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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 1297–1330

Tetrahedron report number 784

Chiral sulfur-containing ligands for asymmetric catalysis

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Received 15 September 2006
Available online 20 October 2006

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1. Introduction

The preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry.[1] In particular, the preparation of new chiral ligands for application in asymmetric catalysis has been and continues to be an important area of synthetic organic research.[2] New classes of ligands that might offer new opportunities for applications or provide insight into fundamental chemical processes are always of interest. One relatively rare class of ligands is that in which stereogenicity resides not at carbon atoms, but at heteroatomic sites such as sulfur atoms. Practical asymmetric catalysis using transition-metal complexes was inspired by the work of Kagan[3] and Knowles.[4] Their important results, based on the use of chiral phosphines as ligands for asymmetric hydrogenation, have induced a tremendous amount of work, dealing with the synthesis and use of new chiral phosphine-containing complexes as catalysts. Numerous catalytic asymmetric reactions have been discovered over the last 30 years, often with spectacular results in terms of efficiency and selectivity, allowing access to biologically important molecules. Nevertheless, the contribution of asymmetric catalysis in the overall production of chiral chemicals is much lower than originally expected, which is surprising given the huge amount of work devoted to this subject. Factors such as the price of the catalyst precursor and the difficulties

Abbreviations: Ac, acetyl; acac, acetylacetone; Ad, adamantyl; Ar, aryl; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-binaphthalene-2,2′-diol; BITIANP, 2,2′-bis(diphenylphosphino)-3,3′-bi(benzo[*b*]thiophene); BITIOP, 4,4′-bis(diphenylphosphino)-3,3′-bithiophene; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu, butyl; BSA, *N*,*O*-bis(trimethylsilyl)acetamide; Bz, benzoyl; *c*, *cyclo*; cod, cyclooctadiene; Cp, cyclopentadienyl; Dec, decyl; dba, (*E*,*E*)-dibenzylideneacetone; de, diastereomeric excess; EDA, ethyl diazoacetate; ee, enantiomeric excess; Et, ethyl; Fm, fluorenylmethyl; Fur, furyl; Hept, heptyl; Hex, hexyl; L, ligand; M, metal; Me, methyl; Mes, mesyl; Naph, naphthyl; NBD, norbornadiene; Pent, pentyl; Ph, phenyl; Piv, pivaloyl; Pr, propyl; py, pyridine; siam, bis(sulfinyl)imidoamidine; SES, 2-(trimethylsilyl)ethanesulfonyl; suc, succinimide; TADDOL, α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; Tf, trifluoromethanesulfonyl; TMBTP, 4,4′-bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene; TMS, trimethylsilyl; Tol, toluene; Tr, triphenylmethyl (trityl); Ts, 4-toluenesulfonyl (tosyl); TsDPEN, *N*-tosyl-1,2-diphenylethylenediamine; TsOH, *p*-toluenesulfonic acid; VERDI, verbenone dimers.

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0040–4020/$ - see front matter
doi:10.1016/j.tet.2006.09.068

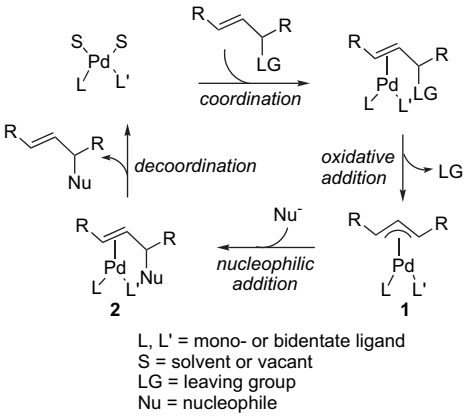
encountered in the separation and recycling of the catalyst are responsible for this lack of practical application. Only a few processes have, however, permitted high turnovers. Apart from these economic considerations, it is almost impossible to recycle, for example, phosphine-containing catalysts, due to their low stability towards oxidation. Indeed, the chemical and economic characteristics of these catalysts were partly responsible for problems encountered in the development of catalytic asymmetric processes in general. The field of asymmetric catalysis is witnessing an ever-growing interest, and several highly efficient catalytic methods are nowadays known in the literature. Despite the positive results, knowledge in this field is still limited, and much work will be needed to make this methodology a comprehensive and well-established technique. The nature of the ancillary ligands used for a given metal-catalysed process is central, with chiral P- and N-based ligands occupying an incontestable leading position. Despite the vast knowledge on sulfur-metal interactions in coordination chemistry,[5] the use of chiral S-based ligands in catalysis appears, however, to be still rather underdeveloped.

Over the last three decades, more than 40 different classes of chiral sulfur compounds have been described in the literature, and a large number of useful procedures for the synthesis of enantiomerically pure sulfur compounds have been developed.[6] Transition-metal complexes with chiral sulfur ligands are powerful catalysts in a considerable number of reactions, although, they have been generally less investigated than complexes with other donor atoms. The goal of the present review is to cover the recent advances in the use of chiral sulfur-containing ligands in asymmetric catalysis, focusing on those, which have been published since the beginning of 1999. In fact, a preceding review has reported the chemistry of transition-metal complexes containing, more generally, both achiral and chiral sulfur ligands, covering the literature up to the end of 1998.[7] The present review is divided into seven sections corresponding to the different types of reactions based on the use of complexes containing chiral sulfur ligands, such as allylic substitution, hydrogenation, hydrogen transfer, conjugated additions, addition of organometallic reagents to aldehydes, Diels–Alder reactions and miscellaneous reactions.

The coordination chemistry of sulfur ligands has shown a unique variety of structures with most of the transition metals in different oxidation states.[8,5] The use of chiral sulfur ligands in reactions catalysed by transition metals is still relatively unexplored, however, compared with other ligands.[9] It is important to note that the synthesis and applications of chiral thioether ligands were reported by Masdeu-Bulto et al. in 2003.[10] Moreover, the use of chiral sulfoxides in enantioselective metal-catalysed asymmetric synthesis was reviewed in 2003 by Fernandez and Khiar.[11] Indeed, sulfur donor ligands have been used much less than phosphorus donor ligands in asymmetric homogeneous catalysis,[12] although, in recent decades, the number of studies with chiral sulfur-containing catalytic systems has increased considerably.[7,10] Compared to phosphorus, sulfur has less donor and acceptor character. In addition to these electronic considerations, the sulfur atom, in thioether ligands, for example, has only two substituents, which can create a less hindered environment than trivalent phosphorus. In addition, compared to phosphorus or nitrogen, sulfur is known to have a tendency to poison heterogeneous catalysts. The formation of mixtures of diastereomeric complexes, and the difficulty to control their interconversion in solution have been regarded as a problem for asymmetric induction in catalytic reactions. Nevertheless, in recent years, chiral bidentate S-donor ligands, in particular, have proved to be as useful as other classical asymmetric ligands, especially when combined with other donor atoms.[13]

2. Allylic substitution

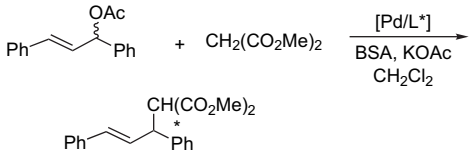
Carbon–carbon bond formation is one of the most important reactions in synthetic organic chemistry. One useful and popular method is the palladium-catalysed allylation,[14] e.g., the Tsuji–Trost reaction,[15] and asymmetric versions of this reaction have been extensively studied over the last decade.[16] Strategies for controlling enantioselectivity in palladium-catalysed asymmetric reactions have depended on the design and application of chiral ligands. Many of the efficient homo- and hetero-donor chiral ligands such as N/N- (e.g., bis-oxazolines[17]), P/P- (e.g., Trost's P/P ligands[18]), and N/P- (phosphinooxazolines[19]) types have been exploited. A particular efficient method of C–C bond formation was opened up by the reaction of carbon nucleophiles with allylpalladium complexes, the generation of which is in situ accomplished, and requires only a catalytic amount of the transition metal. Considerable efforts have been devoted to study the reaction between allylic substrates and nucleophiles catalysed by chiral palladium complexes. The palladium-catalysed allylic substitution is one of the catalytic homogeneous processes that has attracted most attention in recent decades, and for which the catalytic cycle is well established (Scheme 1).[20]



Scheme 1. Mechanism for Pd-catalysed allylic substitution with soft nucleophiles.

This is due in part to the relative ease of isolating catalytic intermediates, especially the palladium allylic species **1** (Scheme 1), although some related Pd(0) species (**2**) have also been characterised in solution.[21] The enantioselectivity of the process with soft nucleophiles (derived from conjugated acids with $pK_a<25$) is controlled by the external nucleophilic attack on the more electrophilic terminal allylic carbon of **1**. The chemo-, regio-, diastereo- and enantioselectivities of this process have been widely analysed, and the

results applied to the synthesis of target molecules.[22] Since the first enantioselective catalytic process, described by Trost and van Vranken in 1977,[15] the enantioselective allylic alkylation reaction catalysed by Pd has been of great interest in recent years, involving many chiral auxiliary ligands, allowing excellent ees.[23] The catalysts often consist of a palladium complex containing a chiral chelate ligand, but they can also be in situ generated. The mechanism of this palladium-mediated allylic reaction is reasonably well understood.[24] A chiral Pd(0) olefin complex oxidatively adds the prochiral allylic acetate to afford an isolable η^3-allylic cationic compound, which is next attacked by the nucleophile. The most widely investigated sulfur ligands have been the N/S-donor type,[25] often derived from a chiral oxazoline moiety.[26] Oxazolines are known to have several advantages as sources of chirality, the main one being that they are readily accessible from homochiral amino alcohols, and have proved to be effective catalysts in a variety of reactions.[17,26d,e] Furthermore, these ligands are easily modifiable and can incorporate different donor atoms in the side chains of the heterocyclic ring.[27] Other combinations of donor atoms with sulfur have also been explored such as chiral P/S-donor ligands,[28] chiral S/O-donor ligands[29] and chiral bis-sulfoxide ligands.[30] These processes are commonly catalysed by palladium systems, but other metals such as rhodium, platinum, molybdenum, tungsten, nickel, or iridium are also efficient.[14d,20,31] The fact that a mixture of diastereomers can be obtained upon coordination of the ligand (thioether, for example) to a metal can cause a decrease of stereoselectivity if the relative rates of the intermediates are similar. In spite of this feature, however, excellent ees have been achieved. To evaluate the selectivity of a new chiral ligand for allylic substitutions, the reaction usually performed, called the test reaction in the text, is the transformation of *rac*-1,3-diphenylprop-2-enyl acetate with dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a base (Scheme 2).

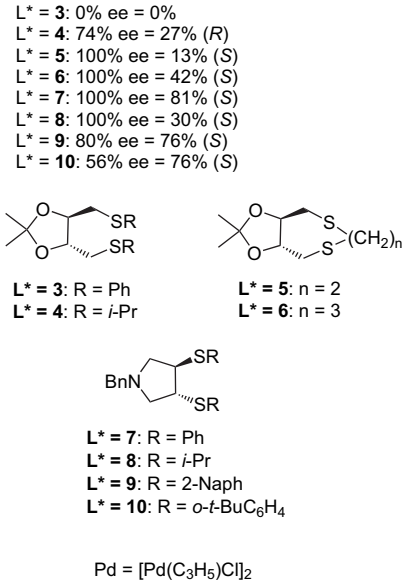


Scheme 2. Test reaction: Pd-catalysed allylic alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate.

2.1. S/S-ligands

Very few chiral dithioether ligands have been used, even though the coordinating capability of thioether donors in transition-metal complexes is known. An inherent characteristic of thioether ligands is that, upon coordination to the metal, the sulfur atom becomes stereogenic. While the close proximity of the chiral sulfur centre to the coordination sphere of the transition metal may be beneficial,[32] the low inversion barrier of the sulfur–metal bond may account for the scarce use of dithioethers in asymmetric catalysis.[33] Hence, any attempts to incorporate a thioether into a chiral ligand must firstly address stereocontrol at the sulfur atom. Such control may be accomplished by steric bias as the involvement of efficient catalysts based on chiral mixed S/P-ligands.

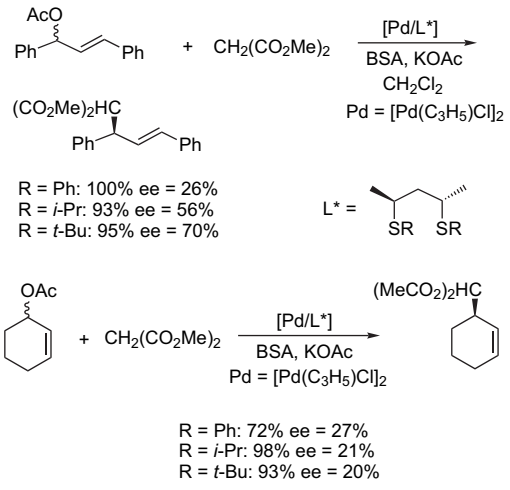
Unlike other homo- and hetero-donor chiral ligands, the S/S-type ligand has hardly been involved, in spite of having advantages such as lower cost, toxicity and oxidation potential. In 2001, Gomez et al. reported the first example employing C_2-symmetric S/S-type ligands **3**–**10** (Scheme 3) in the test reaction depicted in Scheme 2.[34] For unexplained reasons, the major focus in academia has been on this particular allylic alkylation, although this system does not seem to have any industrial importance. These workers showed that the enantioselectivity could be increased to high values with the appropriate combination of chiral backbone rigidity and substituent at the sulfur atom (Scheme 3). The modest asymmetric induction observed (up to 81% ee) was owing to the donor sites being insufficiently different for discrimination between both terminal allylic carbons in the intermediate.



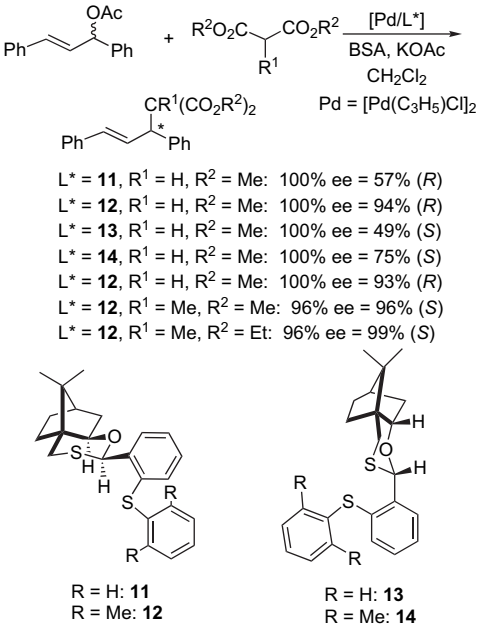
Scheme 3. Chiral dithioether ligands.

In order to rationalise these results, the same authors have studied more examples of palladium systems, in which systematic changes of chelate ring size and electronic and steric effects of the sulfur substituents were performed.[35] In the course of this systematic study, novel chiral dithioether ligands were shown to afford high activities and excellent selectivities in all palladium-catalysed allylic reactions (Scheme 4). The study of the allylic intermediates, which were fully characterised both in solution and in the solid state, has demonstrated that the selectivity in the palladium-catalysed allylic alkylation containing homo-donor dithioether ligands could be controlled by the thermodynamics of the palladium diastereomer formation (high-energy barrier between Pd isomers, as is the case for these new ligands), or by the kinetics of the nucleophilic attack (low-energy barrier among the palladium species), depending on the nature of the metallacycle.

In 2003, Nakano et al. planned to synthesise novel chiral S/S-type ligands having a borneol backbone and without C_2-symmetry.[36] These readily prepared chiral sulfideoxathiane ligands **11**–**14** were shown to give excellent enantioselectivity (up to 99% ee) in the palladium-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with a range of alkyl malonate nucleophiles (Scheme 5).



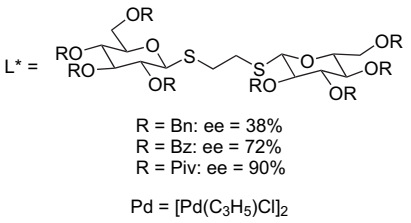
Scheme 4. Chiral dithioether ligands in Pd-catalysed allylic alkylations.



Scheme 5. Chiral sulfideoxathiane ligands in Pd-catalysed allylic alkylations.

As previously mentioned, an inherent characteristic of the thioether ligands is that, upon coordination to the metal, the sulfur atom becomes stereogenic. While the close proximity of the chirality to the coordination sphere of the transition metal may be beneficial, the low inversion barrier of the sulfur–metal bond may be responsible for the poor results observed. In this context, Khiar et al. have reported the synthesis of C_2-symmetric bis-thioglycosides as new ligands for the test reaction depicted in Scheme 2 (Scheme 6).[37] The sugar residue was intended to provide a well-defined chiral environment, while the control of the sulfur configuration was expected, due to stereoelectronic factors acting at the anomeric centre.

Although the use of chiral sulfoxides as chiral controllers in asymmetric synthesis is well documented, their utilisation as ligands in asymmetric catalysis has met with little success.[11] In 2005, Khiar et al. reported the synthesis of C_2-symmetric



Scheme 6. C_2-Symmetric bis-thioglycoside ligands.

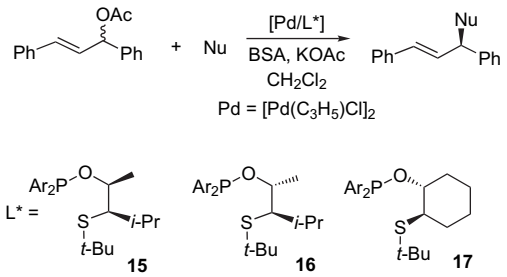
bis-sulfoxides, but, surprisingly, when used as chiral ligands in the palladium-catalysed asymmetric alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate, they were completely inactive,[38] whereas the corresponding C_2-symmetric bis-thioethers afforded the (*R*)-isomer with 42% ee.

2.2. S/P-ligands

The incorporation of C_2-symmetry into chiral ligand design is a well-recognised strategy for restricting the number of diastereomeric transition states in metal-catalysed enantioselective processes.[39] Equally powerful stereochemical restrictions may also be realised with chiral ligands lacking C_2-symmetry through the use of electronic effects such as the trans influence.[5] Such effects are a natural consequence of the use of chiral bidentate ligands equipped with strong and weak donor heteroatom pairs (e.g., PR_3/NR_3, PR_3/SR_2). Such electronic effects have the potential to influence both the stability and reactivity of the intervening diastereomeric reaction intermediates in the catalytic cycle. While mixed P/N-bidentate ligands have been applied in enantioselective palladium-catalysed nucleophilic alkylation, chiral thioether-containing donor ligands and, more generally, P/S-ligands have been less well developed. In 1999, Evans et al. reported a new class of mixed P/S-ligands incorporating a metal-bound thioether as a chiral control element in asymmetric catalysis.[13c] The utility of these thioether-phosphinite ligands **15–17** was illustrated in the palladium-catalysed allylic alkylation with enol-malonate and amine nucleophiles (Scheme 7).

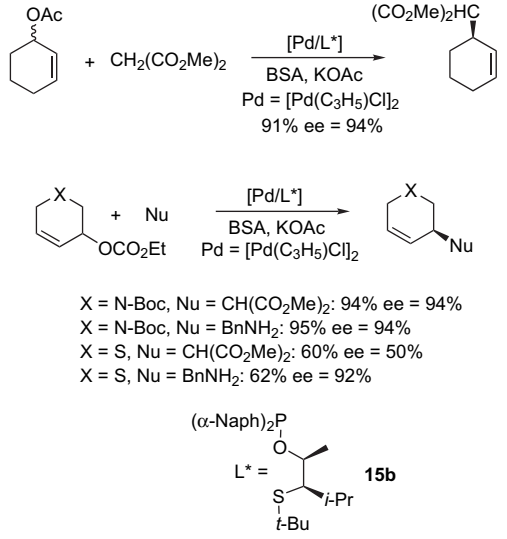
After a systematic variation of the ligand substituents at sulfur, phosphorus and the ligand backbone, the P/S-ligand **16a** was found to be optimal in the palladium-catalysed allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate or benzylamine.[40] A similar optimisation of the mixed P/S-ligand for the palladium-catalysed allylic substitution of cycloalkenyl acetates showed that the ligand **15b** afforded the highest enantioselectivities (91–97% ees). Application of this methodology to heterocyclic substrates was developed as an efficient approach to the enantioselective synthesis of 3-substituted piperidines and dihydrothiopyrans (Scheme 8). The authors could furthermore prove the contribution of sulfur in the coordination of the palladium atom by X-ray analysis of crystals of these chiral organometallic complexes.

In order to involve organosulfur functionality as an alternative enantiocontrollable coordinating element in chiral phosphine ligands, Hiroi et al. have reported the synthesis of (*S*)-proline-derived phosphines bearing organosulfur groups **18–22**, and their successful use as chiral ligands in the test reaction depicted in Scheme 2 (Scheme 9).[41] A nine-membered



L* = **15a**, Nu = $CH_2(CO_2Me)_2$: 91% ee = 93%
L* = **16a**, Nu = $CH_2(CO_2Me)_2$: 98% ee = 97%
L* = **17a**, Nu = $CH_2(CO_2Me)_2$: 94% ee = 95%
L* = **15b**, Nu = $CH_2(CO_2Me)_2$: 28% ee = 91%
L* = **16b**, Nu = $CH_2(CO_2Me)_2$: 30% ee = 94%
L* = **17b**, Nu = $CH_2(CO_2Me)_2$: 69% ee = 92%
L* = **15a**, Nu = $BnNH_2$: 99% ee = 96%
L* = **16a**, Nu = $BnNH_2$: 95% ee = 97%
L* = **17a**, Nu = $BnNH_2$: 95% ee = 95%
L* = **15b**, Nu = $BnNH_2$: 78% ee = 90%
L* = **16b**, Nu = $BnNH_2$: 66% ee = 95%
L* = **17b**, Nu = $BnNH_2$: 89% ee = 93%

Scheme 7. Chiral mixed P/S-ligands for Pd-catalysed allylic alkylations and aminations.



X = N-Boc, Nu = $CH(CO_2Me)_2$: 94% ee = 94%
X = N-Boc, Nu = $BnNH_2$: 95% ee = 94%
X = S, Nu = $CH(CO_2Me)_2$: 60% ee = 50%
X = S, Nu = $BnNH_2$: 62% ee = 92%

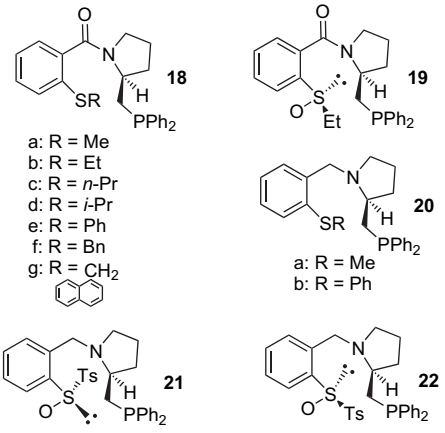
Scheme 8. Chiral mixed P/S-ligands for Pd-catalysed allylic substitution of cycloalkenyl acetates.

chelate was proposed to be formed by coordination of the organosulfur functionality and the phosphine group to the palladium catalyst.

The test reaction (Scheme 2) was performed by Yan and RajanBabu in the presence of monophospholanes bearing a pendant *t*-BuS group, demonstrating that chirality of the C3 and C5 oxygens played a crucial role in the asymmetric induction (Scheme 10).[42]

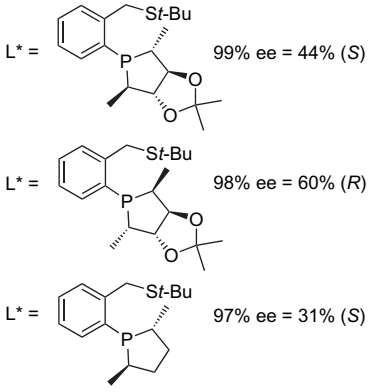
In 2001, Imamoto et al. reported the preparation of novel chiral P/S-bidentate ligands containing a chirogenic centre at the phosphorus atom and their stereoinduction capability in palladium-catalysed asymmetric allylic substitution reactions (Scheme 11).[43]

L* = **18a**: 65% ee = 62% (*S*)
L* = **18b**: 72% ee = 72% (*S*)
L* = **18c**: 68% ee = 77% (*S*)
L* = **18d**: 54% ee = 31% (*S*)
L* = **18e**: 42% ee = 41% (*R*)
L* = **18f**: 76% ee = 84% (*S*)
L* = **18g**: 59% ee = 88% (*S*)
L* = **19**: 72% ee = 60% (*S*)
L* = **20a**: 76% ee = 82% (*R*)
L* = **20b**: 74% ee = 87% (*R*)
L* = **21**: 69% ee = 59% (*R*)
L* = **22**: 76% ee = 79% (*R*)

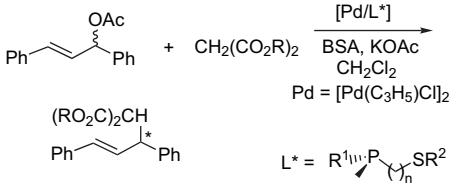


Pd = $[Pd(C_3H_5)Cl]_2$

Scheme 9. (*S*)-Proline-derived sulfur-containing phosphines as chiral ligands.



Scheme 10. Chiral monophospholanes with a pendant *t*-BuS group.

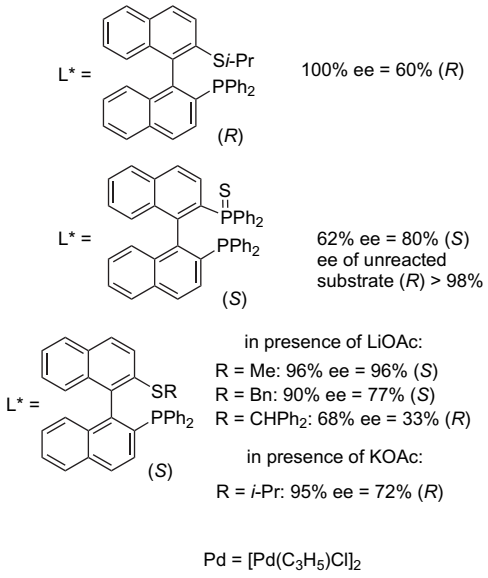


R = Me, R^1 = *t*-Bu, R^2 = Ph, n = 1: 94% ee = 85% (*R*)
R = R^1 = *t*-Bu, R^2 = Ph, n = 1: 99% ee = 90% (*R*)
R = Me, R^1 = *t*-Bu, R^2 = Ph, n = 2: 85% ee = 71% (*S*)
R = R^1 = *t*-Bu, R^2 = Ph, n = 2: 50% ee = 74% (*S*)
R = Me, R^1 = *t*-Bu, R^2 = Tol, n = 1: 81% ee = 59% (*R*)
R = Me, R^1 = *t*-Bu, R^2 = Bn, n = 1: 90% ee = 48% (*R*)
R = Me, R^1 = Ad, R^2 = Ph, n = 1: 99% ee = 65% (*R*)

Scheme 11. P-chirogenic P/S-ligands for Pd-catalysed allylations.

The preparation of BINAP reported in 1980 has marked a landmark in asymmetric catalysis and has illustrated the

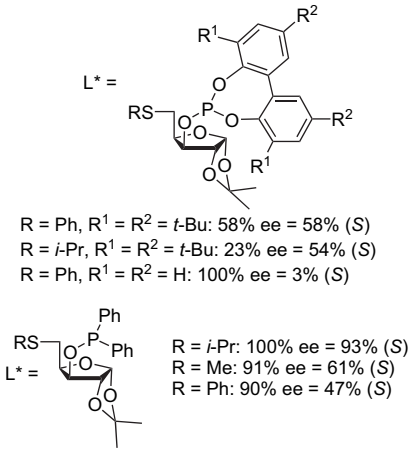
peculiar stereorecognitive properties inherent with the axially chiral 1,1′-binaphthalene framework. Since then, a great deal of work has been devoted to the preparation of binaphthalene-templated ligands of related design. These efforts have resulted in the generation of a library of bidentate binaphthyl ligands, featuring equal (or diverse) substituents with the same (or different) donors on the 2,2′-positions of the binaphthalene backbone. In this context, Gladiali et al. have developed an axially chiral P/S-heterodonor ligand based on a binaphthalene backbone, which was further submitted to the test palladium-catalysed allylic alkylation (Scheme 2), providing a 60% ee and a quantitative yield (Scheme 12).[44] In 2004, Zhang and Shi extended the scope of this reaction to various P/S-ligands (BINAPS) with different alkyl groups on the sulfur atom.[45] It was demonstrated that an alkyl group on the sulfur atom acted as a key factor in forming the reversal of the enantioselectivity. The steric bulkiness of an (*S*)-alkyl group in the BINAPS was sufficient to control the orientation of the nucleophilic attacks to give the product with a different absolute configuration (Scheme 12).



Scheme 12. P/S-heterodonor ligands (BINAPS).

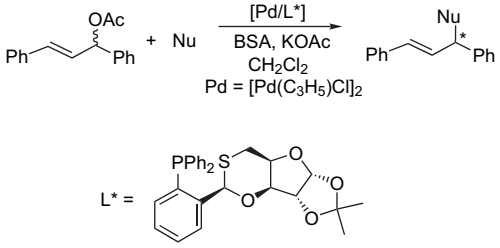
In addition, another BINAP-derived P/S-ligand was developed by Faller et al., demonstrating that this palladium-catalysed allylic alkylation could also be used to achieve effective kinetic resolution of acyclic allylic acetates, since the unreacted allylic acetate was recovered in >98% ee (Scheme 12).[46]

Since carbohydrates constitute an inexpensive and highly modular chiral source for preparing ligands, Claver et al. have reported the use of a series of thioether-phosphite[47] and thioether-phosphinite furanoside ligands[48] in the test palladium-catalysed allylic substitution reaction (Scheme 2). In the first type of ligand, a systematic variation of the donor group attached to the carbon atom C5 indicated that the presence of a bulky phosphite functionality had a positive effect on the enantioselectivity. Indeed, the enantioselectivity was controlled mainly by the phosphite moiety. This was confirmed by the use of a ligand containing the smaller unsubstituted biphenol moiety, which resulted in a drop in the ee value from 58 to 3% (Scheme 13). Interestingly, the thioether-phosphinite ligands showed a much higher degree of enantioselectivity and higher reaction rates than their thioether-phosphite analogues (Scheme 13). In this case, the ees were strongly dependent on the steric proprieties of the substituent in the thioether moiety of the carbohydrate backbone.



Scheme 13. Furanoside thioether-phosphite or -phosphinite ligands.

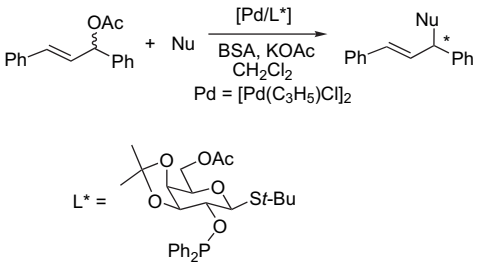
On the other hand, a novel chiral xylofuranose-based phosphinooxathiane ligand was found by Nakano et al. to provide high levels of enantioselectivity (up to 94% ee) in palladium-catalysed asymmetric allylic alkylations and aminations (Scheme 14).[49] These authors have previously reported the synthesis of other phosphinooxathiane ligands such as norbornane- and pulegone-based phosphinooxathianes, and their successful application to the test reaction.[50] In 2005, these results were further extended to the synthesis of related polymer-supported chiral phosphinooxathiane ligands, which were found to provide high levels of enantioselectivity (up to 99% ee) in palladium-catalysed asymmetric allylic alkylations and aminations.[51]



Scheme 14. Xylofuranose-based phosphinooxathiane ligands for Pd-catalysed allylations and aminations.

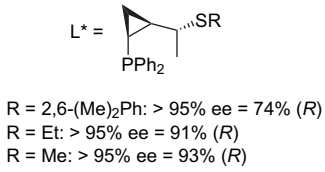
In 2005, Khiar et al. reported the preparation and use of other novel phosphinite thioglycosides, showing that bulky alkyl thioglycosides such as the *tert*-butyl thioglycoside, depicted in Scheme 15 allowed the syntheses of the expected alkylated and aminated products in, respectively, 92 and 94% ees in the palladium-catalysed allylic substitutions.[52]

Although a large variety of structurally diverse ligands have already been tested in asymmetric catalysis, the cyclopropane



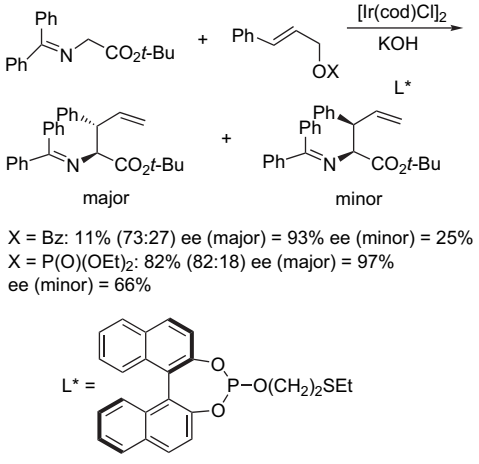
Scheme 15. Phosphinite thioglycoside ligands for Pd-catalysed allylation and amination.

skeletons have received relatively little attention to date. In this context, Molander et al. have developed the synthesis of a series of new chiral cyclopropane-based P/S-ligands and have evaluated them in the test palladium-catalysed allylic alkylation reaction.[53] Variations of the ligand substituents at phosphorus, sulfur and the carbon backbone revealed the ligands depicted in Scheme 16 to have the optimal configuration for the test reaction.



Scheme 16. Cyclopropane-based P/S-ligands.

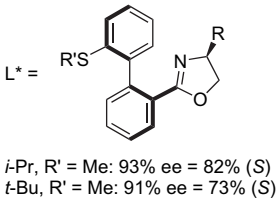
Recent studies have reported good results by using metals other than palladium. As an example, Pregosin et al. have performed rhodium- and iridium-catalysed asymmetric allylic alkylations in the presence of chiral phosphito-thioether ligands.[54] More recently, Takemoto et al. have developed an elegant synthesis of β-substituted α-amino acids on the basis of the first iridium-catalysed asymmetric allylic substitutions of diphenylimino glycinates with allylic phosphates by using a chiral bidentate phosphite bearing a 2-ethylthioethyl group as the chiral ligand (Scheme 17).[55]



Scheme 17. Synthesis of β-substituted α-amino acids through Ir-catalysed asymmetric allylic substitutions.

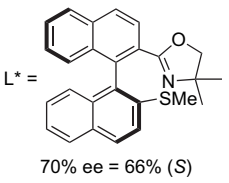
2.3. S/N-ligands

Chiral oxazoline ligands derived from readily available amino acids have found widespread use in metal-catalysed asymmetric reactions, although only a few oxazoline ligands bearing sulfur-functional groups have been reported for these reactions. In 1999, Ikeda et al. reported a new type of sulfur-oxazoline ligands with an axis-fixed or -unfixed biphenyl backbone.[56] These ligands, depicted in Scheme 18, were evaluated for the test palladium-catalysed asymmetric allylic alkylation reaction (Scheme 2). It was found that axial chirality of the biphenyl backbone in the ligands exerted a considerable influence on the catalytic activity, and the alkylthio group similarly influenced the enantioselectivity. Those ligands, which have a free-rotation biphenyl axis affording only one of two possible diastereomeric complexes with palladium showed the highest catalytic activity and enantioselectivity.



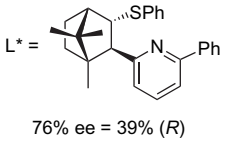
Scheme 18. Axial sulfur-oxazoline ligands with a biphenyl backbone.

In the same context, novel chiral binaphthalene-core ligands, in which an oxazoline pendant was flanked by a sulfur group such as that depicted in Scheme 19, have been prepared and successfully involved in the test reaction (Scheme 2).[57]



Scheme 19. Binaphthalene-templated N/S-ligand with an achiral oxazoline pendant.

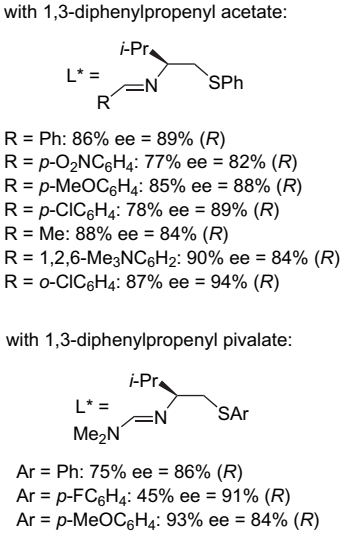
In contrast to the large number of chiral pyridine derivatives used as ligands for metal complexes in asymmetric catalysis, only a few examples of chiral sulfur-containing pyridine ligands have so far been reported such as pyridine thioethers derived from (+)-camphor, which are depicted in Scheme 20, and which were assessed in the test reaction, providing enantioselectivities of up to 76%.[58] The related 2,2′-bipyridine thioethers were also prepared, but, showed a lower stereodifferentiating capability in the test reaction (Scheme 2).



Scheme 20. (+)-Camphor-derived pyridine thioether.

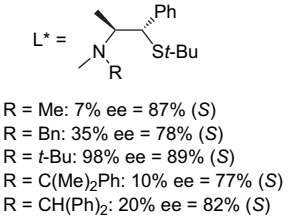
The test reaction was also investigated by Anderson et al. employing chiral imine-sulfide ligands derived from amino

acids.[59] The ligand of choice, depicted in Scheme 20, (*S*)-*N*-2′-chlorobenzylidene-2-amino-3-methyl-1-thiophenylbutane, readily prepared from (*S*)-valinol, led to a 94% ee. The authors were able to isolate and characterise a Pd-allyl intermediate by X-ray diffraction. The corresponding amidine ligands were studied by Morimoto et al., giving excellent results for the palladium-catalysed allylic alkylation of 1,3-diphenylpropenyl pivalate with dimethyl malonate (Scheme 21).[60]



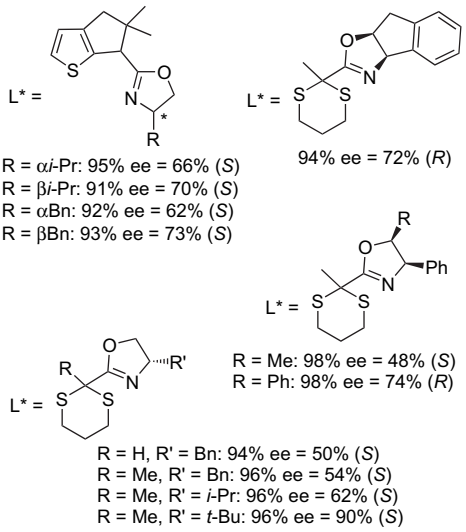
Scheme 21. Imine-sulfide ligands for Pd-catalysed allylic alkylation of 1,3-diphenylpropenyl alkanoates with dimethyl malonate.

The first successful use of simple 1,2-aminothioethers as hybrid ligands in the test reaction was reported by Bulman Page et al.[61] In this work, the involvement of 2-[2-thioethyl]tetrahydroisoquinoline derivatives, readily available from the norephedrine-derived iminium salt, as ligands resulted in quantitative yields and ees of up to 72%. Other heterobidentate sulfide-tertiary amine ligands, incorporating 1,2-aminothioethers derived from ephedrine and pseudoephedrine, have been prepared and used successfully in the test reaction, giving ees of up to 89% (Scheme 22).[62] The enantioselectivities observed did not seem to be greatly dependent upon the nature of the group at the nitrogen atom.



Scheme 22. Sulfide-tertiary amine ligands incorporating 1,2-aminothioethers.

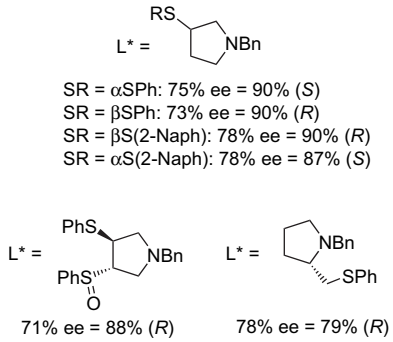
On the other hand, good enantioselectivities (up to 74% ee), and almost quantitative yields in all cases, were obtained for the test reaction using a new class of N/S-ligands developed by Bonini et al. in 2004 (Scheme 23).[63] These latter ligands included rigid cyclopenta[*b*]thiophene and oxazoline moieties as sources of chirality, the sulfur atom being part of a strong π-donor structure. In 2005, the same group reported new chiral oxazoline-1,3-dithianes (Scheme 23) as new efficient N/S-donating ligands for the test reaction, providing almost quantitative yields and up to 90% enantioselectivity.[64]



Scheme 23. Cyclopenta[*b*]thiophene-alkyloxazoline ligands.

In 2002, Gomez et al. reported the synthesis of chiral bis-oxazoline ligands with a biphenyl backbone.[65] When thioether groups were present on the oxazoline moieties, N/S-bidentate bimetallic complexes were involved in order to explain the good enantioselectivity (up to 89% ee) observed for the test reaction.

Simpler chiral pyrrolidine thioethers, reported in 2004 by Skarzewski et al., proved to be effective ligands in the test reaction (Scheme 2).[66] The sense of the stereoinduction was in agreement with the nucleophilic attack directed at the allylic carbon located trans to the sulfur atom in the intermediate complex (Scheme 24).

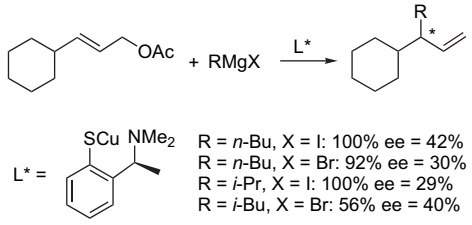


Scheme 24. Pyrrolidine thioether ligands.

In order to study the role of the [2.2]paracyclophane-type planar chirality in asymmetric induction, Hou et al. have developed the synthesis of novel N/S-chiral [2.2]paracyclophane ligands with planar and central chirality based on the [2.2]paracyclophane backbone.[67] These ligands, bearing the two coordinating atoms at the benzylic and benzene ring positions, have shown excellent enantioselectivity (up to 94% ee) and reactivity in Pd-allylic alkylation reactions.

In addition, a large number of chiral bidentate ligands with a chiral sulfoxide and another heteroatom were synthesised and evaluated by Hiroi's group.[41e,f]

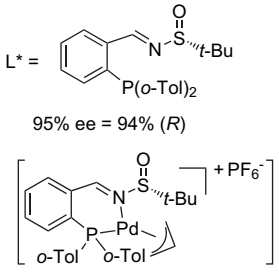
In a different context, Bäckvall et al. have reported another kind of substitution, the arenethiolatocopper(I)-catalysed substitution reaction of Grignard reagents with allylic substrates, providing the corresponding γ-products in ees of up to 50% (Scheme 25).[68]



Scheme 25. Arenethiolatocopper(I)-catalysed substitution reaction of RMgX with allylic substrates.

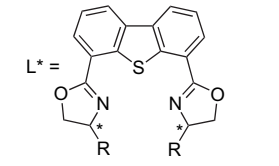
2.4. Sulfur-containing P/N-, P/O-, and N/N-ligands

In 2003, a novel class of P/N-sulfinyl-imine ligands, incorporating chirality at sulfur, was evaluated for the test reaction (Scheme 2).[69] The first crystal structure of a Pd-bound sulfinyl-imine provided insight into the binding mode and origins of the stereoselectivity. This structure confirmed that the ligand bound to palladium through phosphorus and nitrogen to form a six-membered ring chelate (Scheme 26).



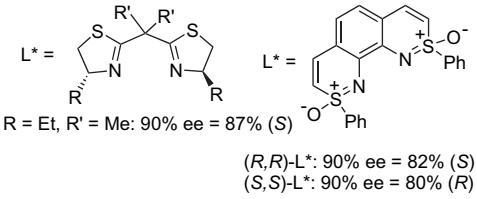
Scheme 26. A P/N-sulfinyl-imine ligand.

New asymmetric sulfur-containing oxazoline ligands have been described by Schulz et al.[70] Their structure included a dibenzothiophene or benzothiophene ring as backbone, in which the sulfur atom was enclosed in a strong π-donor structure. These ligands have been successfully tested in asymmetric palladium-catalysed allylic substitutions, leading to the expected products with ees of up to 77% (Scheme 27).



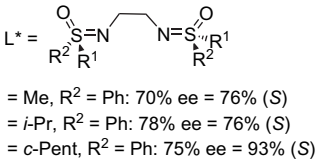
Scheme 27. Dibenzothiophene-bis-oxazoline ligands.

In the same way, Masson et al. have studied new chiral thiazoline-containing ligands, analogues of known oxazolines, and showed their capability to act as chiral catalysts in the test reaction depicted in Scheme 2 (Scheme 28).[71] Similarly, a new chiral bis-benzothiazine ligand was reported by Harmata and Ghosh and successfully applied to the test reaction (Scheme 28).[72]



Scheme 28. Bis-thiazoline or bis-benzothiazine ligands.

Sulfoximines bearing a chiral sulfur atom have emerged recently as valuable ligands for metal-catalysed asymmetric synthesis.[73] In particular, C_2-symmetric bis-sulfoximines such as those depicted in Scheme 29 were applied to the test palladium-catalysed asymmetric alkylation reaction (Scheme 2), achieving enantioselectivities of up to 93%.[74]



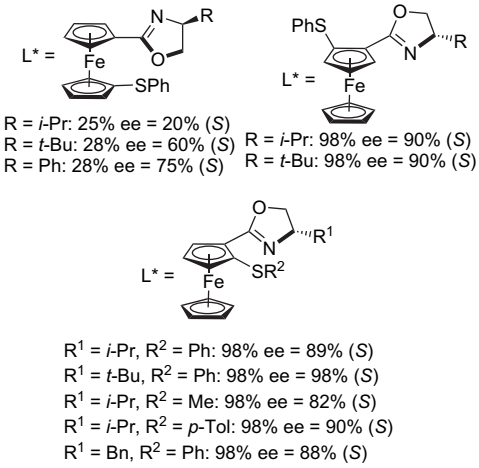
Scheme 29. C_2-Symmetric bis-sulfoximine ligands.

In 2005, Reetz et al. prepared BINOL-derived *N*-phosphino sulfoximines for the first time, and evaluated them as ligands for the test reaction, resulting in ≤66% ees.[75] It was not clear, in this case, whether the ligand was monodentate at phosphorus, or whether it underwent a P/O-chelation.

2.5. Sulfur-containing ferrocenyl ligands

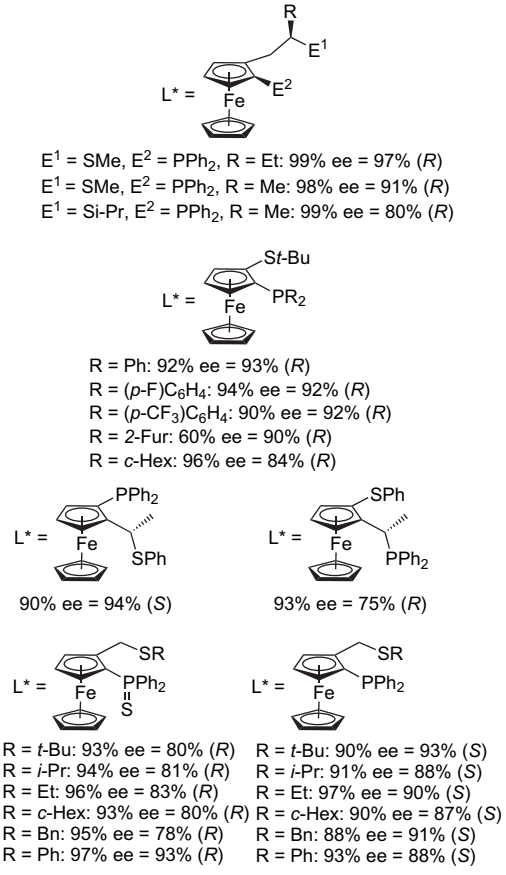
Chiral ferrocene ligands have been widely used in asymmetric catalysis. In particular, numerous reports are available on the chemistry of allylic alkylations using ferrocenyl ligands.[76] The advantages of using ferrocene as a scaffold for chiral ligands are its planar chirality, rigid bulkiness, stability, inherent special electronic and stereochemical properties and ease of derivatisation. In recent years, various sulfur-containing chiral ferrocene derivatives have been successfully implicated in the test reaction (Scheme 2) such as chiral 1-oxazolinyl-1′-(phenylthio)ferrocenes,[77] which gave modest results, whereas high enantioselectivity was obtained by using thioether derivatives of ferrocenyloxazolines with central and planar chiralities[13b] (Scheme 30).

Several groups have reported the synthesis of various chiral P/S-ferrocenyl ligands (Scheme 31) and have investigated them in the test reaction. As an example, Enders et al. have employed novel bidentate planar ferrocenyl ligands, bearing a stereogenic centre at the β-position to the metallocene backbone, which led to quantitative yields and ees of up to 97%.[78] Similar results were observed by Dai et al. using other planar chiral P/S-bidentate ferrocenyl ligands, prepared from



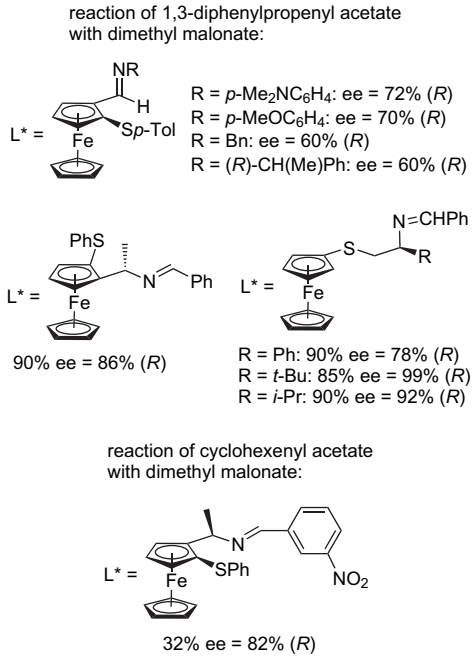
Scheme 30. Sulfur-containing ferrocenyloxazoline ligands.

the commercially available starting material, *N*,*N*-dimethyl-(*S*)-α-ferrocenylethylamine.[79] In addition, readily available 1-phosphino-2-sulfenylferrocenes, possessing planar chirality as the only source of chirality, were reported by Carretero et al., providing very high enantioselectivities in the test reaction.[80] Very recently, Manoury et al. have reported various new chiral ferrocenyl-phosphine thioethers and -thiophosphine thioethers having only a planar chirality, which proved to be successful in the test reaction (Scheme 2).[81]



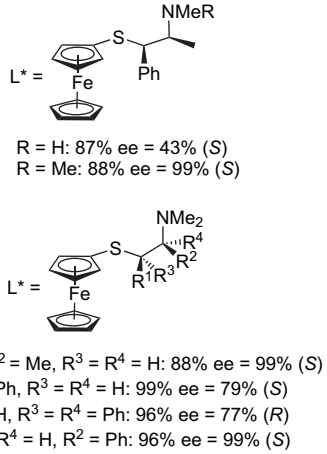
Scheme 31. P/S-ferrocenyl ligands.

Moreover, a few chiral ferrocenylsulfur-imine ligands were investigated in the palladium-catalysed asymmetric allylic alkylation of 1,3-diphenylpropenyl acetate, and cyclohexenyl acetate, with dimethyl malonate (Scheme 32).[79,82,83]



Scheme 32. Ferrocene-based sulfur-imine ligands for Pd-catalysed allylic alkylations.

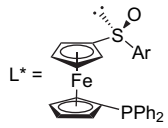
The first monosubstituted ferrocene derivatives containing chiral amino-sulfide backbones in the side chain were reported by Bonini et al.[83] These ligands were compared for their efficiency in the test reaction to the known families of ligands, providing asymmetric induction of up to 99% ee (Scheme 33).



Scheme 33. β-Aminoalkyl ferrocenyl sulfide ligands.

Although, many excellent results have been observed using planar chiral ferrocenyl ligands, Toru et al. reported in 2004 the first chiral ferrocenyl ligand bearing a chiral sulfinyl group as the sole chirality.[84] These new chiral 1-phosphinyl-1′-sulfinylferrocene ligands were evaluated in the standard reaction (Scheme 34).

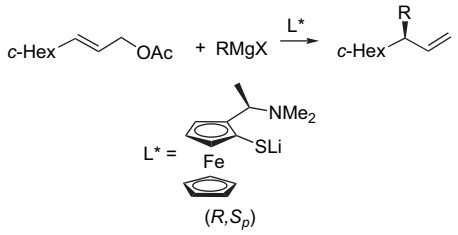
In addition, Bäckvall et al. reported in 2001 the application of ferrocenylthiolates as ligands in copper-catalysed substitution



Ar = Ts: 82% ee = 58% (*R*)
Ar = *p*-MeOC$_6$H$_4$: 99% ee = 56% (*R*)
Ar = *p*-ClC$_6$H$_4$: 45% ee = 25% (*R*)
Ar = 1-Naph: 96% ee = 68% (*R*)

Scheme 34. 1-Phosphinyl-1′-sulfinylferrocene ligands.

reactions of allylic acetates with Grignard reagents, providing a good enantioselectivity (Scheme 35).[85] Neutral thioether ligands were not suitable for this other type of reaction, showing the importance of anionic coordination to copper.



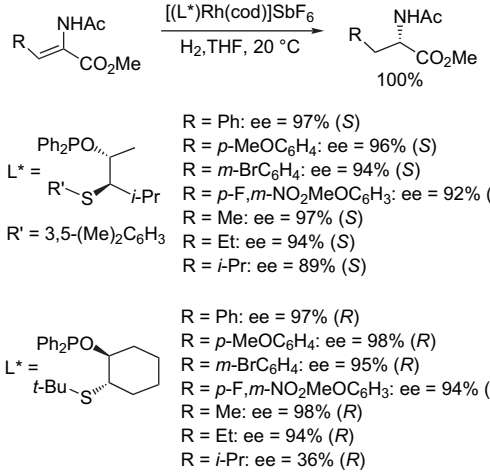
R = *n*-Bu, X = I: 88% ee = 64%
R = Et, X = I: 55% ee = 62%
R = *n*-Pr, X = I: 77% ee = 54%
R = *i*-Pr, X = Br: 51% ee = 52%
R = Me, X = I: 42% ee = 44%

Scheme 35. Cu-catalysed substitution of allylic acetates by RMgX with ferrocenylthiolate ligands.

3. Hydrogenation

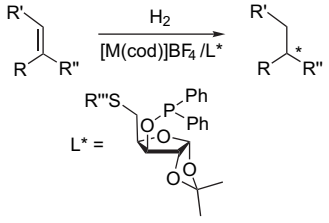
The asymmetric hydrogenation of prochiral compounds catalysed by chiral transition-metal complexes has been in widespread use in stereoselective organic synthesis, and some processes have found industrial applications.[86] Over the years, the scope of this reaction has been gradually extended in terms of both the reactant structure and the catalyst efficiency. Although phosphorus ligands such as diphosphines and diphosphinites are among the most widely used chiral ligands in this process,[87] mixed donor ligands have only recently demonstrated their potential utility. In particular, the hydrogenation of unsaturated substrates using complexes with chiral sulfur donor ligands has recently been reported in the literature. In 1999, Hauptman et al. reported the rhodium-catalysed asymmetric hydrogenation of α-enamide esters in the presence of P/S-ligands, in which the sulfur group was a sulfide, providing only low to moderate ees (ranging from 5 to 51%).[88] In general, of the few mixed phosphorus-thioether ligands, which have been used in this process, the thioether–phosphinite ligands have shown the best results in asymmetric hydrogenation. Hence, a new class of thioether-phosphinite ligands, developed by Evans et al., has recently proved to be very efficient for the rhodium-catalysed asymmetric hydrogenation of a variety of α-acylaminoacrylates (Scheme 36).[89]

In order to extend the success encountered with the thioether-phosphinite ligands, Diéguez et al. have recently



Scheme 36. Hydrogenation of substituted α-acylaminoacrylates with thioether-phosphinite ligands.

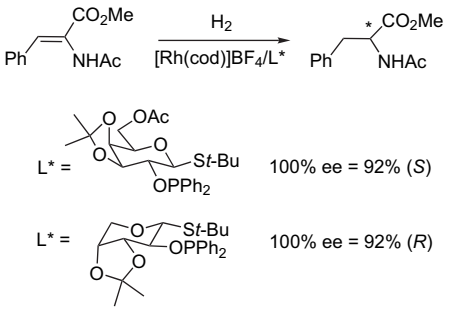
developed the synthesis of carbohydrate-based thioether-phosphinite ligands, since carbohydrate ligands are known to be highly effective ligands for asymmetric hydrogenation.[90] Hence, thioether-phosphinite ligands, containing a furanoside as a simple, but effective, backbone, were tested in the rhodium- and iridium-catalysed asymmetric hydrogenation of α-acylaminoacrylates and itaconic acid derivatives, providing high enantioselectivities (Scheme 37). In 2000, the same group investigated the corresponding thioether-phosphite ligands for the asymmetric iridium-catalysed hydrogenation of itaconic acid, giving good conversions and enantioselectivities of up to 51%.[91]



M	R'''	R	R'	R"	Yield (%)	ee (%)
Rh	Ph	NHAc	H	CO_2Me	86	68 (*R*)
Ir	Ph	NHAc	H	CO_2Me	100	50 (*R*)
Rh	*i*-Pr	NHAc	H	CO_2Me	83	96 (*R*)
Ir	*i*-Pr	NHAc	H	CO_2Me	95	63 (*R*)
Rh	Me	NHAc	H	CO_2Me	75	54 (*R*)
Ir	Me	NHAc	H	CO_2Me	60	30 (*R*)
Rh	Ph	NHAc	Ph	CO_2Me	100	68 (*R*)
Ir	Ph	NHAc	Ph	CO_2Me	100	50 (*R*)
Rh	*i*-Pr	NHAc	Ph	CO_2Me	100	93 (*R*)
Rh	Me	NHAc	Ph	CO_2Me	75	45 (*R*)
Rh	Ph	CH_2CO_2H	H	CO_2H	83	47 (*S*)
Ir	Ph	CH_2CO_2H	H	CO_2H	85	32 (*S*)
Rh	*i*-Pr	CH_2CO_2H	H	CO_2H	83	55 (*S*)

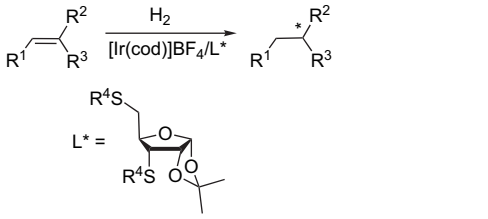
Scheme 37. Hydrogenation of prochiral olefins with furanoside thioether-phosphinite ligands.

Other S/P-ligands derived from carbohydrates, and depicted in Scheme 38, were found to be efficient catalysts for the rhodium-catalysed methyl acetamidocinnamate hydrogenation, leading to protected (*S*)-phenylalanine in quantitative yield and in 92% ee.[52] The use of 2-phosphinite *tert*-butylthioarabinoside as ligand afforded the (*R*)-isomer in 92% ee.



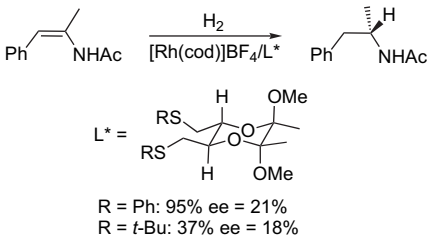
Scheme 38. Hydrogenation of methyl acetamidocinnamate with P/S-ligands from carbohydrates.

In 1999, Ruiz et al. reported the synthesis of the first family of sugar-derivative dithioethers containing sulfur as a unique donor atom.[92] These chiral C_1-symmetric dithioether ligands were tested in the iridium-catalysed asymmetric hydrogenation of various acrylic acid derivatives, providing modest enantioselectivities (Scheme 39).



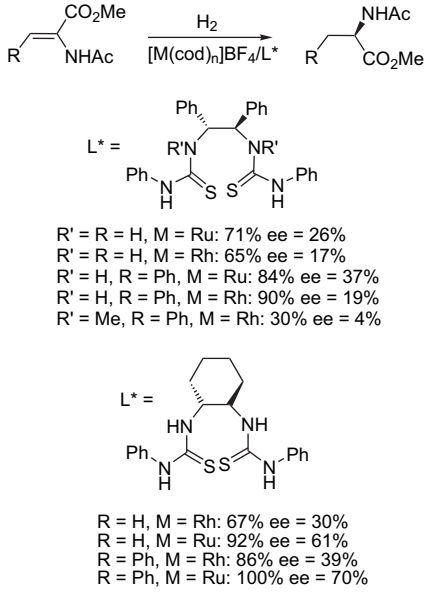
Scheme 39. Hydrogenation of acrylic acid derivatives with sugar dithioether ligands.

Moderate enantioselectivities were obtained in the rhodium-catalysed asymmetric hydrogenation of an α-aryl enamide performed in the presence of a chiral C_2-symmetric dithioether ligand with a 1,4-dioxane backbone derived from tartrates (Scheme 40).[93] A series of cationic iridium complexes containing chiral dithioether ligands have recently been prepared by Martin et al., in order to study the influence of the sulfur substituents and the metallacycle size on the acetamidoacrylate hydrogenation reaction, but, again, low enantioselectivities were observed.[94]



Scheme 40. Hydrogenation of an α-aryl enamide with 1,4-dioxane dithioether ligands.

Asymmetric enamide hydrogenations were also carried out in the presence of N/S-ligands and rhodium or ruthenium catalysts by Lemaire et al., giving enantioselectivities of up to 70%.[95] Two new types of stable and readily available chiral ligands, mono- and dithioureas, have been tested, but only the dithioureas provided a significant enantioselection. This suggested that, for enamide hydrogenation, the C_2-symmetry of the dithiourea ligands was a key factor in the degree of control observed (Scheme 41). The use of these ligands was extended to the rhodium- and iridium-catalysed hydrogenation of phenylglyoxylate methyl ester, giving a good enantioselectivity with ee values of up to 72%.[96]



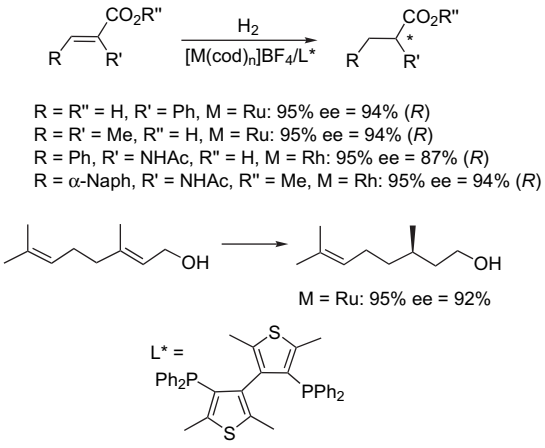
Scheme 41. Hydrogenation of enamides with dithiourea ligands.

In 2000, Benincori et al. reported the synthesis of a new C_2-symmetry chelating ligand, 2,2′,5,5′-tetramethyl-4,4′-bis-(diphenylphosphino)-3,3′-bithiophene (tetraMe-BITIOP).[97] The complexes of this electron-rich diphosphine with Ru(II) and Rh(I) were used as catalysts in the homogeneous hydrogenation reaction of prostereogenic double bonds of substituted acrylic acids, and *N*-acetylenamino acids. The ees were found to be excellent, in general, and comparable with the best results reported in the literature for the same reactions. Hence, this ligand constituted one of the most efficient diphosphine chiral ligands available today for asymmetric hydrogenation. An important advantage offered by this ligand over its competitors was its very good synthetic accessibility (Scheme 42). The success of this ligand was extended to the asymmetric hydrogenation of α- and β-ketoesters, providing ees of up to 99%.

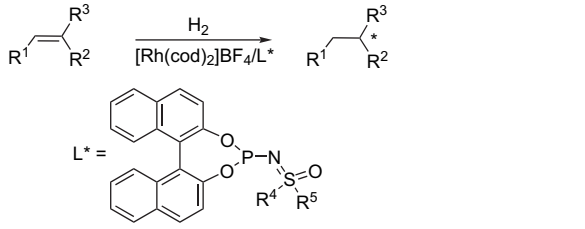
In addition, Bolm et al. have reported, very recently, the use of BINOL-derived *N*-phosphino sulfoximines as ligands in the rhodium-catalysed hydrogenation of dimethyl itaconate and α-acetamidoacrylates, achieving high enantioselectivities (Scheme 43).[75] The question of whether these ligands behave in a monodentate manner, or whether a P/O-bidentate chelation was involved needed to be addressed.

4. Hydrogen transfer

Hydride-transfer reactions use sources of hydrogen other than molecular hydrogen such as cyclohexene, cyclohexadiene, alcohols, acids, cyclic ethers and other molecules



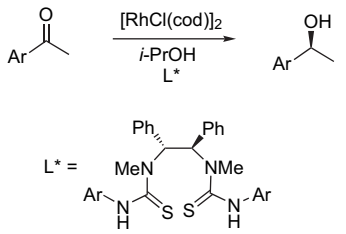
Scheme 42. Hydrogenation of olefins with tetraMe-BITIOP ligand.



R^1 = H, R^2 = CH_2CO_2Me, R^3 = CO_2Me, (*R*)-L*, R^4 = Ph, R^5 = Me: ee > 99% (*R*)
R^1 = H, R^2 = CH_2CO_2Me, R^3 = CO_2Me, (*S*)-L*, R^4 = Ph, R^5 = Me: ee = 99% (*S*)
R^1 = H, R^2 = CH_2CO_2Me, R^3 = CO_2Me, (*R*)-L*, R^4 = R^5 = Me: ee > 99% (*R*)
R^1 = H, R^2 = CH_2CO_2Me, R^3 = CO_2Me, (*R*)-L*, R^4 = R^5 = Ph: ee = 98% (*R*)
R^1 = H, R^2 = CH_2CO_2Me, R^3 = CO_2Me, (*R*)-L*, R^4 = Ph, R^5 = Me: ee = 99% (*S*)
R^1 = H, R^2 = CH_2CO_2Me, R^3 = CO_2Me, (*S*)-L*, R^4 = Ph, R^5 = Me: ee = 98% (*R*)
R^1 = H, R^2 = CH_2CO_2Me, R^3 = CO_2Me, (*R*)-L*, R^4 = R^5 = Me: ee = 98% (*R*)
R^1 = H, R^2 = CH_2CO_2Me, R^3 = CO_2Me, (*R*)-L*, R^4 = R^5 = Ph: ee = 98% (*S*)
R^1 = Ph, R^2 = CO_2Me, R^3 = NHAc, (*R*)-L*, R^4 = Ph, R^5 = Me: ee = 97% (*S*)
R^1 = Ph, R^2 = CO_2Me, R^3 = NHAc, (*S*)-L*, R^4 = Ph, R^5 = Me: ee = 94% (*R*)
R^1 = Ph, R^2 = CO_2Me, R^3 = NHAc, (*R*)-L*, R^4 = R^5 = Me: ee = 95% (*S*)
R^1 = Ph, R^2 = CO_2Me, R^3 = NHAc, (*R*)-L*, R^4 = R^5 = Ph: ee = 94% (*S*)
R^1 = H, R^2 = Ph, R^3 = NHAc, (*R*)-L*, R^4 = Ph, R^5 = Me: ee = 87% (*R*)
R^1 = H, R^2 = Ph, R^3 = NHAc, (*S*)-L*, R^4 = Ph, R^5 = Me: ee = 76% (*R*)
R^1 = H, R^2 = Ph, R^3 = NHAc, (*R*)-L*, R^4 = R^5 = Me: ee = 85% (*S*)
R^1 = H, R^2 = Ph, R^3 = NHAc, (*R*)-L*, R^4 = R^5 = Ph: ee = 64% (*S*)

Scheme 43. Hydrogenation of olefins with BINOL-derived *N*-phosphino sulfoximine ligands.

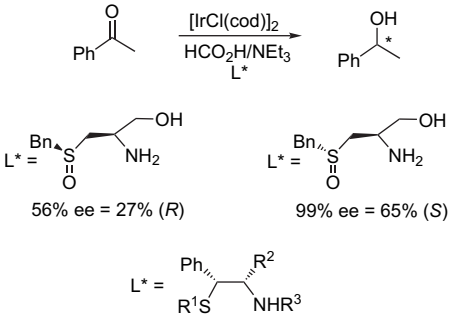
that are fairly readily dehydrogenated. This method avoids all the risks inherent to molecular hydrogen, and the chemoselectivities can be modulated by the proper choice of hydride donor. Different substrates can be hydrogenated with the appropriate catalysts and hydrogen donors.[98] Considerable efforts have been devoted to the study of the asymmetric version of these processes,[99] the most widely studied of which is, perhaps, the asymmetric hydrogenation of ketones with alcohols, normally *i*-PrOH, as the source of hydrogen. In 2001, Lemaire et al. reported the rhodium-catalysed hydride-transfer reduction of ketones using dithiourea ligands bearing an aromatic ring on their terminal nitrogen atoms. The most satisfactory results are summarised in Scheme 44.[100] In this work, the effects of structural modifications of both the ligand and the substrate on the ee and conversion have been studied, demonstrating that the coordination of the dithioureas took place through the S atom. As a consequence of this coordination, thiourea should be considered as an S ligand rather than an N ligand.



Ar = Ph: 97% ee = 63% (*S*)
Ar = 2,6-$(Me)_2C_6H_3$: 92% ee = 66% (*S*)

Scheme 44. Rh-catalysed hydride-transfer reduction of ketones with dithiourea ligands.

A new class of efficient ligands, chiral aminosulf(ox)ides, was developed by van Leeuwen et al. for the iridium-catalysed asymmetric transfer hydrogenation of acetophenone in the presence of formic acid as hydrogen donor.[101] Both the sulfoxide-containing β-amino alcohols and the amino sulfides derived from 1,2-disubstituted amino alcohols gave rise to high reaction rates and moderate to excellent enantioselectivities in the reduction of acetophenone, as shown in Scheme 45. In 2001, a screening study for the enantioselective reduction of various aryl alkyl ketones was developed with amino sulfide (1*R*,2*S*)-2-amino-1,2-diphenyl-1-benzylthioethane ligands.[102] The choice of substrate did not markedly affect the outcome of the reactions. In most cases, the use of ruthenium gave rise to a higher selectivity than the use of iridium.

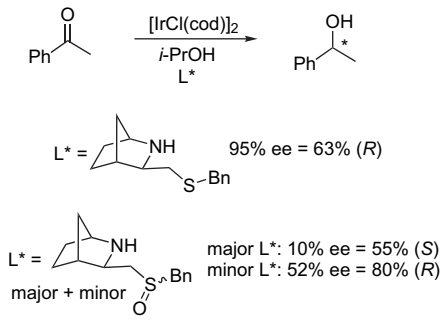


R^1 = *i*-Pr, R^2 = Me, R^3 = H: > 99% ee = 41% (*S*)
R^1 = Bn, R^2 = Me, R^3 = H: > 99% ee = 65% (*S*)
R^1 = Bn, R^2 = R^3 = Me: 91% ee = 42% (*S*)

Scheme 45. Ir-catalysed hydride-transfer reduction of acetophenone with aminosulf(ox)ide ligands.

In 2003, two new classes of nitrogen- and sulfur-containing ligands, 2-azanorbornyl amino sulfides and the corresponding sulfoxides, have been synthesised and evaluated in the asymmetric transfer hydrogenation of acetophenone.[103] Using iridium as the metal, the most satisfactory result, 80% ee, was obtained using a bicyclic sulfoxide ligand (Scheme 46).

In order to improve the performance of Noyori's catalytic system, Ru(II)-TsDPEN (*N*-tosyl-1,2-diphenylethylenediamine), which is very efficient, but suffers from a long reaction time and a generally low activity, Mohar et al. have modified the diamine ligand by introducing electron-withdrawing fluorosulfonyl groups.[104] Hence, (η6-arene)-*N*-perfluorosulfonyl-1,2-diamines and *N*-(*N*,*N*-dialkylamino)sulfamoyl-1,2-diamines were successfully used as ligands in the ruthenium-catalysed hydride-transfer

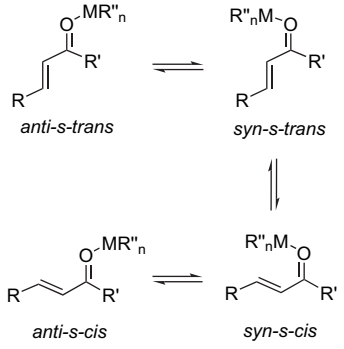


Scheme 46. Ir-catalysed hydride-transfer reduction of acetophenone with 2-azanorbornyl amino-sulfide or -sulfoxide ligands.

reduction of various aromatic ketones, α-keto esters, and α,α,α-trifluoromethyl ketones in high yields and excellent selectivities. Similarly, water-soluble analogues of Noyori's TsDPEN ligand containing an additional sulfonic acid group were examined in the ruthenium-catalysed reduction of aromatic ketones, achieving a high enantioselectivity and a moderate activity.[105]

5. Conjugated additions

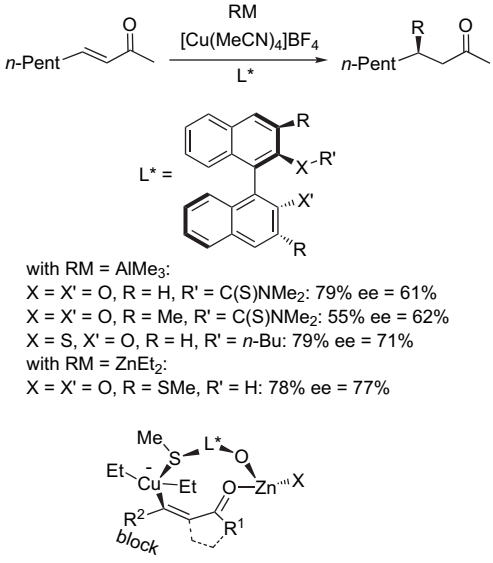
Enantioselective metal-catalysed 1,4-conjugate addition of organometallic reagents to linear or cyclic enones is an important procedure for making C–C bonds.[106] Despite recent successes in the area of asymmetric copper-catalysed 1,4-organometallic additions to Michael acceptors, there is an ongoing quest for improved systems showing very high enantioselectivities. One problematic substrate class for this reaction is linear aliphatic enones. The high conformational mobility of these species, together with the presence of only subtle substrate–catalyst steric interactions, makes the design of effective enantioselective systems a real challenge. The accepted mechanism for this reaction involves the activation of the enone with the metal reagent through the carbonyl.[107] Since conformational exchange can take place between the *syn*/*anti* *s*-cis and *s*-trans forms of the activated enone (Scheme 47), linear enones usually provide lower ees than cyclic enones.



Scheme 47. *Syn*/*anti* *s*-cis and *s*-trans forms of activated enones.

A prominent position in this rapidly expanding field is occupied by the copper-catalysed and chiral ligand-accelerated conjugate addition of organozinc reagents. This latter process has attracted considerable attention, because of the mild reaction conditions and the high functional-group tolerance that the zinc reagents offer.[108] The enantioselective version of the 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds has been less studied in recent years, but extensively developed in the past, using different mono- and bidentate chiral ligands such as monodentate thiosugars,[109] heterobidentate S,N-ligands,[110] oxazoline arenethiolates,[111] S,O-ligands[112] and S,P-ligands.[113] Other chiral N,S-donor ligands, derived from L-proline and (*S*)-phenylglycine, have been used in the copper-catalysed conjugate addition of MeLi to enones.[114] Trialkylaluminium reagents were also involved in only a few reactions, but these represent an interesting alternative.

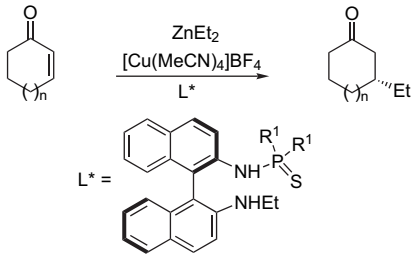
In 1999, Woodward et al. developed copper-catalysed asymmetric conjugate additions of various organometallic reagents (ZnR_2 and AlR_3) to linear enones in the presence of sulfur-containing 1,1′-binaphthyl-based ligands.[115] Thiourethane and thioether 1,1′-binaphthyl-based ligands were effective for the copper-catalysed 1,4-addition of $ZnEt_2$ and $AlMe_3$ to *trans*-alkyl-3-en-2-ones, yielding the products with enantioselectivities of up to 77% (Scheme 48). In comparison, the 1,4-addition of $ZnEt_2$ to 2-cyclohexenone proceeded in up to 77% ee with the same ligand family. Ligand optimisation studies have indicated that 3,3′-dimethylthio-1,1′-binaphthalene-2,2′-diol was the most effective with respect to enantioselectivity.[116] In addition, variation of the enone structure has revealed that the catalyst derived from the (*S*)-binaphthalene-derived ligand caused linear enones to adopt an *s*-cis conformation with a zinc-derived Lewis acid bound to the carbonyl lone pair *anti* to the ene function (Scheme 48). A probable transition state is given in Scheme 48, taking into account that the nature of the steric block was the apparent cause of the enantioselectivity.



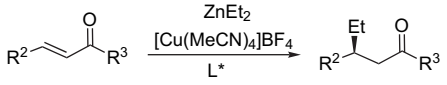
Scheme 48. Cu-catalysed 1,4-addition of ZnR_2 or AlR_3 to linear aliphatic enones with 1,1′-binaphthalene-derived ligands.

Better results were reported by Shi et al. in 2004, dealing with the enantioselective conjugate addition of $ZnEt_2$ to enones catalysed by Cu(I) and axially chiral binaphthylthiophosphoramides as ligands, which are readily available, quite stable, recoverable and reusable (Scheme 49). Their system allowed an efficient and highly enantioselective

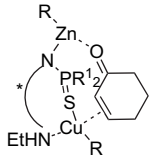
functionalisation of not only six- and seven-membered cyclic enones (97% ee), but also cyclopentenone (98% ee) and acyclic enones (up to 97% ee).[117] The mechanism of the reaction was investigated, confirming that this series of chiral phosphoramides was a novel type of S,N-bidentate ligands through ^{31}P and ^{13}C NMR spectroscopic experiments. The mechanism was postulated to be a bimetallic catalytic process, in which the acidic proton of thiophosphoramide in the ligands played a significant role in the formation of the active species (Scheme 49). The linear effect of the product ee and the ligand ee further revealed that the active species was a monomeric Cu(I) complex bearing a single ligand.



R^1 = Me, n = 1: 95% ee = 97%
R^1 = Me, n = 2: 93% ee = 97%
R^1 = Ph, n = 2: 94% ee = 91%
R^1 = Me, n = 0: 73% ee = 96%
R^1 = Ph, n = 0: 62% ee = 85%



R^1 = Me, R^2 = R^3 = Ph: 97% ee = 87%
R^1 = R^2 = R^3 = Ph: 98% ee = 97%
R^1 = R^3 = Ph, R^2 = *p*-$MeOC_6H_4$: 98% ee = 96%
R^1 = R^2 = Ph, R^3= *p*-$MeOC_6H_4$: 87% ee = 97%

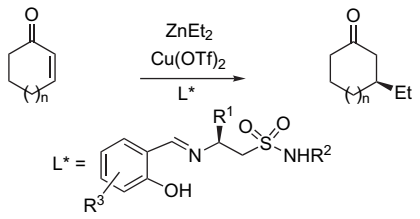


possible active species

Scheme 49. Cu-catalysed 1,4-addition of $ZnEt_2$ to enones with binaphthylthiophosphoramide ligands.

At the same time, Gennari et al. discovered a new family of chiral Schiff-base ligands, which were tested in the copper-catalysed conjugate addition of diethylzinc to cyclic enones (Scheme 50) and, less efficiently, to acyclic enones such as benzalacetone (50% ee) or chalcone (34% ee).[118] These easily available ligands contained a set of different metal-binding sites such as a phenol, an imine and a secondary sulfonamide moiety.

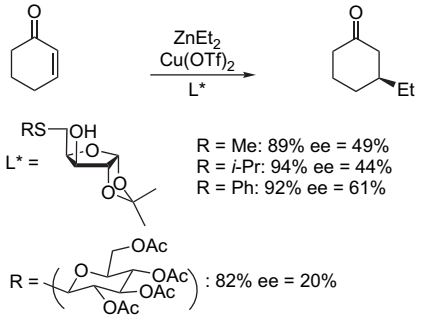
The copper-catalysed conjugate addition of $ZnEt_2$ to cyclohexenone was also performed by Pamies et al. in the presence of thioether-alcohol ligands bearing a xylofuranose backbone.[119] These ligands, readily prepared from the inexpensive (D)-xylose, provided the Michael adducts in ≤62% ees (Scheme 51). The condensation of $AlMe_3$ onto (*E*)-non-3-en-2-one was, however, less efficient, since the enantioselectivity was only 34% ee.



R^1 = *i*-Pr, R^2 = (*S*)-CH(Me)Cy, R^3 = 3,5-Cl_2, n = 1: ee = 90%
R^1 = *i*-Pr, R^2 = (*S*)-CH(Me)Cy, R^3 = 3,5-Cl_2, n = 2: ee = 81%
R^1 = *t*-Bu, R^2 = (*S*)-CH(Me)Cy, R^3 = 3,5-*t*-Bu_2, n = 1: ee = 80%
R^1 = *t*-Bu, R^2 = (*S*)-CH(Me)Cy, R^3 = 3,5-*t*-Bu_2, n = 2: ee = 79%
R^1 = R^2 = *i*-Pr, R^3 = 3,5-(*t*-Bu)$_2$, n = 1: ee = 76%
R^1 = R^2 = *i*-Pr, R^3 = 3,5-(*t*-Bu)$_2$, n = 2: ee = 72%
R^1 = *t*-Bu, R^2 = $CHPh_2$, R^3 = 3,5-(*t*-Bu)$_2$, n = 1: ee = 74%
R^1 = *t*-Bu, R^2 = $CHPh_2$, R^3 = 3,5-(*t*-Bu)$_2$, n = 2: ee = 75%
R^1 = *i*-Bu, R^2 = (*S*)-CH(Me)Cy, R^3 = 3,5-Cl_2, n = 1: ee = 73%
R^1 = *i*-Bu, R^2 = (*S*)-CH(Me)Cy, R^3 = 3,5-Cl_2, n = 2: ee = 74%
R^1 = *t*-Bu, R^2 = $CHPh_2$, R^3 = 3,5-(*t*-Bu)$_2$, n = 0: ee = 70%
R^1 = *i*-Bu, R^2 = (*S*)-CH(Me)Cy, R^3 = 3,5-(*t*-Bu)$_2$, n = 0: ee = 80%

Cy = *c*-C_6H_{11}

Scheme 50. Cu-catalysed 1,4-addition of $ZnEt_2$ to cyclic enones with chiral Schiff-base ligands.

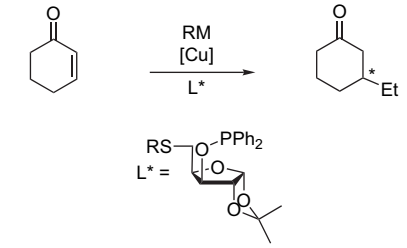


Scheme 51. Cu-catalysed 1,4-addition of $ZnEt_2$ to cyclohexenone with thioether-alcohol ligands bearing a xylofuranose backbone.

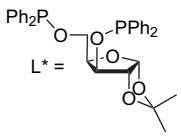
In 2005, the same group extended this methodology to the corresponding thioether-phosphinite and -diphosphinite ligands derived from D-xylose for the copper-catalysed 1,4-addition of $ZnEt_2$ and $AlEt_3$ to cyclohexenone, obtaining good enantioselectivities (≤72% ees).[120] Systematically varying the functional groups at the C5 position (thioether and phosphinite), and different substituents in the thioether moieties had a strong effect on the rate and enantioselectivities (Scheme 52). The highest enantioselectivity was achieved with the catalyst precursor containing the thioether-phosphinite ligand, which had an isopropyl substituent in the thioether moiety. The activity was, however, generally best with the diphosphinite ligands.

A new application of bis(oxazoline) ligands was reported by Reiser et al., who obtained some excellent results such as that depicted in Scheme 53 for the 1,4-addition of $ZnEt_2$ to cyclohexenone.[121] The authors involved a bimetallic complex such as that depicted in Scheme 49, in which the substrate is locked in a two-point binding mode via a zinc and a copper atom.

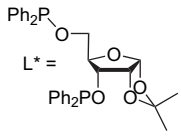
Whereas the mono- and the *S*,*S*-di-thioether moiety has been used to date, the 1,3-dithianyl motif was used for the first



R = *i*-Pr, MR = $ZnEt_2$, CuCN: 100% ee = 72% (*R*)
R = Me, MR = $ZnEt_2$, $[Cu(MeCN)_4]BF_4$: 100% ee = 53% (*R*)
R = Me, MR = $AlEt_3$, $[Cu(MeCN)_4]BF_4$: 100% ee = 33% (*S*)
R = Ph, MR = $AlEt_3$, $[Cu(MeCN)_4]BF_4$: 100% ee = 48% (*S*)
R = Ph, MR = $AlEt_3$, $Cu(OTf)_2$: 95% ee = 27% (*R*)
R = Ph, MR = $AlEt_3$, $[Cu(MeCN)_4]BF_4$: 100% ee = 33% (*S*)

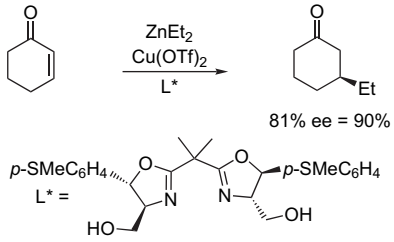


MR = $ZnEt_2$, $[Cu(MeCN)_4]BF_4$: 69% ee = 25% (*S*)



MR = $ZnEt_2$, $[Cu(MeCN)_4]BF_4$: 68% ee = 29% (*S*)

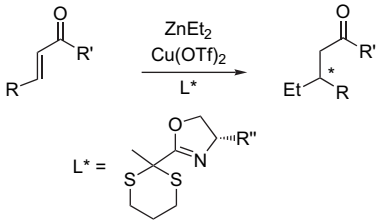
Scheme 52. Cu-catalysed 1,4-addition of $ZnEt_2$ or $AlEt_3$ to cyclohexenone with thioether-phosphinite or -diphosphinite ligands bearing a xylofuranose backbone.



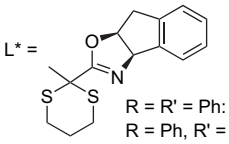
Scheme 53. Cu-catalysed 1,4-addition of $ZnEt_2$ to cyclohexenone with a thioether-bis(oxazoline) ligand.

time by Ricci et al. as a new hybrid ligand in asymmetric catalysis. Hence, a series of new chiral oxazoline-1,3-dithianes has been successfully applied to the copper-catalysed diethylzinc addition to enones (Scheme 54).[64] The expected products were obtained in almost quantitative yields and up to 90% enantioselectivity. The asymmetric induction appeared to be closely related to the steric hindrance exerted by the group adjacent to the oxazoline nitrogen. The conformation of the ligand has been explored using a combination of X-ray and NMR measurements, indicating the presence of a remarkable anomeric effect, which accounted for the preference of the oxazoline ring for the axial location.

In order to prepare a new range of ligands incorporating both sulfoximide and phosphine moieties, Kinahan and Tye reported, in 2001, the synthesis of a novel chiral sulfoximide, which was tested as a ligand in the copper-catalysed 1,4-addition of $ZnEt_2$ to enones.[122] Whilst the reaction of acyclic enones gave racemic 1,4-products, the best result was obtained upon reaction of cycloheptenone (44% ee),



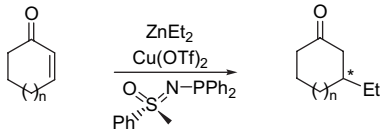
R = R' = Ph, R'' = Bn: 80% ee = 62% (*S*)
R = Ph, R' = Me, R'' = Bn: 55% ee = 46% (*S*)
R = H, R' = -$(CH_2)_3$-, R'' = Bn: > 95% ee = 37% (*S*)
R = R' = Ph, R'' = *i*-Pr: 73% ee = 50% (*S*)
R = Ph, R' = Me, R'' = *i*-Pr: 49% ee = 36% (*S*)
R = H, R' = -$(CH_2)_3$-, R'' = *i*-Pr: > 95% ee = 24% (*S*)



R = R' = Ph: 77% ee = 69% (*R*)
R = Ph, R' = Me: 55% ee = 53% (*R*)
R = H, R' = -$(CH_2)_3$-: > 95% ee = 51% (*R*)

Scheme 54. Cu-catalysed 1,4-addition of $ZnEt_2$ to enones with chiral oxazoline-1,3-dithiane ligands.

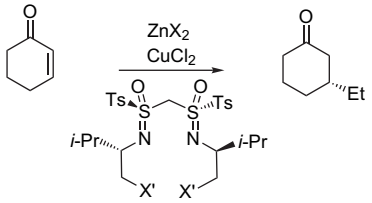
demonstrating that the ligand performed best with unhindered cyclic substrates (Scheme 55). The absolute configuration of the major product was not specified.



n = 1: 95% ee = 23%
n = 2: 60% ee = 44%

Scheme 55. Cu-catalysed 1,4-addition of $ZnEt_2$ to cyclic enones with a chiral sulfoximide ligand.

Chiral sulfoximines and, in particular, chiral bidentate β-hydroxysulfoximines, are one of the most successful chiral sulfur-based ligands used in asymmetric catalysis. The X-ray analysis of complexes of ethylzinc[123] and vanadium[124] coordinated to β-hydroxysulfoximines has shown that the metal was coordinated to the hydroxy oxygen and the sulfoximine nitrogen atom. In this context, Bolm et al. have developed the synthesis of a number of new C_2-symmetric geminal bis(sulfoximine)s, which were further investigated for the copper-catalysed 1,4-addition of $ZnEt_2$ to cyclohexenone.[125] All of the ligand–copper complexes were found to be highly active catalysts, but the enantioselectivities were rather disappointing, with 36% ee being the best value (Scheme 56). Based on the observed results, it was difficult

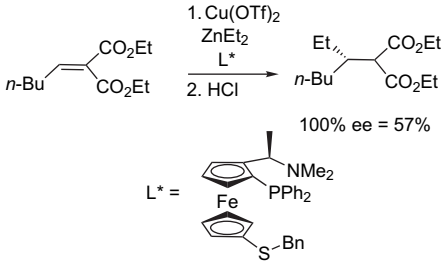


X' = OH, X = Cl: 89% ee = 22%
X' = Cl, X = OTf: 99% ee = 36%

Scheme 56. Cu-catalysed 1,4-addition of $ZnEt_2$ to cyclohexenone with C_2-symmetric geminal bis(sulfoximine) ligands.

to analyse the potential role of the ligand oxygen atoms as a possible coordination site for zinc.

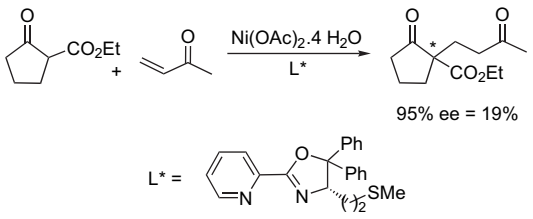
The first asymmetric conjugate addition of $ZnEt_2$ to aryl- and alkylidene malonates by using catalytic copper in the presence of chiral phosphorus ligands was reported by Alexakis and Benhaim.[126] Among these ligands, a chiral phenylphosphorus ferrocenyl ligand bearing a benzothioether gave a better enantioselectivity than the corresponding phenylphosphorus ferrocenyl ligand without the sulfur group (53% ee) (Scheme 57).



Scheme 57. Cu-catalysed 1,4-addition of $ZnEt_2$ to ethyl pentylidene malonate with a sulfur-containing phenylphosphorus ferrocenyl ligand.

On the other hand, the enantioselective 1,4-addition of carbanions such as enolates to linear enones is an interesting challenge, since relatively few efficient methods exist for these transformations. The Michael reaction of β-dicarbonyl compounds and α,β-unsaturated ketones can be catalysed by a number of transition-metal compounds. The asymmetric version of this reaction has been performed using chiral diol, diamine and diphosphine ligands. In the past few years, bidentate and polydentate thioethers have begun to be considered as chiral ligands for this reaction. As an example, Christoffers and Röβler have developed the synthesis of several S/O-bidentate and S/O/S-tridentate thioether ligands derived from chiral α-hydroxy acids.[127] These latter ligands were tested in the asymmetric catalysis version of the Michael reactions, giving, unfortunately, an enantioselectivity lower than 11% ee. As an extension of this work, the same authors have prepared *N*,*S*,*N*-tridentate diamino thioethers and the corresponding diimino thioethers with C_2-symmetry from chiral α-amino acids.[128] These ligands were further submitted to the Michael reaction of β-oxo esters with methyl vinyl ketone, resulting in an optimal ee of only 17%. In addition, various tridentate oxazoline ligands bearing adjacent thioether and heteroaryl donor groups were synthesised from L-cysteine and L-methionine by the same group.[129] All ligands have been screened with 13 metal salts with regard to the asymmetric catalysis version of the Michael reaction of a β-ketoester with methyl vinyl ketone to give an optimal result of 19% ee (Scheme 58). The absolute configuration of the major product was not specified.

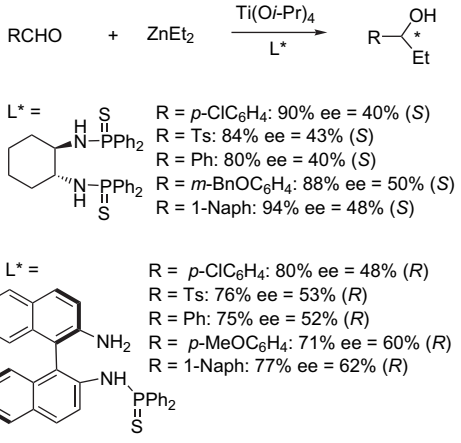
In addition, Woodward et al. have described the asymmetric chemo- and regiospecific copper-catalysed addition of organozinc reagents to Baylis–Hillman-derived allylic electrophiles using sulfur-containing 1,1′-binaphthyl-based ligands, as depicted in Scheme 48.[130] Although this reaction, giving up to 64% ee, was actually an S_N2' reaction of the organometallic reagent, it was decided, however, to include it in this section.



Scheme 58. Ni-catalysed Michael reaction with tridentate oxazoline ligands.

6. Addition of organometallic reagents to aldehydes

The enantioselective addition of diethylzinc to aldehydes mediated by chiral ligands is one of the most studied examples of ligand-accelerated catalysis.[131] Such asymmetric reactions allow the synthesis of chiral alcohols that are ubiquitous in the structures of natural products and drug compounds. Over the past few decades, a large number of chiral catalysts including amino alcohols, diamines and diols have been developed and high enantioselectivities have been achieved for all different types of aldehydes. Several characteristics of these reactions such as the very important nonlinear effects,[132] the autocatalysis phenomena and the derived amplification of the ee, making them attractive from both an intellectual and industrial perspective, have ensured that sufficiently active catalytic ligands have been developed. In order to extend the diversity of the ligand structures even further, sulfur-containing chiral ligands such as amino thiols, amino sulfides, disulfides, disulfonamides, arylthiophosphoramides and sulfinylferrocenes have recently been synthesised and subsequently applied to the catalytic asymmetric dialkylzinc addition to aldehydes, allowing this process to become a mature method. In 1999, Shi and Sui showed that a diphenylthiophosphoramide derived from (1*R*,2*R*)-1,2-diaminocyclohexane could be used as a ligand in the catalytic asymmetric addition of $ZnEt_2$ to aldehydes in the presence of Ti(O*i*-Pr)$_4$, providing the corresponding alcohols in 40–50% ees (Scheme 59).[133] Another class of new ligands such as the phenylthiophosphoramide of (*R*)-1,1′-binaphthyl-2,2′-diamine was developed by the same group, and further tested as a ligand in the same conditions (Scheme 59).[134]

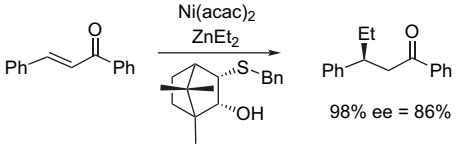


Scheme 59. (Di)phenylthiophosphoramides for Ti-promoted addition of $ZnEt_2$ to aldehydes.

Several chiral disulfonamides have been successfully involved in the same conditions. As an example, the use of the chiral C_2-symmetric trifluoromethanesulfonamide derived from (*R*)-1,1′-binaphthyl-2,2′-diamine led to the formation of the expected alcohols with 43–54% ees.[134] Better enantioselectivities were observed by Paquette and Zhou, resulting from the use of chiral C_2-symmetric VERDI (verbenone dimers) disulfonamides derived from the dimerisation of (+)-verbenone. Stereoselectivity levels ranging from 72 to 98% ees were observed, depending on the structural characteristics of the aldehyde (Scheme 60).[135] In 2000, Yus et al. described other disulfonamide ligands, which could be easily prepared from chiral camphorsulfonyl chloride, and could be successfully used in the enantioselective addition of various dialkylzinc reagents, e.g., $ZnEt_2$ to aldehydes in ≤96% ees (Scheme 60).[136] It is worthy of note that the enantioselectivity was higher for aliphatic aldehydes than for aromatic aldehydes, this behaviour being unusual for this type of reaction. In addition, Walsh et al. have studied in the same conditions the use of disulfonamide ligands derived from 1,2-diaminocyclohexane, 1,2-diaminoethane, 1,3-diaminopropane and 2,2′-diaminobiphenyl.[137] Among these disulfonamide ligands, only *meso*-1,2-diaminocyclohexane was shown to give both good yield and enantioselectivity (up to 84% ee) for the Ti-promoted addition of $ZnEt_2$ to *p*-tolualdehyde. In particular, the use of bis-(*R*,*R*)-trifluoromethanesulfonamide cyclohexane as a ligand in the Ti-promoted enantioselective addition of $Zn(n\text{-Pent})_2$ to 5-hexenal provided the corresponding (*S*)-alcohol in excellent enantiomeric purity (ee>99%).[138] In order to synthesise the pyrrolidine alkaloid, (+)-197B, the corresponding (*S*,*S*)-ligand was employed in the enantioselective addition of $Zn(n\text{-Bu})_2$ to an allene-aldehyde, affording the corresponding (*R*)-alcohol in 70% yield and 94% ee.[139] In addition, the bis-(*R*,*R*)-trifluoromethanesulfonamide ligand derived from *meso*-1,2-diaminocyclohexane was also applied to the Ti-catalysed enantioselective reaction of $ZnMe_2$ with a dialdehyde-$Fe(CO)_3$ complex, giving rise to the corresponding monomethylated complex with 96% ee.[140]

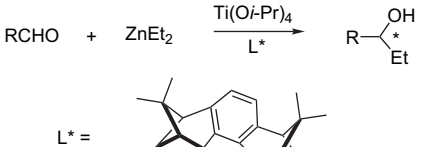
Moreover, Cho and Chun have demonstrated that the zinc complexes chirally modified by β-*N*-sulfonamidoalcohols, used in the absence of $Ti(O\textit{i}\text{-Pr})_4$, were effective as chiral catalysts for the addition of $ZnEt_2$ to aldehydes affording the corresponding secondary alcohols with a moderate enantioselectivity.[141]

In 2000, Yang et al. discovered a series of (1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol derivatives,[142] which proved to be efficient ligands in the conjugate addition of $ZnEt_2$ to chalcones upon catalysis with $Ni(acac)_2$ (Scheme 61).

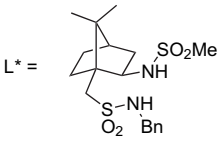


Scheme 61. (1*R*,2*S*,3*R*)-3-Mercaptocamphan-2-ol-derived ligand for Ni-promoted addition of $ZnEt_2$ to chalcone.

The observation that amino sulfur catalysts offer improvements in enantioselectivity over their amino alcohol counterparts is known for a number of transition-metal-mediated C–C bond-forming processes. This has led to the development of a wide range of chiral S/N-ligands for the enantioselective 1,2-addition of dialkylzinc reagents to aldehydes. In this context, Gibson has prepared an L-proline-based β-amino tertiary thiol (Scheme 62), which provided

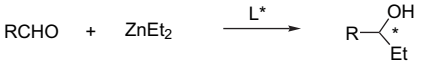


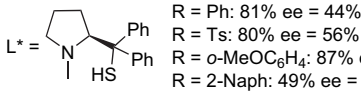
R = Ph, R' = Me: 93% ee = 98% (*R*)
R = Ph, R' = Ts: 93% ee = 89% (*R*)
R = Ph, R' = CF_3: 90% ee = 95% (*R*)
R = *p*-FC_6H_4, R' = Me: 97% ee = 81% (*R*)
R = *p*-FC_6H_4, R' = Ts: 83% ee = 81% (*R*)
R = *p*-FC_6H_4, R' = CF_3: 83% ee = 86% (*R*)
R = $Ph(CH_2)_2$, R' = Me: 86% ee = 97% (*R*)
R = $Ph(CH_2)_2$, R' = Ts: 74% ee = 96% (*R*)
R = *n*-Pent, R' = Me: 87% ee = 98% (*R*)
R = *n*-Pent, R' = Ts: 77% ee = 92% (*R*)



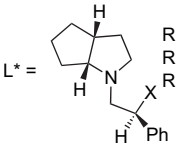
R = *n*-Hex: > 95% ee = 96% (*R*)
R = *c*-Hex: > 95% ee = 92% (*R*)
R = $Ph(CH_2)_2$: > 95% ee = 94% (*R*)

Scheme 60. VERDI disulfonamide and camphordisulfonamide ligands for Ti-promoted addition of $ZnEt_2$ to aldehydes.

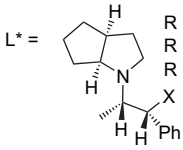




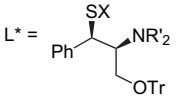
R = Ph: 81% ee = 44% (*R*)
R = Ts: 80% ee = 56% (*R*)
R = *o*-$MeOC_6H_4$: 87% ee = 64% (*R*)
R = 2-Naph: 49% ee = 56% (*R*)



R = Ph, X = SAc: 95% ee = 60% (*S*)
R = Ph, X = SH: 100% ee = 64% (*S*)
R = Ph, X = $S)_2$: 88% ee = 60% (*S*)



R = Ph, X = SAc: 100% ee = 90% (*R*)
R = Ph, X = SH: 100% ee = 90% (*R*)
R = Ph, X = $S)_2$: 92% ee = 86% (*R*)

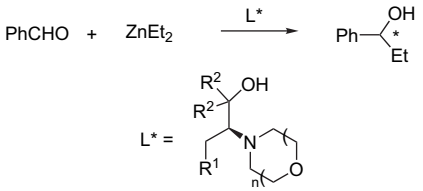


R = Ph, X = Ac, R' = *n*-Bu: 62% ee = 95% (*S*)
R = Ph, X = Ac, R',R' = $-(CH_2)_5$: 99% ee = 96% (*S*)
R = Ph, X = H, R',R' = $-(CH_2)_5$: 98% ee = 99% (*R*)
R = Ts, X = H, R',R' = $-(CH_2)_5$: 99% ee = 99% (*R*)
R = 3-MeC_6H_4, X = H, R',R' = $-(CH_2)_5$: 99% ee = 99% (*R*)
R = 1-Naph, X = H, R',R' = $-(CH_2)_5$: 99% ee = 98% (*R*)
R = *n*-Hept, X = H, R',R' = $-(CH_2)_5$: 99% ee = 66% (*R*)

Scheme 62. β-Amino thiol derivatives as ligands for addition of $ZnEt_2$ to aldehydes.

(*R*)-secondary alcohols in ees of up to 64%.[143] Martens et al. have reported the synthesis of other N/S-ligands with a rigid 2-azabicyclo[3.3.0]octane framework, which were tested for their general effectiveness as chiral catalysts in the reaction of benzaldehyde with $ZnEt_2$ (Scheme 62).[144] In addition, a high enantioselectivity (up to 99% ee) was obtained in the same conditions by Pericas et al., using a new family of amino thiols, the norephedrine thiols (Scheme 62).[145]

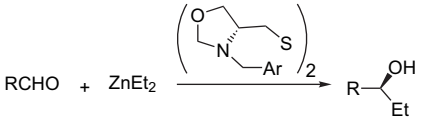
The enantioselectivity exerted by a series of new chiral sulfur-containing catalysts containing *N*,*O*-heterocycles, derived from natural chiral amino acids, has been checked in the addition of $ZnEt_2$ to benzaldehyde (Scheme 63).[146] Molecular mechanics calculations suggested that the production of the (*R*)-alcohol might be explained by a mechanism similar to that described by Noyori, in which $ZnEt_2$ interacts solely with the N–C–C–OH fragment, whereas the formation of the (*S*)-enantiomer needed the direct participation of the lateral chain of the parent amino acid and the *N*,*O*-heterocycle. In the same context, Reiser et al. have successfully used bis(oxazoline) ligands bearing a thioether group for the addition of $ZnEt_2$ to benzaldehyde.[121]



R^1 = *i*-PrS, R^2 = Et: 84% ee = 92% (*R*)
R^1 = *i*-PrS, R^2 = $(CH_2)_4$: 85% ee = 70% (*R*)
R^1 = $MeSCH_2$, R^2 = Et: 79% ee = 83% (*R*)
R^1 = $MeSCH_2$, R^2 = Ph: 94% ee = 91% (*S*)

Scheme 63. Sulfur-containing *N*,*O*-heterocycle ligands for addition of $ZnEt_2$ to benzaldehyde.

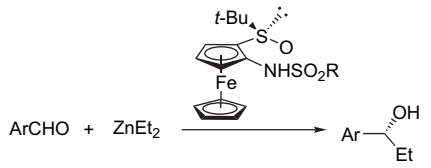
In 2001, Braga et al. reported the synthesis of new chiral C_2-symmetric oxazoline disulfide ligands from (*R*)-cysteine and successfully applied them as catalysts in the asymmetric addition of $ZnEt_2$ to various aldehydes (Scheme 64).[147]



R = Ar = Ph: 81% ee > 99%
R = *n*-Hex, Ar = Ph: 58% ee > 99%
R = Ph, Ar = Ts: 100% ee = 92%
R = *n*-Dec, Ar = Ts: 64% ee > 99%
R = Ph, Ar = *p*-$MeOC_6H_4$: 83% ee = 84%
R = *n*-Hex, Ar = *p*-$MeOC_6H_4$: 81% ee > 99%
R = *n*-Dec, Ar = *p*-$MeOC_6H_4$: 86% ee = 94%

Scheme 64. Oxazoline disulfide ligands for addition of $ZnEt_2$ to aldehydes.

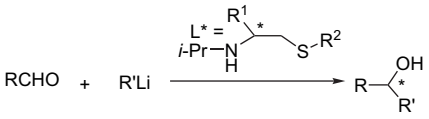
There are relatively few studies in the literature dealing with the use of sulfoxides as chiral ligands in this type of reaction. In this context, Carretero et al. demonstrated, in 2001, the utility of a new family of chiral ligands, 2-amino-substituted *tert*-butylsulfinylferrocenes, for the asymmetric addition of $ZnEt_2$ to aromatic aldehydes (Scheme 65).[148] In addition, Bonini et al. have shown that planar chiral sulfur-containing ferrocenyloxazoline carbinol ligands could also be used to catalyse the addition of $ZnEt_2$ to benzaldehyde with 46% ee.[149]



Ar = Ts, R = Ph: 80% ee = 88%
Ar = *p*-$MeOC_6H_4$, R = Ph: 76% ee = 86%
Ar = Ts, R = *p*-$MeOC_6H_4$: 65% ee = 66%
Ar = Ts, R = *p*-$MeO_2CC_6H_4$: 71% ee = 88%
Ar = Ts, R = 2-Naph: 73% ee = 82%
Ar = Ts, R = *m*-FC_6H_4: 76% ee = 80%
Ar = *p*-$MeOC_6H_4$, R = Ts: 72% ee = 66%
Ar = *p*-$MeOC_6H_4$, R = *p*-$MeO_2CC_6H_4$: 78% ee = 96%
Ar = *p*-$MeOC_6H_4$, R = 2-Naph: 79% ee = 92%
Ar = *p*-$MeOC_6H_4$, R = *m*-FC_6H_4: 74% ee = 72%

Scheme 65. 2-Amino-substituted *tert*-butylsulfinylferrocene ligands for addition of $ZnEt_2$ to aromatic aldehydes.

A second class of organometallic derivatives, alkyllithium reagents, has been condensed onto aldehydes in the presence of chiral sulfur-containing ligands. Hence, six chiral amino sulfides have been synthesised by Hilmersson et al. from the amino acids, phenylalanine, phenylglycine and valine. These amino sulfides were used as chiral ligands in the asymmetric addition of *n*-butyllithium and methyllithium to various aldehydes. The highest stereoselectivities were obtained with benzaldehyde, giving rise to 1-phenyl-1-pentanol and 1-phenyl-1-ethanol in >98 and 95% ee, respectively (Scheme 66).[150]

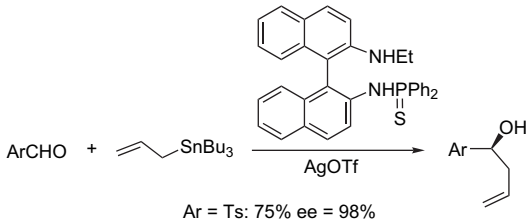


(*R*)-L*, R = R^1 = R^2 = Ph, R' = *n*-Bu: 82% ee > 98% (*S*)
(*S*)-L*, R = R^1 = Ph, R^2 = Et, R' = *n*-Bu: 84% ee = 94% (*R*)
(*S*)-L*, R = R^2 = Ph, R^1 = R' = *n*-Bu: 87% ee = 68% (*R*)
(*S*)-L*, R = Ph, R^1 = R' = *n*-Bu, R^2 = Et: 92% ee = 81% (*R*)
(*S*)-L*, R = R^2 = Ph, R^1 = *i*-Pr, R' = *n*-Bu, R^2 = Et: 80% ee = 97% (*R*)
(*R*)-L*, R = R^1 = R^2 = Ph, R' = Me: 67% ee = 95% (*S*)
(*S*)-L*, R = R^1 = R^2 = Ph, R' = *n*-Bu: 79% ee = 90% (*R*)
(*S*)-L*, R = Ts, R^1 = *n*-Bn, R^2 = Ph, R' = Me: 69% ee = 91% (*R*)

Scheme 66. Chiral amino sulfide ligands for addition of alkyllithium reagents to aldehydes.

An extension of the asymmetric condensation of organometallics onto aldehydes is the enantioselective Ag-promoted allylation reaction of aldehydes with allyltributyltin, which has recently been performed by Shi et al. in the presence of chiral diphenylthiophosphoramide ligands and more efficiently, with binaphthylthiophosphoramide ligands.[151] According to the nature of the ligand substituents, the corresponding allylation products were obtained in up to 98% ee, as depicted in Scheme 67.

The immobilisation of organic compounds on highly porous SiO_2 instead of organic polymers for solid-phase synthesis and catalysis has several advantages such as rigidity of the structure, the fact that it does not swell in solvents, and the stability at low and high temperature and pressure. In



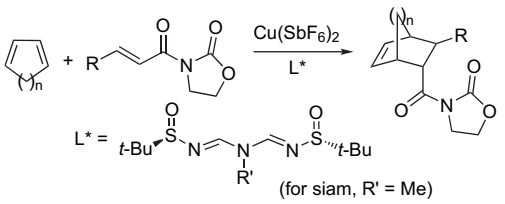
Ar = Ts: 75% ee = 98%
Ar = *p*-ClC_6H_4: 74% ee = 96%
Ar = *p*-$MeOC_6H_4$: 56% ee = 80%
Ar = (*E*)-PhCH=CH: 80% ee = 68%
Ar = Ph: 84% ee = 94%

Scheme 67. Ag-promoted allylation of aldehydes with a binaphthylthiophosphoramide ligand.

2000, Heckel and Seebach succeeded in grafting a TADDOL sulfur-containing derivative onto a commercially available controlled-pore glass, and then loaded the TADDOL moieties with titanates. The resulting material was tested in the enantioselective addition of $ZnEt_2$ to benzaldehyde, giving a quantitative yield and 98% ee.[152]

7. Diels–Alder reactions

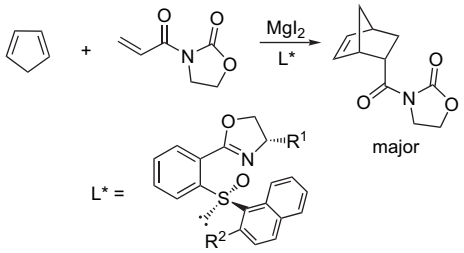
The Diels–Alder reaction is one of the rare C–C bond-forming reactions that permit the rapid development of molecular complexity.[153] It allows the stereoselective formation of as many as four stereogenic centres, and as many as three carbocyclic rings in the intramolecular and transannular variations. For this reason, the recent development of highly enantioselective catalytic Diels–Alder reactions[154] represents a great advance in synthetic chemistry. A large number of metals, ligands and dienophiles have been studied. Although chiral auxiliary-based reactions retain a position of central importance, catalytic variants are developing rapidly. Until recently, most of the successful catalysts contained chelating oxygen ligands, but more recent success was obtained using diphosphine ligands such as BINAP, chiral N-containing ligands such as oxazoline ligands,[155] and chiral S-containing ligands. The most active chiral catalysts used till date employing a chiral sulfur atom as a unique source of chirality were reported very recently by Ellman's group.[156] Hence, a novel bis(sulfinyl)imidoamidine (siam) ligand, readily available, was proved to catalyse, in the presence of $Cu(SbF_6)_2$, the Diels–Alder reaction of a variety of dienophiles with exceptional levels of enantio- and diastereoselectivity (Scheme 68). Furthermore, the Cu(II)–siam complex was shown by X-ray analysis to exhibit a unique mode of binding, self assembling to form a rarely observed M_2L_4 quadruple-stranded helicate. Additionally, while the siam ligand could coordinate to the metal through the N-, S- and O-atoms, it was shown that, both in the crystalline state and in CH_2Cl_2 solution, the ligand was O-coordinated to the Cu. In 2003, the scope of this reaction was extended to the use of relatively unreactive acyclic dienes such as 2-methylbutadiene or 2,3-dimethylbutadiene, which gave 93 and 92% ees, respectively, by reaction with *N*-acryloyloxazolidinone.[157] The selectivity of the catalyst system was, however, sensitive to the size of the substituents on the 2-position of the diene. As an example, while the reactivity (87% yield) was maintained for 2-phenylbutadiene, the selectivity was poor (45% ee).



R = H, R' = Me, n = 1: 96% de > 98% ee > 98%
R = Me, R' = Me, n = 1: 76% de = 96% ee = 97%
R = Ph, R' = Me, n = 1: 58% de = 90% ee = 94%
R = CO_2Et, R' = Me, n = 1: 85% de = 94% ee = 96%
R = H, R' = Me, n = 2: 50% de = 96% ee = 90%
R = H, R' = *i*-Bu, n = 1: de = 98% ee = 97%
R = H, R' = Ph, n = 1: de = 98% ee = 96%
R = H, R' = CH_2CF_3, n = 1: de = 98% ee = 98%

Scheme 68. Cu-catalysed Diels–Alder reaction with siam ligand.

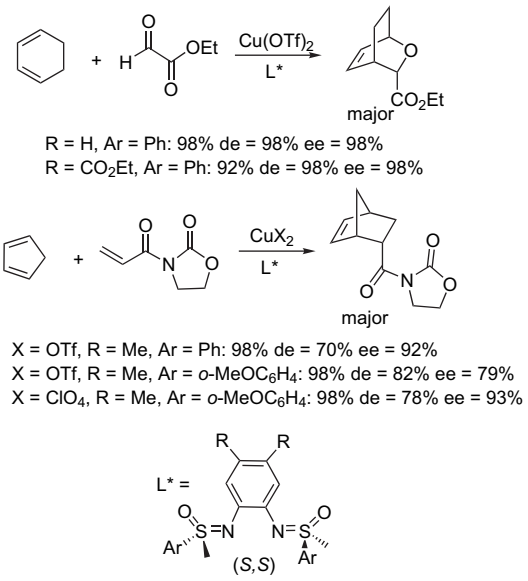
Relatively few chiral sulfoxide ligands have been useful for catalytic asymmetric Diels–Alder reactions. As an example, Hiroi et al. have developed new ligands bearing a chiral sulfinyl function and a 1,3-oxazoline ring with an asymmetric carbon centre, in which the chiral sulfinyl group has been revealed to play a crucial role in achieving a high enantioselectivity in asymmetric Diels–Alder reactions (Scheme 69).[158] The best results were obtained using MgI_2 as the Lewis acid catalyst. A study of the mechanistic pathway showed that, for the first time, seven-membered chelates of sulfoxide-magnesium complexes (normally six-membered chelates were formed in previous oxazoline ligands) were involved, indicating particularly, the potential advantage of the chirality of the sulfoxide functionality for achieving a high enantioselectivity. The scope of the reaction was extended to the use of other similar ligands such as chiral 2-(arylsulfinylmethyl)-1,3-oxazoline derivatives, giving, in the same conditions, a relatively low enantioselectivity (≤32% ees). Nevertheless, when copper complexes were used to catalyse the reaction, a better, but still moderate, enantioselectivity was observed (≤66% ees).[159] Moreover, the introduction of a counterion (triflate or hexafluoroantimonate) into the copper catalysts represented a higher degree of asymmetric induction (≤75% ees).[160]



R^1 = Ph, R^2 = OMe: 83% de = 88% ee = 50% (*S*)
R^1 = *t*-Bu, R^2 = OMe: 90% de = 94% ee = 81% (*S*)
R^1 = $C(Me)_2OMe$, R^2 = OMe: 90% de = 88% ee = 92% (*S*)

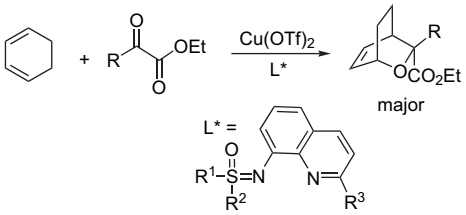
Scheme 69. Mg-catalysed Diels–Alder reaction with sulfoxide-oxazoline ligands.

The enantioselective (hetero) Diels–Alder reaction has been extensively studied recently by Bolm et al. using chiral mono- or bis-sulfoximine ligands.[161,74b] Bis-sulfoximine ligands have proved to be highly efficient in Cu(II)-catalysed Diels–Alder and hetero-Diels–Alder reactions, where products with up to 99% ees were obtained (Scheme 70).[162]



Scheme 70. Cu-catalysed (hetero) Diels–Alder reactions with C_2-symmetric bis-sulfoximine ligands.

In order to ascertain whether the C_2-symmetry of the efficient bis-sulfoximine ligands was really essential, or if C_1-symmetric monosulfoximine derivatives could also be applied in asymmetric hetero-Diels–Alder reactions and lead to high enantioselectivities, the same group has developed the synthesis of various sulfoximines, in which the second donor atom was a quinolyl nitrogen.[163] The use of these novel ligands in the copper-catalysed hetero-Diels–Alder reaction between 1,3-cyclohexadiene and ethyl glyoxylate or diethyl ketomalonate led to the corresponding cycloadducts in good yield and with up to 96% ee (Scheme 71).

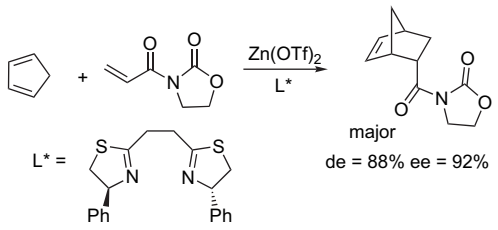


(*R*)-L*, R^1 = Me, R^2 = Ph, R = R^3 = H: 97% de = 94% ee = 75%
(*R*)-L*, R = CO_2Et, R^1 = Me, R^2 = Ph, R^3 = H: 80% de = 96% ee = 91%
(*R*)-L*, R^1 = Me, R^2 = *o*-$MeOC_6H_4$, R = R^3 = H: 98% de = 96% ee = 91%
(*R*)-L*, R = CO_2Et, R^1 = Me, R^2 = *o*-$MeOC_6H_4$, R^3 = H: 86% ee = 89%
(*R*)-L*, R^1 = *n*-Pent, R^2 = *o*-$MeOC_6H_4$, R = R^3 = H: 93% de = 94% ee = 86%
(*S*)-L*, R^1 = Me, R^2 = *o*-$MeOC_6H_4$, R = R^3 = H: 88% de = 96% ee = 91%

Scheme 71. Cu-catalysed hetero-Diels–Alder reaction with C_1-symmetric monosulfoximine ligands.

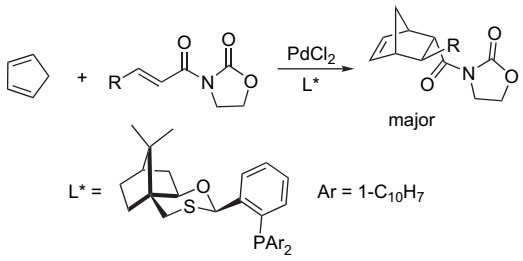
In 2005, another class of chiral ligands, bis-thiazoline derivatives, were prepared by Nishio et al. from chiral bis-(*N*-acylamino alcohols) with Lawesson's reagent.[164] These new compounds have proved to be useful chiral ligands for the Zn-catalysed Diels–Alder reaction of 3-acryloyloxazolidine-2-one with cyclopentadiene, giving the corresponding cycloadducts as a 94:6 diastereomeric mixture, where the major diastereomer was formed with 92% ee (Scheme 72).

On the other hand, chiral cationic palladium-phosphinooxathiane complexes have been found to be efficient catalysts



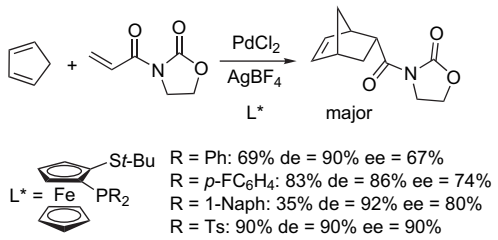
Scheme 72. Zn-catalysed Diels–Alder reaction with a bis-thiazoline ligand.

for the enantioselective Diels–Alder reaction of cyclopentadiene with acryloyl- and fumaroyl-1,3-oxazolidin-2-ones, giving the corresponding cycloadducts in good yield and high enantioselectivity of up to 93% ee (Scheme 73).[165] This result was the first example using an S/P-type phosphinooxathiane ligand for the enantioselective Diels–Alder reaction.



Scheme 73. Pd-catalysed Diels–Alder reaction with phosphinooxathiane ligands.

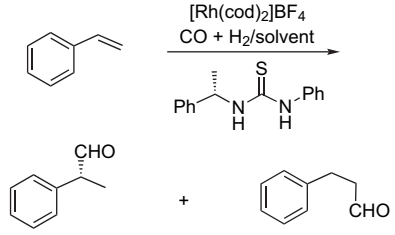
In 2005, Carretero et al. reported a second example of chiral catalysts based on P/S-coordination employed in the catalysis of the enantioselective Diels–Alder reaction, namely palladium complexes of chiral planar 1-phosphino-2-sulfenylferrocenes (Fesulfos).[166] This new family of chiral ligands afforded, in the presence of $PdCl_2$, high enantioselectivities of up to 95% ee, in the asymmetric Diels–Alder reaction of cyclopentadiene with *N*-acryloyl-1,3-oxazolidin-2-one (Scheme 74). The P/S-bidentate character of the Fesulfos ligands has been proved by X-ray diffraction analysis of several metal complexes. In addition, the same group has used copper complexes of these ligands as efficient catalysts for enantioselective aza-Diels–Alder reactions of *N*-sulfonyl imines with Danishefsky's dienes, providing, in some cases, enantiopure products (>99% ees).[167]



Scheme 74. Pd-catalysed Diels–Alder reaction with Fesulfos ligands.

8. Miscellaneous

Hydroformylation is one of the most studied reactions in homogeneous catalysis.[168] The regio- and enantioselective syntheses of optically pure branched aldehydes, in the case of functionalised olefins, are important challenges for this reaction. Cobalt was the first metal used in asymmetric hydroformylation, and rhodium was rapidly studied afterwards in the presence of chiral phosphines. On the other hand, ruthenium, iridium and palladium were also involved in this reaction, but, $Pt/SnCl_2$ and rhodium catalysts are currently the most promising asymmetric systems. The first report on the use of chiral sulfur ligands in rhodium-catalysed asymmetric hydroformylation appeared in 1993.[169] In 2000, the same group reported the synthesis of novel chiral P/S-ligands with a xylofuranose backbone.[91] These thioether-phosphite ligands derived from carbohydrates were investigated for the rhodium-catalysed hydroformylation of styrene, but in spite of good conversions (>99%) and excellent regioselectivities in 2-phenylpropanal (94%), ees close to 0% were found for all ligands. Rhodium complexes of (*R*,*R*)-1-benzyl-3,4-dithioether-pyrrolidines were also prepared by these workers, who investigated them as catalysts in the hydroformylation of styrene, but, in all experiments, the ee was lower than 3%, whereas the chemoselectivity was 97%.[170] Better results were obtained by Bonnet et al. in 2000 with the use of readily available chiral thioureas as new ligands in the asymmetric rhodium-catalysed hydroformylation of styrene.[171] In general, conversion of styrene and ees was modest, but, when the reaction was carried out in heptane as the solvent, an ee value of up to 41% was obtained (Scheme 75).

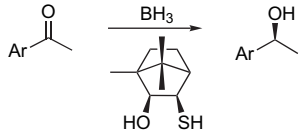


solvent = toluene: 98% b:n = 91:9 ee = 24%
solvent = heptane: 92% b:n = 93:7 ee = 41%

Scheme 75. Rh-catalysed hydroformylation of styrene with a thiourea ligand.

Asymmetric borane reduction has attracted much attention owing to its usefulness in preparing optically active secondary alcohols.[172] Several chiral catalysts have been involved in this reaction such as [(1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol)] (MerCO), which produced, when applied to aryl methyl ketones, the corresponding 1-aryl ethyl alcohols in ees of up to 92% (Scheme 76).[173] The formation of a transitional chiral ligand–borane–ketone complex was postulated as essential for the stereoselective reduction. In 2001, this ligand was reacted with nickel boride in order to form a heterogeneous Ni-supported oxathiaborolidine, which was further investigated in the borane reduction of acetophenone, affording moderate enantioselectivity (≤24% ee).[174]

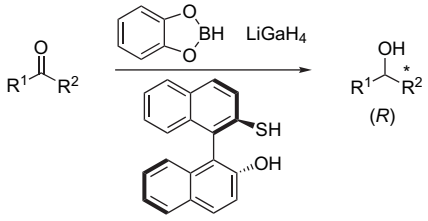
In 2000, Woodward et al. reported that $LiGaH_4$, in combination with the S/O-chelate, 2-hydroxy-2′-mercapto-1,1′-



Ar = Ph: 96% ee = 87%
Ar = 2-Naph: 92% ee = 75%
Ar = *p*-$MeOC_6H_4$: 88% ee = 70%
Ar = *p*-ClC_6H_4: 90% ee = 80%
Ar = *p*-$NO_2C_6H_4$: 94% ee = 92%
Ar = 1-Naph: 98% ee = 64%

Scheme 76. Borane reduction of aryl methyl ketones with MerCO ligand.

binaphthyl ($MTBH_2$), formed an active catalyst for the asymmetric reduction of prochiral ketones, with catecholborane as the hydride source (Scheme 77).[175] The enantioface differentiation was on the basis of the steric requirements of the ketone substituents. Aryl *n*-alkyl ketones were reduced in 90–93% ees, whereas alkyl methyl ketones (e.g., *i*-Pr, *c*-C_6H_{11}, *t*-Bu) gave 60–72% ees.

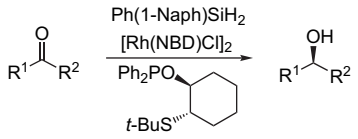


R^1 = Ph, R^2 = Me: 90% ee = 90%
R^1 = Ph, R^2 = Et: 96% ee = 93%
R^1 = Ph, R^2 = *n*-Bu: 80% ee = 92%
R^1 = Ph, R^2 = *i*-Pr: 65% ee = 24%
R^1 = Ph, R^2 = *i*-Bu: 65% ee = 92%
R^1 = *p*-BrC_6H_4, R^2 = Me: 80% ee = 87%
R^1 = Ts, R^2 = Me: 95% ee = 87%
R^1 = Ph, R^2 = CH_2Br: 60% ee = 70%
R^1 = 2-Fur, R^2 = *n*-Hex: 76% ee = 81%
R^1 = 2-$C_{10}H_7$, R^2 = Me: 83% ee = 73%
R^1 = *i*-Pr, R^2 = Me: 81% ee = 69%
R^1 = *i*-Bu, R^2 = Me: 93% ee = 46%
R^1 = *c*-Hex, R^2 = Me: 72% ee = 72%
R^1 = *t*-Bu, R^2 = Me: 76% ee = 79%

Scheme 77. Ga-catalysed borane reduction of ketones with $MTBH_2$ ligand.

The asymmetric catalytic hydrosilylation of ketones or alkenes with organosilanes is a versatile method, providing optically active compounds such as alcohols and alkanes.[176] Asymmetric hydrosilylation has been an active field of research in the last 20 years.[177] The most studied reaction has probably been the hydrosilylation of acetophenone to yield the corresponding silyl ether, which, when hydrolysed, gives the enantiomerically enriched 1-phenylethanol. In 2003, Evans et al. studied the application of new chiral mixed P/S-ligands to enantioselective rhodium-catalysed ketone hydrosilylation processes.[89] For a wide variety of ketones such as aryl alkyl, dialkyl, as well as cyclic aryl alkyl ketones, and also cyclic ketoesters, the reaction gave high levels of enantioselectivity (Scheme 78).

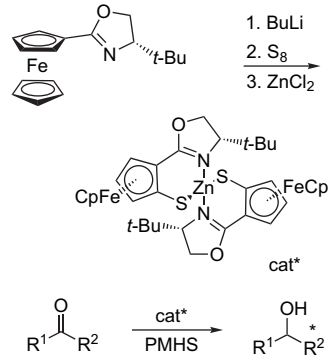
In 2005, Riant et al. reported the synthesis of a new air-stable N/S-chelating zinc catalyst, depicted in Scheme 79, which was fully characterised by all spectroscopic methods. This



R^1 = Ph, R^2 = Me: 80% ee = 95%
R^1 = *o*-Tol, R^2 = Me: 98% ee = 95%
R^1 = Ts, R^2 = Me: 90% ee = 92%
R^1 = *o*-$MeOC_6H_4$, R^2 = Me: 90% ee = 95%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me: 56% ee = 88%
R^1 = *o*-ClC_6H_4, R^2 = Me: 90% ee = 98%
R^1 = *p*-ClC_6H_4, R^2 = Me: 95% ee = 85%
R^1 = 1-Naph, R^2 = Me: 99% ee = 98%
R^1 = 2-Naph, R^2 = Me: 99% ee = 95%
R^1 = Ph, R^2 = Et: 95% ee = 94%
R^1 = Ph, R^2 = *i*-Bu: 95% ee = 94%
R^1 = Ph, R^2 = Bn: 75% ee = 94%
R^1 = *c*-Hex, R^2 = Me: 90% ee = 92%
R^1 = *t*-Bu, R^2 = Me: 85% ee = 91%
R^1 = Me, R^2 = $(Me)_2CCO_2Me$: 94% ee = 99%

Scheme 78. Rh-catalysed hydrosilylation of ketones with a thioether-phosphinite ligand.

complex, prepared from the corresponding ferrocene oxazoline, was applied to the enantioselective reduction of ketones in the presence of polymethylhydrosiloxane, PMHS, providing modest enantioselectivities.[178] The absolute configuration of the major product was not specified.

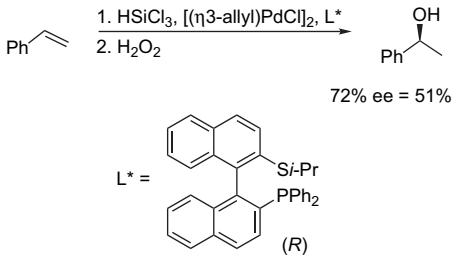


R^1 = Ph, R^2 = Me: 100% ee = 51%
R^1 = C_6H_{10}, R^2 = Me: 6% ee = 42%
R^1 = α-tetralonyl, R^2 = Me: 100% ee = 55%
R^1 = *p*-ClC_6H_4, R^2 = Me: 100% ee = 45%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me: 100% ee = 41%

Scheme 79. Zn-catalysed hydrosilylation of ketones with an N/S-chelating zinc catalyst.

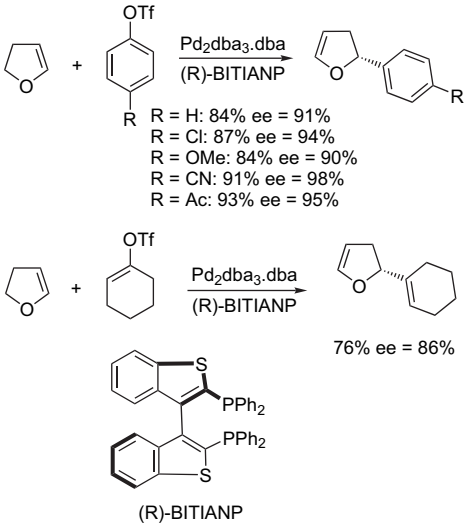
On the other hand, the hydrosilylation of alkenes such as styrene was studied by Gladiali in the presence of palladium complexes and chiral P/S-heterodonor ligands, having a binaphthalene backbone (Scheme 80).[44]

There are many examples of the use of the Heck reaction in organic syntheses.[179] Compared with other transition-metal-catalysed reactions, however, the effect of the ligands has been less investigated.[180] Numerous enantioselective variants of this reaction have been reported.[181] This reaction is, however, often limited by low activity with certain classes of substrates, and also by the formation of byproducts. There is thus a need for the design of new ligands to widen the scope



Scheme 80. Pd-catalysed hydrosilylation of styrene with P/S-heterodonor ligand BINAPS.

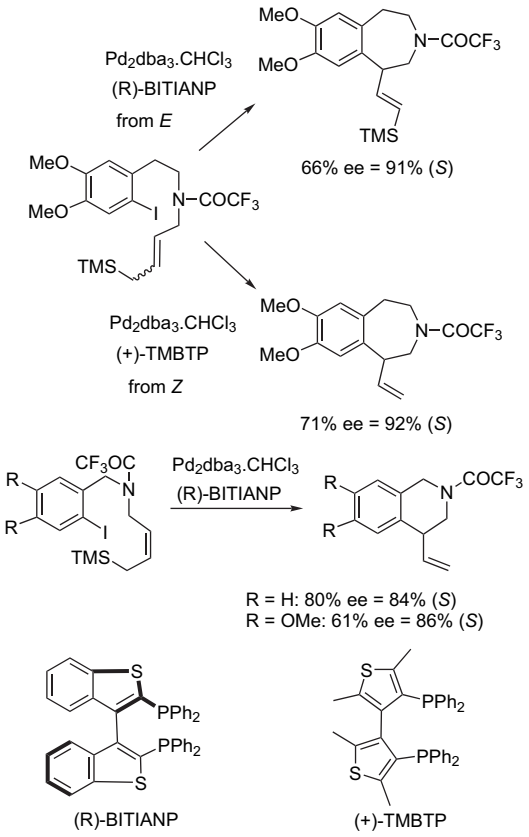
and applications of enantioselective Heck reactions. Only one example in the recent literature deals with the enantioselective Heck reaction using sulfur-containing ligands. Hence, Tietze et al. have developed a new chiral ligand, (*R*)-(+)-2,2′-bis(diphenylphosphino)-3,3′-bi(benzo[*b*]thiophene), (*R*)-BITIANP, which was successfully used in the enantioselective Heck reaction of dihydrofuran with aryl triflates and an alkenyl triflate, providing the corresponding 2-substituted-2,3-dihydrofurans, with complete regioselectivity, high enantioselectivity (86–96% ees) and good yields (76–93%) (Scheme 81).[182]



Scheme 81. Heck reactions of dihydrofuran with aryl or alkenyl triflates with (*R*)-BITIANP as the ligand.

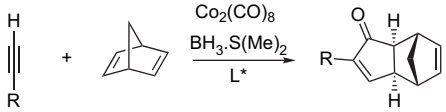
In order to develop an asymmetric synthesis of tetrahydroisoquinolines, Tietze et al. applied these latter conditions to the intramolecular silane-terminated Heck reaction of a few functionalised aryl iodides, obtaining excellent yields and enantioselectivities (Scheme 82).[183] A similar reaction was performed in the presence of another very efficient new chiral P/S-ligand, (+)-4,4′-bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene, (+)-TMBTP, which allowed the synthesis of a benzazepine with excellent yield and enantioselectivity (Scheme 82).

In the past two decades, the Pauson–Khand reaction has attracted much attention from the synthetic chemistry community.[184] Although some progress has been achieved lately on the way to convert the intramolecular Pauson–Khand reaction into a catalytic enantioselective process, the intermolecular version of this process has been omitted from most of

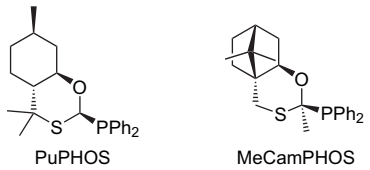


Scheme 82. Synthesis of tetrahydroisoquinolines and a benzazepine by intramolecular silane-terminated Heck reactions with (*R*)-BITIANP or (+)-TMBTP ligands.

these advances. In this context, an efficient asymmetric version of the intermolecular Pauson–Khand reaction of alkynes with norbornadiene was recently reported by Verdaguer et al. using pulegone-derived P/S-chiral ligands, PuPHOS and MeCamPHOS (Scheme 83).[185] This new type of ligands illustrated a significant diastereoselectivity in their coordination to the prochiral dicobalt complex by thermodynamic equilibration, an increased reactivity with respect to normal phosphine-coordinated alkyne-dicobalt complexes, and an efficient stereocontrol by directing the reaction to the cobalt atom where sulfur was coordinated.

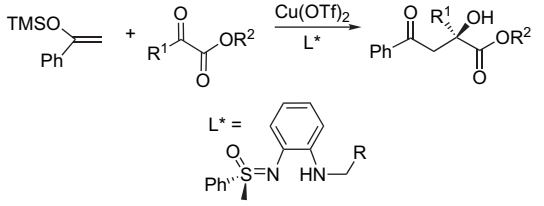


R = Ph, L* = PuPHOS: 99% ee = 99%
R = TMS, L* = PuPHOS: 93% ee = 97%
R = C(Me)$_2$OH, L* = PuPHOS: 98% ee = 70%
R = Ph, L* = MeCamPHOS: 93% ee = 97%
R = TMS, L* = PuPHOS: 72% ee = 79%
R = C(Me)$_2$OH, L* = PuPHOS: 90% ee = 50%
R = *t*-Bu, L* = PuPHOS: 80% ee = 40%

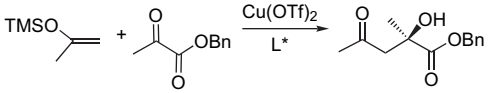


Scheme 83. Intermolecular Pauson–Khand reaction with PuPHOS or MeCamPHOS ligands.

Chiral sulfur-containing ligands have also been involved in other reactions such as copper-catalysed enantioselective Mukaiyama-type aldol reactions. As an example, Langner and Bolm described in 2004 the synthesis of new chiral C_1-symmetric benzene-bridged aminosulfoximines, which were capable of serving as efficient ligands in the Mukaiyama-type aldol reaction between 1-phenyl-1-(trimethylsilyloxy)-ethane and a pyruvate derivative.[186] The corresponding aldol products with quaternary centres, which are commonly difficult to prepare in enantiomerically enriched form, have been obtained with up to 99% ee in high yields (Scheme 84). The scope of the reaction was extended to the use of another enolsilane, 1-methyl-1-(trimethylsilyloxy)ethane, affording the corresponding product with a similar efficiency.



R = Ph, R^1 = R^2 = Me: 64% ee = 70%
R = 1-Naph, R^1 = R^2 = Me: 77% ee = 83%
R = 2-MeOC$_6$H$_4$, R^1 = R^2 = Me: 72% ee = 86%
R = Mes, R^1 = R^2 = Me: 88% ee = 93%
R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R^1 = R^2 = Me: > 99% ee = 93%
R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R^1 = Me, R^2 = Bn: 86% ee = 98%
R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R^1 = Me, R^2 = *i*-Pr: 90% ee = 99%
R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R^1 = Et, R^2 = Me: 78% ee = 89%
R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$, R^1 = CH$_2$Bn, R^2 = Et: 86% ee = 96%



R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$: 71% ee = 91%

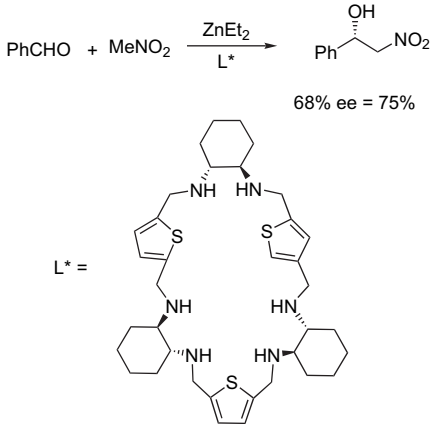
Scheme 84. Cu-catalysed Mukaiyama-type aldol reactions with C_1-symmetric benzene-bridged aminosulfoximine ligands.

In 2003, an asymmetric Henry (nitroaldol) reaction was developed using Zn(II) complexes of new chiral hydrophobic macrocyclic ligands, containing chiral diamino and thiophene moieties synthesised by the Schiff-base condensation approach (Scheme 85).[187] The reaction between benzaldehyde and nitromethane was performed in the presence of the trimeric catalyst, which was preformed from 3 equiv of $ZnEt_2$ and 1 equiv of the chiral ligand.

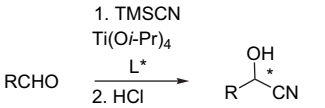
A catalytic asymmetric version of the cyanohydrin synthesis was reported in 2003 by Rowlands using chiral sulfoxide-containing titanium-oxazoline complexes, providing the corresponding enantiomerically enriched cyanohydrins (Scheme 86).[188]

In 2004, Shibasaki et al. achieved the first catalytic enantioselective Reissert reaction of pyridine derivatives through the development of new Lewis acid (Et_2AlCl)–Lewis base chiral S/O-catalysts (Scheme 87).[189] Both sulfoxides and phosphine sulfides have played the role of efficient Lewis bases, providing high regio- and enantioselectivity.

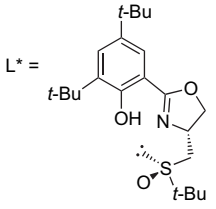
Free radical reactions have received renewed interest because of relatively recent discoveries demonstrating that



Scheme 85. Zn-catalysed Henry reaction with N/S-macrocyclic ligands.



R = Ph: 95% ee = 60% (*R*)
R = *p*-MeOC$_6$H$_4$: 80% ee = 57% (*R*)
R = 3,5-(MeO)$_2$C$_6$H$_3$: 72% ee = 61% (*R*)
R = 2-Naph: 80% ee = 40% (*R*)
R = (*E*)-PhCH=CH: 78% ee = 50% (*R*)
R = Hept: 62% ee = 37% (*S*)
R = *t*-Bu: 26% ee = 40% (*R*)
R = *i*-Pr: 87% ee = 37% (*S*)

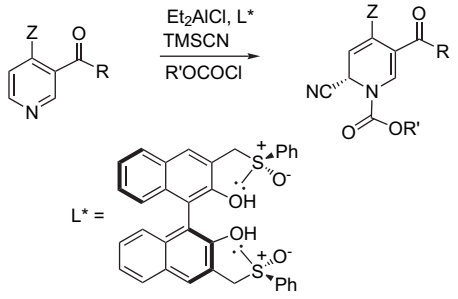


Scheme 86. Ti-catalysed cyanohydrin synthesis with a sulfoxide ligand.

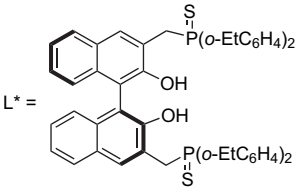
the stereochemistry of these transformations can be controlled.[190] Relatively few reports have been published to date concerning radical C–C bond-forming reactions performed in the presence of chiral ligands. In 2000, Hiroi and Ishii reported the first example of asymmetric synthesis via radicals using chiral sulfoxides as chiral ligands.[191] Hence, asymmetric induction was observed in the intermolecular radical C–C bond-forming reactions of *N*-arylsulfonyl-α-bromocarboxamides using chiral sulfoxides in the presence of a Lewis acid such as Mg(OTf)$_2$ (Scheme 88). The intramolecular version of these radical reactions was investigated, but gave, however, much lower enantioselectivities (≤5% ee).

The first use of chiral sulfoxides as Lewis base catalysts in the allylation of aldehydes with allyltrichlorosilane was reported in 2003. The formation of the corresponding homoallylic alcohols could be obtained in satisfactory yields and with moderate enantioselectivity (Scheme 89).[192]

Moreover, Kobayashi et al. have introduced chiral sulfoxides into the reactions of *N*-acylhydrazones with allyltrichlorosilanes as highly efficient neutral coordinating-organocatalysts (Scheme 90).[193] The corresponding chiral homoallylic amine derivatives were prepared in these conditions with high enantioselectivity. The scope of the reaction

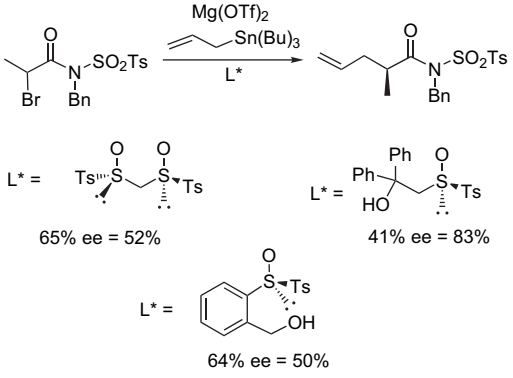


R = NMe$_2$, Z = H, R' = Me: 98% ee = 91%
R = NMe$_2$, Z = H, R' = Fm: 89% ee = 93%
R = N(*i*-Pr)$_2$, Z = H, R' = Me: 98% ee = 96%
R = N(*i*-Pr)$_2$, Z = H, R' = *n*-Pent: 98% ee = 93%
R = OMe, Z = H, R' = Fm: 85% ee = 57%

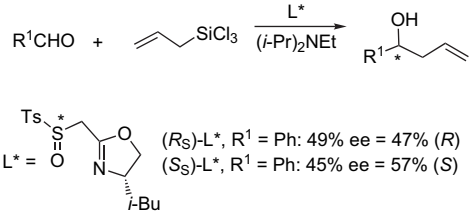


R = N(*i*-Pr)$_2$, Z = Cl, R' = *n*-Pent: 92% ee = 91%
R = N(*i*-Pr)$_2$, Z = Br, R' = *n*-Pent: 89% ee = 86%

Scheme 87. Al-catalysed Reissert reaction of pyridine derivatives with S/O-ligands.



Scheme 88. Radical C–C bond-forming reactions of sulfonamides with sulfoxide ligands.



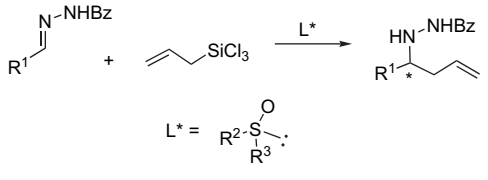
(*R*$_S$)-L*, R^1 = Ph: 49% ee = 47% (*R*)
(*S*$_S$)-L*, R^1 = Ph: 45% ee = 57% (*S*)

L* = Ts, O

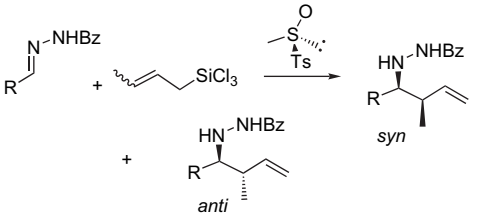
R^1 = Ph: 62% ee = 55% (*S*)
R^1 = 2-Fur: 88% ee = 42% (*S*)
R^1 = (*E*)-PhCH=CH: 79% ee = 46% (*S*)

Scheme 89. Allylation of aldehydes with allyltrichlorosilane promoted by sulfoxides.

was extended to asymmetric crotylations with (*Z*)- and (*E*)-crotyltrichlorosilanes, which proved to be highly stereospecific, since the (*E*)-crotylsilane afforded the corresponding *syn*-adducts, whereas the (*Z*)-crotylsilane led to the corresponding *anti*-adducts with excellent diastereoselectivity and good to high enantioselectivity.



(*R*)-L*, R^1 = CH_2Bn, R^2 = Me, R^3 = Ts: 73% ee = 93% (*R*)
(*R*)-L*, R^1 = CH_2Bn, R^2 = Et, R^3 = Ts: 77% ee = 50% (*R*)
(*S*)-L*, R^1 = CH_2Bn, R^2 = *o*-$MeOC_6H_4$, R^3 = Me: 79% ee = 42% (*S*)
(*S*)-L*, R^1 = CH_2Bn, R^2 = *p*-$MeOC_6H_4$, R^3 = Me: 91% ee = 69% (*S*)
(*R*)-L*, R^1 = R^2 = Me, R^3 = Ts: 78% ee = 90% (*R*)
(*R*)-L*, R^1 = *n*-Hept, R^2 = Me, R^3 = Ts: 81% ee = 88% (*R*)
(*R*)-L*, R^1 = *i*-Pr, R^2 = Me, R^3 = Ts: 80% ee = 98% (*R*)
(*R*)-L*, R^1 = *c*-Hex, R^2 = Me, R^3 = Ts: 77% ee = 91% (*R*)
(*R*)-L*, R^1 = *p*-$MeOC_6H_4$, R^2 = Me, R^3 = Ts: 82% ee = 81% (*S*)
(*R*)-L*, R^1 = *p*-ClC_6H_4, R^2 = Me, R^3 = Ts: 69% ee = 89% (*S*)



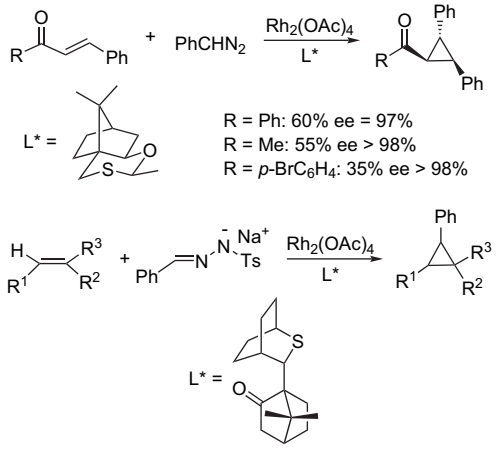
R = CH_2Bn, (*Z*)-silane: *syn* <1% + *anti* > 99% (ee = 91%)
R = CH_2Bn, (*E*)-silane: *syn* = 99% (ee = 89%) + *anti* = 1%
R = Me, (*Z*)-silane: *syn* <1% + *anti* > 99% (ee = 73%)
R = Me, (*E*)-silane: *syn* = 98% (ee = 82%) + *anti* = 2%
R = *n*-Hept, (*Z*)-silane: *syn* <1% + *anti* > 99% (ee = 86%)
R = *n*-Hept, (*E*)-silane: *syn* = 95% (ee = 91%) + *anti* = 5%

Scheme 90. Allylation of *N*-acylhydrazones with allyltrichlorosilanes promoted by sulfoxides.

With the aim of discovering novel chiral oxomolybdenum catalysts able to perform enantioselective alkene epoxidations, Kühn et al. have reported the exploration of the catalytic behaviour of a series of dioxomolybdenum(VI) complexes with chiral *cis*-8-phenylthiomenthol ligands derived from (+)-pulegone.[194] The epoxidation of *cis*-β-methylstyrene using *tert*-butylhydroperoxide as the oxidant, however, did not produce significant optical induction in these conditions.

The enantioselective synthesis of compounds containing the cyclopropyl fragment has recently received considerable attention, largely because of the frequent occurrence of cyclopropanes in natural products and their importance as valuable synthetic intermediates. Although, many methods have been developed, the transition-metal-catalysed asymmetric cyclopropanation has emerged as one of the most efficient routes for the formation of chiral cyclopropanes.[195] Chiral sulfides have been used as the chiral ligands in these processes. As an example, the chiral 1,3-oxathiane derived from camphorsulfonyl chloride mediated the rhodium-catalysed asymmetric cyclopropanation of electron-deficient alkenes with phenyldiazomethane, furnishing the corresponding cyclopropanes in good yields and very high ees (>97%) (Scheme 91).[196]

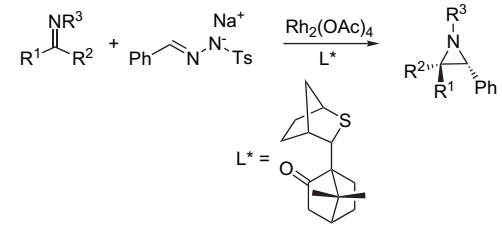
The application of these conditions to ethyl diazoacetate (EDA) was, however, unsuccessful. Moreover, the process could not be easily scaled up, and the sulfide could not be fully recovered. In order to solve these problems, these authors have developed a second process, involving the in situ generation of the diazo compound, together with the use of another class of chiral [2.2.2] bicyclic sulfides, depicted in Scheme 91.[197] In these conditions, the process could be generalised to a broad range of electron-deficient alkenes, providing high enantioselectivity with all alkenes, and the sulfide could be recovered in quantitative yield.



R^1 = Ph, R^2 = H, R^3 = Bz: 73% *trans:cis* = 4:1 ee = 91% (1*R*,1*R*)
R^1 = Me, R^2 = H, R^3 = Bz: 50% *trans:cis* = 4:1 ee = 90% (1*R*,1*R*)
R^1 = H, R^2 = 1-suc, R^3 = CO_2Et: 55% *trans:cis* = 1:7 ee = 91% (1*R*,1*S*)
R^1 = H, R^2 = $N(Boc)_2$, R^3 = CO_2Me: 72% *trans:cis* = 1:6 ee = 92% (1*R*,1*S*)

Scheme 91. Rh-catalysed cyclopropanations with sulfides.

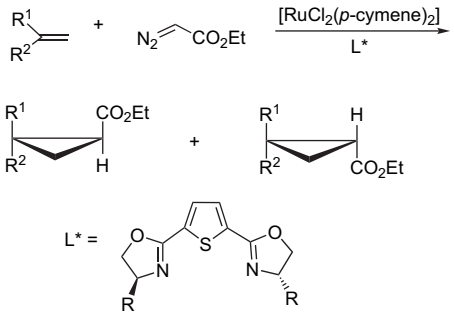
As an extension of this work, Aggarwal et al. have developed a highly efficient asymmetric rhodium-catalysed aziridination of various imines derived from aromatic, heteroaromatic, unsaturated and even aliphatic aldehydes and ketones (Scheme 92).[197] In addition, this methodology was applied to the synthesis of the side chain of taxol.[198]



R^1 = Ph, R^2 = H, R^3 = SES: 75% *trans:cis* = 2.5:1 ee = 94%
R^1 = Ph, R^2 = H, R^3 = Ts: 68% *trans:cis* = 2.5:1 ee = 98%
R^1 = Ph, R^2 = H, R^3 = $SO_2C_{10}H_7$: 75% *trans:cis* = 3:1 ee = 97%
R^1 = *p*-ClC_6H_4, R^2 = H, R^3 = SES: 82% *trans:cis* = 2:1 ee = 98%:81%
R^1 = *p*-$MeOC_6H_4$, R^2 = H, R^3 = SES: 60% *trans:cis* = 2.5:1 ee = 92%:78%
R^1 = *n*-Hex, R^2 = H, R^3 = SES: 50% *trans:cis* = 2.5:1 ee = 98%:89%
R^1 = *t*-Bu, R^2 = H, R^3 = Ts: 53% *trans:cis* = 2:1 ee = 73%:95%
R^1 = 3-Fur, R^2 = H, R^3 = Ts: 72% *trans:cis* = 8:1 ee = 95%
R^1 = (*E*)-PhCH=CH, R^2 = H, R^3 = SES: 59% *trans:cis* = 8:1 ee = 94%

Scheme 92. Rh-catalysed aziridination of imines with a sulfide ligand.

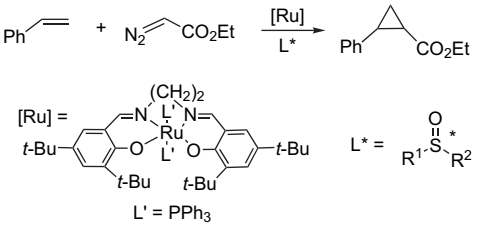
In 2004, Zingaro et al. reported novel structure-defined chiral bis(oxazolinyl)thiophenes for the ruthenium-catalysed asymmetric cyclopropanation of alkenes with EDA.[199] A high enantioselectivity (ee>99%) was observed in the case of cyclopropanation of diphenylethene (Scheme 93).



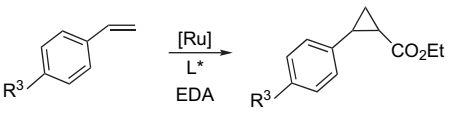
R = Et, $R^1 = R^2$ = Ph: 70% ee (*trans*) > 99% ee (*cis*) > 99%
R = *i*-Pr, $R^1 = R^2$ = Ph: 77% ee (*trans*) = 98% ee (*cis*) = 98%
R = Bn, $R^1 = R^2$ = Ph: 72% ee (*trans*) = 96% ee (*cis*) = 96%
R = *t*-Bu, $R^1 = R^2$ = Ph: 63% ee (*trans*) = 98% ee (*cis*) = 98%
R = *i*-Pr, R^1 = H, R^2 = Ph: 83% *trans:cis* = 76:24
ee (*trans*) = 81% ee (*cis*) = 84%
R = *t*-Bu, R^1 = H, R^2 = Ph: 79% *trans:cis* = 79:21
ee (*trans*) = 89% ee (*cis*) = 82%
R = *t*-Bu, R^1 = H, R^2 = *p*-$MeOC_6H_4$: 78% *trans:cis* = 82:18
ee (*trans*) = 91% ee (*cis*) = 85%
R = *t*-Bu, R^1 = H, R^2 = *p*-ClC_6H_4: 82% *trans:cis* = 80:20
ee (*trans*) = 87% ee (*cis*) = 83%

Scheme 93. Ru-catalysed cyclopropanation of alkenes with bis(oxazolinyl)thiophene ligands.

More recently, Nguyen et al. reported the first example of the asymmetric cyclopropanation of olefins with EDA mediated by a combination of a (salen)ruthenium(II) catalyst and a catalytic amount of a chiral sulfoxide (Scheme 94).[200] These authors proposed that the mechanism of the asymmetric induction involved the axial coordination of the chiral sulfoxide to the ruthenium centre as a key induction step in the reaction stereoselectivity.



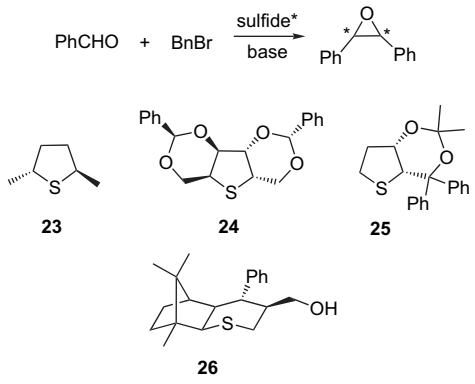
(*R*)-L*, R^1 = Me, R^2 = Ts: 92% *cis:trans* = 1:6.7
ee (*cis*) = 93% ee (*trans*) = 87%
(*S*)-L*, R^1 = Me, R^2 = Ts: 84% *cis:trans* = 1:7.5
ee (*cis*) = 50% ee (*trans*) = 42%
(*R*)-L*, R^1 = Bn, R^2 = Ts: 90% *cis:trans* = 1:7.3
ee (*cis*) = 56% ee (*trans*) = 45%
(*S*)-L*, R^1 = Me, R^2 = 2-Naph: 90% *cis:trans* = 1:6.7
ee (*cis*) = 41% ee (*trans*) = 45%



(*R*)-L*, R^1 = Me, R^2 = Ts, R^3 = OMe: 97%
cis:trans = 1:5.9 ee (*cis*) = 89% ee (*trans*) = 87%
(*R*)-L*, R^1 = Me, R^2 = Ts, R^3 = O*t*-Bu: 97%
cis:trans = 1:4.8 ee (*cis*) = 93% ee (*trans*) = 87%
(*R*)-L*, R^1 = Me, R^2 = Ts, R^3 = F: 86%
cis:trans = 1:5.8 ee (*cis*) = 80% ee (*trans*) = 83%
(*R*)-L*, R^1 = Me, R^2 = Ts, R^3 = CF_3: 98%
cis:trans = 1:7.8 ee (*cis*) = 79% ee (*trans*) = 86%

Scheme 94. Ru-catalysed cyclopropanation of alkenes with sulfoxides.

The asymmetric synthesis of epoxides from carbonyl compounds using chiral sulfur ylide intermediates has emerged as a powerful method for not only creating C–C bonds with control of asymmetry, but also for generating a functionality suitable for further manipulation.[201] Two catalytic methods have been developed involving the reaction of a chiral sulfide with an alkyl halide in the presence of a base and an aldehyde or the reaction of a chiral sulfide with a diazo compound or a diazo precursor in the presence of a metal catalyst and an aldehyde. In both cases, the catalytic sulfide was regenerated during the catalytic cycle. The first method has been performed by a number of research groups in the presence of various sulfide structures, as depicted in Scheme 95. The highest enantioselectivities were obtained by Metzner[202] and Goodman[203] using the chiral C_2-symmetric sulfides **23** and **24**, respectively. Other sulfides such as **25** and **26** were employed by Shimizu[204] and Saito,[205] respectively, for a similar reaction performed between benzaldehyde and benzyl bromide, giving better diastereoselectivities, but lower enantioselectivities (Scheme 95). Although modest to high levels of enantio- and diastereoselectivities have been reported, the scope of this method remains somewhat limited. Indeed, only benzyl bromide and substituted allyl halides for the alkyl halide component, and aromatic and heteroaromatic aldehydes for the carbonyl-coupling partner, have mostly been employed.

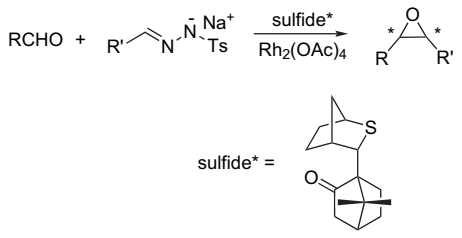


sulfide = **23**: 82% de = 80% ee = 85% (*S,S*)
sulfide = **24**: 41% de = 82% ee = 97% (*R,R*)
sulfide = **25**: 52% de = 100% ee = 78% (*R,R*)
sulfide = **26**: 63% de = 92% ee = 56% (*S,S*)

Scheme 95. Sulfide-catalysed epoxidation of aldehydes with BnBr.

The second method of asymmetric epoxidation has been extensively studied by Aggarwal et al.,[201,206] and is based on the reaction, under neutral conditions, of a chiral sulfide with an in situ generated diazo compound in the presence of a metal catalyst and an aldehyde. Scheme 96 summarises the best results obtained using a chiral bicyclic sulfide, prepared from camphorsulfonyl chloride, with a range of aromatic, heteroaromatic and α,β-unsaturated aldehydes, as well as aliphatic substrates, in the presence of various tosylhydrazone salts. In addition, this methodology was successfully applied to the synthesis of biologically important β-hydroxy-δ-lactones such as (+)-prelactone B.[207]

Although, this process has quite a broad scope, it also has, like most catalytic processes, its limitations. As an example, aldehydes with basic groups (e.g., pyridylcarboxaldehydes) were poor electrophiles, and, moreover, α,β-unsaturated

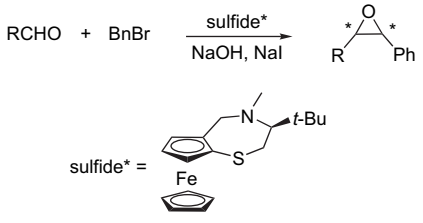


R = R' = Ph: 82% *trans:cis* > 98:2 ee = 94%
R = *p*-$NO_2C_6H_4$, R' = Ph: 75% *trans:cis* > 98:2 ee = 92%
R = *p*-$MeOC_6H_4$, R' = Ph: 68% *trans:cis* > 98:2 ee = 92%
R = Fur, R' = Ph: 60% *trans:cis* > 98:2 ee = 91%
R = (*E*)-PhCH=CH, R' = Ph: 70% *trans:cis* > 98:2 ee = 87%
R = Ph, R' = *p*-$MeOC_6H_4$: 95% *trans:cis* = 80:20 ee = 93%
R = Ph, R' = *p*-CNC_6H_4: 70% *trans:cis* = 80:20 ee = 64%
R = Ph, R' = *o*-$MeOC_6H_4$: 70% *trans:cis* > 98:2 ee = 93%
R = Ph, R' = Fur: 53% *trans:cis* = 90:10 ee = 61%

Scheme 96. Rh-catalysed epoxidation of aldehydes by tosylhydrazones with a sulfide.

hydrazones were poor carbene precursors. As an alternative strategy, the same group has considered the use of a stochiometric process, ideally involving the efficient recovery of the chiral transfer sulfur reagent. Hence, high levels of selectivity were obtained through the initial formation of a sulfonium salt, as for the reaction between 2-pyridinecarboxaldehyde and the benzylsulfonium salt of the same sulfide, as depicted in Scheme 96 (88% yield, trans:cis=98:2, ee=99%). In addition, this methodology was applied for the synthesis of the anti-inflammatory agent, CDP-840.[208]

On the other hand, Seki et al. have developed a catalytic asymmetric synthesis of glycidic amides by the reaction of diazoacetamides with aromatic aldehydes in the presence of 20% molar equivalent of a chiral binaphthyl sulfide and 10% molar equivalent of copper(II)-acetylacetonate with up to 64% ee.[209] In 2004, Metzner et al. reported that ferrocenyl derivatives, bearing an adjacent sulfur atom included in a fused ring, and exhibiting planar and central chiralities, could be used as a catalytic source of asymmetric sulfonium ylides.[210] A one-pot reaction was achieved, involving the addition of an aldehyde, benzyl bromide, 20% molar equivalent of the ferrocenyl sulfide and sodium iodide, in a mixture of *tert*-butanol and water. The best results (up to 94% ee) were observed with the chiral sulfide, as depicted in Scheme 97, bearing a *tert*-butyl group on the carbon adjacent to the nitrogen atom, and which was entirely recovered.



R = Ph: 66% *trans:cis* = 76:24 ee = 83%
R = 2-Naph: 67% *trans:cis* = 82:18 ee = 90%
R = (*E*)-PhCH=CH: 47% *trans:cis* = 60:40 ee = 94%
R = 2-Thienyl: 50% *trans:cis* = 81:19 ee = 90%

Scheme 97. Ferrocenyl sulfide-catalysed epoxidation of aldehydes.

A catalytic asymmetric oxidation of sulfides to sulfoxides mediated by chiral 3-substituted-1,2-benzisothiazole 1,1-dioxides was described in 2000 by Bulman Page et al. The best enantioselective efficiencies (83% ee) for the asymmetric oxidation of 2-phenyl-1,3-dithiane were obtained by using chiral *N*-sulfonyloxaziridines.[211]

In 2005, Hashimoto et al. found that the (*R*)-methyl *p*-tolyl sulfoxide/$TiCl_4$ combination was a promoter for the kinetic resolution of several types of racemic phosphines.[212] Another kinetic resolution was described in 2005 by Levacher et al., using a chiral sulfoxide having a 4-(dimethylamino)-pyridine backbone.[213] Selectivity of up to 4.5 could be achieved during the kinetic resolution of secondary alcohols in the presence of 5% molar equivalent of a chiral sulfoxide.

9. Conclusions

This review clearly demonstrates the importance and high potential of chiral sulfur-containing species as chiral ligands for asymmetric catalysis. In this review, which covers the literature since the beginning of 1999, the author has attempted to systematise the role, which chiral sulfur-containing ligands play in asymmetric catalysis. Over the last 10 years, the potential of chiral sulfur-containing ligands in transition-metal-catalysed asymmetric syntheses has been widely developed and explored. Many of the sulfur-containing ligands have only recently appeared in the literature, and it is clear that their application in catalysis will undoubtedly increase in the near future. In particular, S/S-, P/S-, or N/S-ligands are highly efficient for performing catalytic enantioselective C–C bond formations. The key advantages of these new types of catalysts are their easy synthesis, mostly starting from readily available commercial compounds, and their stability, which facilitates the catalytic procedures. Moreover, the catalytic C–C bond formations remain a challenge in terms of activity, enantioselectivity and catalyst loading and recycling.

Ligand design is becoming an increasingly important part of the synthetic activity in chemistry.[214] This is, of course, because of the subtle control that ligands exert on the metal centre to which they are coordinated. It is easy to imagine that chiral sulfur-containing ligands have a promising future for the development of a number of additional asymmetric heterogeneous or homogeneous reactions.

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Biographical sketch

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