol, however the major product was formed in 80% ee. Finally, on the topic of kinetic resolution, Hoveyda and co-workers have reported the resolution of racemic silyl ethers utilising a ring-closing metathesis reaction.[291] Use of 5 mol% of catalyst **30** led to the formation of cyclised products with a high level of stereodifferentiation (k_{rel} 56).



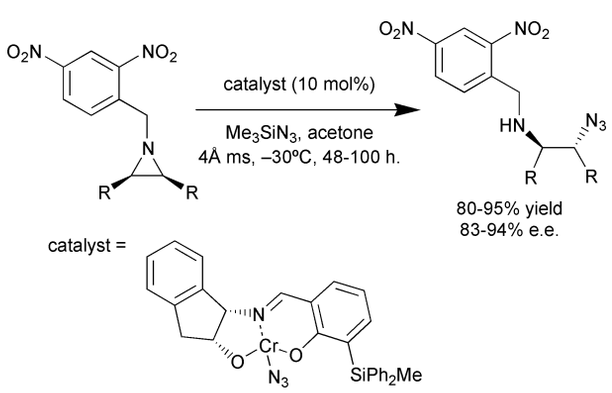
Scheme 61



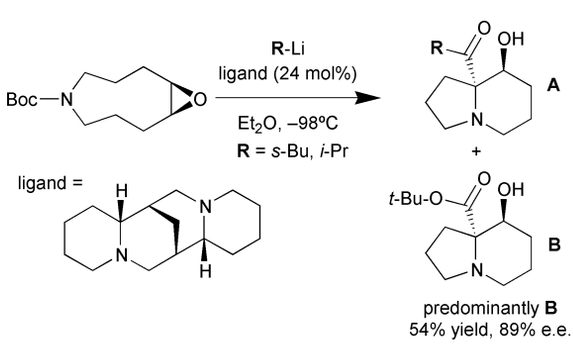
The desymmetrisation of *meso*-substrates is another popular area for the application of synthetic catalysts. Again, epoxides are popular substrates for this type of transformation. The use of a Co–Salen complex **31** as catalyst for the hydrolytic desymmetrisation of *meso*-diepoxides has been demonstrated by Kamada and co-workers.[292] The group has applied this methodology to the formation of 1,4-anhydro-3-methoxy-D-arabinitol in 78% yield and 99% ee (Scheme 62). Sagawa and co-workers have reported the Ti–BINOL-catalysed addition of primary amines to *meso*-epoxides, resulting in the formation of amino alcohols of >85% ee.[293] A similar transformation, using an azide nucleophile, has been reported by Kassab and Ganem who employed a Cr–Salen catalyst to give azido alcohols of up to 98% ee.[294] The group of Jacobsen has prepared a novel tridentate ligand for use in the azide-mediated ring opening of *meso*-aziridines (Scheme 63).[295] Ring-opened products were obtained in high yield (80–95%) and up to 94% ee only when the tridentate ligand was employed. Similar reactions carried out in the presence of tetradentate Salen ligands gave poor catalyst turnover. The desymmetrisation of *meso*-epoxides using a sparteine–alkyllithium combination has been further investigated by Hodgson and Robinson.[296] The application of this methodology to the desymmetrisation of heterocyclic epoxides (Scheme 64) led to the formation of indolizidine derivatives of up to 89% ee when 0.24 equivalents of (−)-α-isosparteine were employed as the chiral modifier. A novel epoxide desymmetrisation involving an electron transfer reaction has been described by Gansäuer and co-workers.[297] The group employed 5 mol% of a chiral titanocene catalyst to give chiral alcohols of up to 93% ee. The reaction is thought to proceed *via* a key β-titanoxy radical species which is formed during the stereodetermining step of the reaction.



Scheme 62

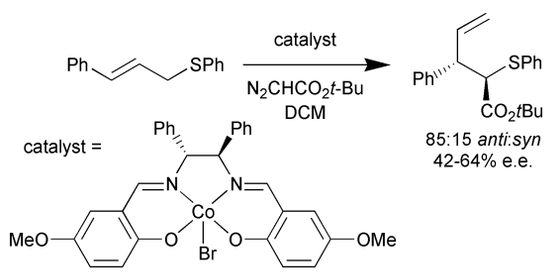


Scheme 63



Scheme 64

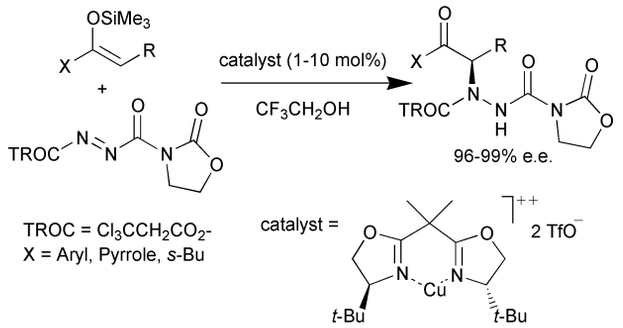
An aza-Claisen rearrangement of allylic imidates to give allylic amides has been described by Jiang and co-workers.[298] High levels of enantioselectivity (83%) were achieved under Pd(II)-catalysed conditions in the presence of a tridentate bis(oxazoline) ligand. Donde and Overman have reported a very similar transformation catalysed by a ferrocenyloxazoline–Pd(0) complex, giving up to 96% ee for certain substrates.[299] A novel [2,3] sigmatropic rearrangment of allylic sulfides has been carried out by Katsuki and co-workers.[300] Reaction of the sulfide with a diazoacetate leads to the formation of an ylide intermediate, which rearranges to a homoallylic sulfide in the presence of a Co(III)–Salen catalyst (Scheme 65). Whilst control of relative stereochemistry was good (*anti–syn* ratio of 85 : 15) the maximum ee of the *anti*-isomer was reported to be 64%. Bohme and Gais have reported a powerful method for the preparation of allylic thiols, by employing a Pd(0)-catalysed rearrangement of *O*-allylic thiocarbamates to *S*-allylic thiocarbamates.[301] Use of Trost's bis(2-diphenylphosphinobenzamide) ligand (see Scheme 40) enabled the conversion of racemic *O*-allylic substrate into *S*-allylic product in up to 92% ee. An enantioselective [1,2] Wittig rearrangement, which is thought to involve the formation of a radical intermediate, has been described by Tomooka and co-workers.[302] The use of a bis(oxazoline) ligand (10 mol%) in the presence of 2 equivalents of *t*-BuLi led to the rearrangement of ethers to tertiary alcohols in up to 60% ee.



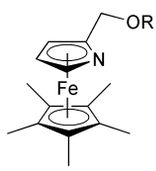
Scheme 65

The addition of phosphorus nucleophiles to C=O or C=N bonds has been reported by two groups. Yamagishi and co-workers have described the use of an aluminium lithium bis(naphthol) complex (ALB) as a catalyst for the addition of a phosphinate nucleophile to benzaldehyde, giving products of up to 85% ee.[303] The group of Shibasaki has reported the addition of diphenylphosphine oxide to cyclic imines in the presence of a heterobimetallic catalyst consisting of praseodymium, potassium and BINOL (PrPB).[304] The use of 3 mol% of catalyst led to the formation of cyclic aminophosphine oxides in 98% yield and 91% ee.

The asymmetric Michael addition of heteronucleophiles to α,β-unsaturated amides has been described by Kanemasa and co-workers.[305] The group employed a tridentate dibenzofuran-derived bis(oxazoline) ligand in the Ni-catalysed addition of thiols to enamides, giving products in up to 96% ee. A related Michael addition of hydrazoic acid to α,β-unsaturated amides was reported by Myers and Jacobsen, who found that an Al–Salen catalyst gave the best levels of enantioselectivity (up to 94% depending on the substrate).[306] Evans and Johnson have reported an enantioselective amination of enol silanes using azodicarboxylate derivatives.[307] Detailed mechanistic studies of this reaction revealed that a cyclic intermediate, resulting from a hetero-Diels–Alder reaction, was formed in the absence of trifluoromethanol. Indeed, addition of trifluoromethanol to the reaction mixture was essential to achieve turnover of the catalyst and release of acyclic product. The use of 1 mol% of a Cu–bis(oxazoline) catalyst resulted in the formation of aminated products of up to 99% ee (Scheme 66). Fu and co-workers have employed a ferrocene-derived catalyst **32** (10



Scheme 66



32

mol%) for the asymmetric methanolysis of ketenes resulting in the formation of chiral esters of up to 77% ee.[308] Finally, in this section, Knolker and co-workers have reported the preparation of η^4-Fe–diene complexes in up to 73% ee using a camphor-derived azadiene to catalyse the reaction between iron pentacarbonyl and a cyclohexadiene derivative.[309,310]

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