Chiral Sulfur Ligands for Asymmetric Catalysis

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Received April 11, 2007

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1. Introduction

The preparation of new enantiopure ligands that provide a chiral environment to metals so that they perform efficient asymmetric catalysis is one of the most straightforward challenges for organic chemists. Numerous reports have been published over the last 40 years on this subject. Highly selective and active catalysts have already been made, with some of them being used in industrial processes, mostly for hydrogenation reactions.[1] The main family of successful ligands belongs to chelates. They are usually chiral diphosphine[2,3] (more generally phosphorus-containing ligands) or nitrogen-[4] or oxygen-containing ligands.[5,6] In addition, due to the high coordination ability of the sulfur atom to most transition metals, asymmetric sulfur ligands have also been developed for enantioselective catalysis in the last 20 years. The sulfur atom is considered as a soft atom and forms strong bonds with soft metals (such as palladium, for example). Sulfur ligands are poor σ-donor and poor π-acceptor ligands, as a particularity contributing to the metal−sulfur bond strength. This is one of the differences with phosphine ligands, which are better σ-donors and π-acceptors. The *trans*-effect of the sulfur ligands, even if it was found lower than that of the phosphine ones, is higher compared to those

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10.1021/cr068440h CCC: $65.00
Published on Web 10/18/2007

Mohamed Mellah was born in Oulmès, Morocco, in 1969. He received his Ph.D. degree from the Université Paris 12 in 2001 for studies concerning the electrochemical synthesis of functionalized organic conducting polymers, under the direction of Pr. J. Périchon at CNRS Thiais. After an industrial postdoctoral position at Electricité de France (EDF) in the development of electrosynthetic processes and an academic postdoc at the Université Rennes 1 (ionic liquids, solvents for electrochemical synthesis), he joined the group of Jean-Claude Fiaud (Laboratoire de Catalyse Moléculaire, ICMMO) in 2003 as Maître de Conférences at the Université Paris-Sud 11. His research interest lies in the electrochemical preparation of chiral polymers for heterogeneous asymmetric catalysis and electrocatalysis and in the development of enantioselective catalytic reactions assisted by electrochemistry.

Arnaud Voituriez was born in Nancy, France, in 1976. He received his DEA (Master's degree) in Organic Chemistry from the Université Paris-Sud 11, working with Profs. Y. Langlois and C. Kouklovsky. He received his Ph.D. degree from the same university in 2004, under the supervision of Dr. E. Schulz. His research focused on the synthesis and use of chiral sulfur-containing ligands in homogeneous and heterogeneous asymmetric catalysis. He then pursued postdoctoral work at the Université de Montréal in the laboratory of Prof. A. B. Charette, for studies concerning the asymmetric Simmons–Smith cyclopropanation reaction. After a CNRS Postdoctoral Fellowship at the Université Paris 6 in the group of Prof. F. Chemla (allenylzinc chemistry and applications in total synthesis), he joined the research group of Dr. A. Marinetti at the Institut de Chimie des Substances Naturelles (ICSN) in 2007, as Chargé de Recherche at the CNRS.

Emmanuelle Schulz graduated from Ecole Supérieure de Chimie Industrielle de Lyon in 1989 and received her Ph.D. degree from the Université de Lyon in 1992 for studies concerning the total synthesis of Strigol, under the direction of Pr. P. Welzel at the Ruhr-Universität Bochum, Germany. After an industrial postdoc at RP Agro, she joined the group of Pr. M. Lemaire in 1993 and obtained a permanent position at the CNRS in 1997. She is now working in the Laboratoire de Catalyse Moléculaire at ICMMO since 2000 and was nominated Directrice de Recherches at the CNRS in 2005. Her research topics include the preparation of chiral ligands for homogeneous and heterogeneous asymmetric catalysis, the development of new methodologies for the recycling of chiral organometallic catalysts, and the synthesis of organic conducting polymers for asymmetric electrocatalysis.

of the nitrogen- and oxygen-containing ligands. Moreover, sulfur-containing compounds are easily available, and they are also highly stable, allowing easy storage and handling, especially compared to phosphine derivatives. Furthermore, these sulfur ligands open new possibilities over other chelates because a new stereogenic center is formed at the sulfur by coordination to the metal. However, the control of this new chiral center is not always feasible due to its low inversion barrier (10−15 kcal·mol^{-1}) when this value approaches 30−35 kcal·mol^{-1} for the phosphorus atom.[7,8] It is noticeable that, in the case of sulfoxides, this inversion barrier is higher (35−45 kcal·mol^{-1}). The close vicinity of the chiral center to the transition metal may however lead to interesting results in terms of enantiofacial discrimination. A wide diversity of chiral sulfur-containing ligands is easily available either directly from the chiral pool or by facile modifications of other heteroatomic ligands for a comparison of their coordinating ability and efficiency to perform asymmetric catalysis.

To the best of our knowledge, the first investigation to use available chiral sulfoxides as potential ligands was in the mid-1970s by James's group. Corresponding ruthenium and rhodium complexes were used for the reduction of olefins with promising results.[9] Some years later, Kellogg's group in Groningen prepared various chiral macrocyclic sulfides and tested them in the Ni(II)-catalyzed cross-coupling reaction, however with only modest success.[10,11] These reactions will be presented in more detail in this review. Since these early works, the efficient use of sulfur-containing ligands has been reported in numerous articles for the preparation of homogeneous chiral complexes. Most of them are active in asymmetric catalytic C−C bond formation.

Two reviews appeared recently[12,13] dealing specifically with the coordination chemistry of transition metal complexes containing sulfur ligands and their use in homogeneous catalysis. Another review was published a few months ago, focusing on the use of sulfur ligands for asymmetric catalysis since 1999.[14]

The impressive number of efficient asymmetric catalytic reactions performed in the presence of sulfur-containing ligands prompted us to present and comment on this literature. We have chosen to classify the results according to the type of catalytic reactions involved.

As already mentioned, most of them report the asymmetric formation of new carbon−carbon bonds and in particular the nucleophilic allylic substitution, probably due to the affinity of the sulfur atom for a strong coordination to

palladium. Other examples are found in which asymmetric Diels−Alder or hetero-Diels−Alder cycloadditions, Heck-type reactions, asymmetric conjugated additions, and various additions to carbonyl bonds are described. To a lesser extent, chiral sulfur-containing complexes have also been successfully used for asymmetric reductions of carbonyl groups or carbon−carbon double bonds.

Some examples of bidentate sulfur/sulfur ligands can be found possessing mainly a C_2-symmetry. Many more chelates were proved as efficient as other usual asymmetric ligands when the sulfur atom was associated to nitrogen, phosphorus, or oxygen.

The easy preparation of chiral sulfoxides from thioethers offers, in addition, the possibility to introduce the chirality directly at the sulfur atom only, allowing other functionalizations of the ligand to be made. Hence, ligands have been tested in which the sulfur atom is present in the molecule, but mainly not as a coordinating atom, especially when it provides the chirality to the ligand (*i.e.*, sulfoxides, sulfoximines). Some examples are also found in which the sulfur atom modifies the electronic properties of the other chelating atoms (the presence of a thiophene ring instead of a benzene ring, for example). These results will be summarized here by a short presentation of the ligand synthesis and the preparation of the corresponding complexes. Special emphasis will then be given to their efficiency (activity and enantioselectivity) in the targeted asymmetric catalytic transformation compared to other ligands. Mechanistic aspects will be discussed as far as they are reported in the original article. The reactions will be described in relation to the structure of the *S*-containing ligand used, according to the chelating counterpart (*S*-, *N*-, *P*-, or *O*- atom).

2. Asymmetric C–C Bond Formation

2.1. Asymmetric Grignard Cross-coupling

2.1.1. Introduction

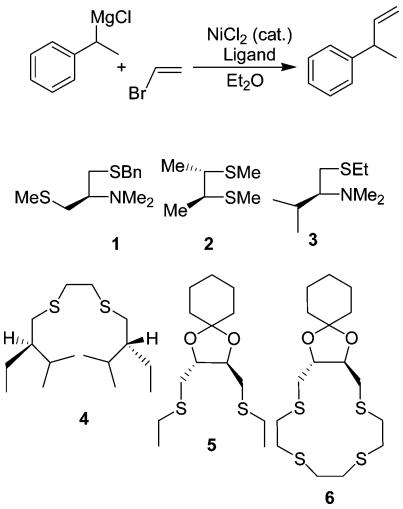
Transition-metal-catalyzed cross-coupling between an organometallic species and aryl or alkenyl halides is a powerful synthetic approach and represents one of the most straightforward methods for C−C bond formation. Asymmetric cross-coupling has been attempted using various kinds of optically active phosphine ligands.[15] The cross-coupling most extensively studied so far is the reaction of 1-phenylethylmagnesium chloride with vinyl bromide, forming 3-phenyl-1-butene (Scheme 1).

2.1.2. Chiral S,S-Ligands

In order to develop more stable ligands for enantioselective carbon−carbon bond formation, Kellogg *et al*. investigated the use of sulfides, instead of the commonly used phosphines,[16] as efficient chiral ligands for catalytic enantioselective Grignard cross-coupling.[10] They were notably the first to imagine the potential use of sulfur-containing ligands in chiral catalytic processes. To demonstrate this concept, various sulfur-containing ligands have been synthesized and tested in the Ni(II)-catalyzed cross-coupling of 1-phenylethylmagnesium chloride with vinyl bromide (Scheme 1).

First, several acyclic chiral ligands **1**−**5** were tested and associated to the nickel precatalyst; in all cases they promoted the cross-coupling but the enantioselectivity never exceeded 8%. In order to improve the enantiomeric excess, the authors increased the rigidity of the best ligand **5** by the synthesis

Scheme 1



of its cyclic analogue **6**. The latter was also tested under different reaction conditions (reagent ratios and temperature); the best reaction conditions (1 mol % catalyst, 2 equiv of 1-phenylethylmagnesium chloride, and variation of the temperature between −10 and 0 °C) lead to a total conversion after 24 h and an enantiomeric excess of 17%. Although these preliminary results remained moderate in terms of selectivity, they clearly showed the potential use of sulfur-containing ligands in transition metal-catalyzed carbon−carbon bond formation.

The same group developed several further synthetic routes for macrocycles derived particularly from (*S*)-phenyl alanine and (*S*)-cysteine.[11] The access routes for macrocycles in which sulfide and amine sites may be combined allow many structural variations. Thus, macrocycles containing sulfides and/or amino linkages were examined as ligands for the nickel-catalyzed Grignard cross-coupling reactions.[17] In another approach, chiral macrocyclic ligands were synthesized from enantiopure (*R*,*R*)-diethyl tartrate, L-phenylalanine, or L-cysteine in several synthetic routes. Both series of macrocycles possessing C_2-symmetry were tested as chiral ligands in the model Grignard cross-coupling reaction between 1-phenylethylmagnesium chloride and vinyl bromide (see Scheme 2).

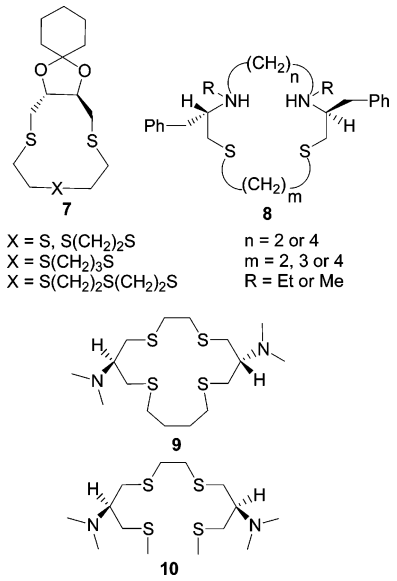
In most cases, catalysts were active, leading to goods yields, but the enantiomeric excesses never exceeded 17%. Ligand **9** derived from L-cysteine was developed to provide a suitable square-planar coordination for the Ni atom. Its use in the same cross-coupling reaction provided the expected product in 46% ee with a moderate yield (50%). The comparison with the open-chain analogue **10** showed that both the open chain and the macrocyclic ligand afforded good yields, but a poor enantioselectivity was observed for the acyclic sulfur-containing ligand (ee < 17%).

2.1.3. Chiral S,N-Ligands

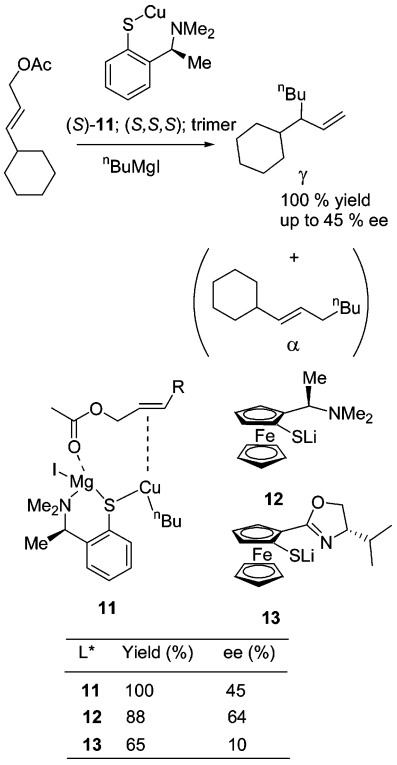
van Koten and Bäckvall reported the use of arenethiolatocopper(I) as a catalyst for the analogous substitution reaction of Grignard reagents with allylic substrates.[18] This cross-coupling reaction with acyclic substrates may occur in an $\alpha(S_N2)$ or $\gamma(S_N2')$ manner, depending on the reaction conditions (see Scheme 3).

The reaction performed in diethyl ether at 0 °C in the presence of *ex situ* prepared complex **11** led exclusively to the formation of the γ product with up to 45% ee, depending

Scheme 2



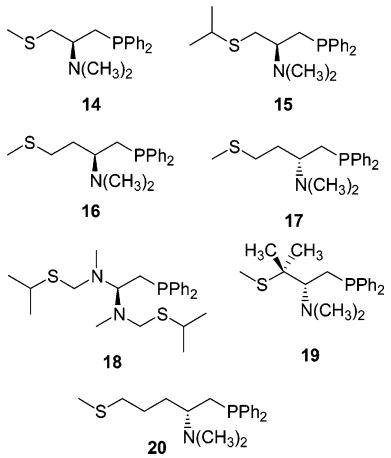
Scheme 3



L*	Yield (%)	ee (%)
11	100	45
12	88	64
13	65	10

on the order of the substrates introduction. The reaction with the bulky Grignard reagent Me_3SiCH_2MgI gave the target compound in 53% ee but with a lower yield (only 30% isolated product). Other arenethiolatocopper(I) complexes were prepared by slight structural modifications around the nitrogen atom, which all led to the γ-product as the major compound, without improving its enantioselectivity. Since all these copper catalysts were air-sensitive compounds and therefore not easy to handle, their *in situ* formation was investigated from corresponding arenethiols, butyllithium, and different copper(I) sources. The use of CuI or CuCl as a precatalyst led to similar results as those obtained by using the preformed complex **11**. More sterically hindered Grignard derivatives, such as ^{i}PrMgI or ^{i}PrMgBr, were also employed with complete γ-selectivity, but the enantioselectivities were

Scheme 4



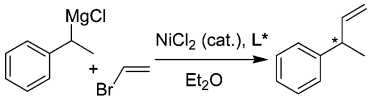
always moderate (up to 34% ee). Following the course of the reaction with *n*-BuMgI over time (and progressively adding the Grignard reagent), the authors noticed that the catalysis actually only started after the addition of at least 1 equiv of the Grignard reagent (relative to the catalyst amount). This observation led them to propose structure **11** (see Scheme 3) as the key intermediate. These authors also synthesized a new ferrocene thiolate ligand, the lithium derivative **12** in Scheme 3, which was stable in the solid state under argon.[19] This ligand was tested in the presence of CuI in the same reaction, giving rise almost selectively to the desired γ-product. The effects of the temperature, solvent, and amount of ligand compared to copper were examined, and the product drawn in Scheme 3 could be obtained in 88% yield with up to 64% ee. The authors mentioned that this is the highest value reported for allylic carboxylates in the copper-catalyzed allylic substitution. The importance of anionic coordination to copper by sulfur was proven by synthesizing an analogous ligand bearing a *tert*-butyl or phenyl group at the sulfur. In those cases, the copper-catalyzed transformation afforded racemic products. The preparation of the lithium salt of the ferrocenyl oxazoline thiol **13** was reported, but this ligand associated with CuI proved less efficient in the transformation discussed.

2.1.4. Ligands with an S-Noncoordinating Atom

In the course of their examination of other sulfur-containing amino acids, *S*-alkylated dimethylamino alcohols derived from commercially available L-methionine and D-penicillamine were synthesized by Griffin and Kellogg.[20] The cross-coupling reaction was carried out from 1-phenylethyl chloride magnesium or 2-octylchloride magnesium with these new ligands (Scheme 4) and nickel chloride as precatalyst. These sulfur-containing ligands derived from amino acids generally provided excellent yields but variable enantiomeric excesses, depending on the Grignard reagent preparation and on the reaction conditions. The enantiomeric excess reached only 14% when 2-octylchloride magnesium was used.

The authors demonstrated an important intramolecular participation of the sulfur atom in the reaction with 1-phenylethyl chloride magnesium.[21] The different ligands **14**−**20** were indeed derived from chiral amino acids in which the sulfur atom was separated from the chiral carbon by a chain of one, two, or three carbon atoms. The results summarized in Scheme 5 clearly show the influence of the

Scheme 5



L*	Yield(%)	ee (%)
14	> 90	38
15	> 90	37
16	> 90	65
17	> 90	40
18	> 90	38
19	nd	42
20	nd	70

carbon linker bridge between the sulfur and the phosphine atoms, and four methylene functionalities gave the best results.

The best result was obtained with the homomethionine derivative **20**, which contains a three-carbon-atom chain (up to 70% ee). The other sulfur-containing ligands have side chains that are perhaps too short to allow the effective participation of sulfur in the nickel coordination.

2.1.5. Conclusion

This pioneering work in the use of sulfur derivatives as chiral ligands in organometallic catalysis highlighted the potential of sulfur coordination to transition metals for the preparation of enantioenriched targeted compounds. As will be developed in the next section of this review, this research opened the way to the preparation of a wide range of sulfur-containing ligands and their efficient use for many carbon−carbon bond formations.

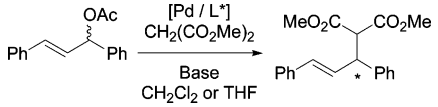
2.2. Asymmetric Allylic Substitution

2.2.1. Introduction

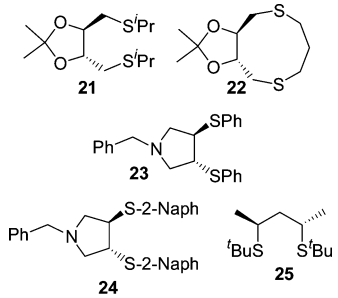
The Pd-catalyzed allylic substitution, called the Tsuji−Trost reaction,[22−24] is by far the most intensively studied reaction with sulfur-containing ligands over the past few years. Since sulfur is a soft complexation site and palladium a soft metal, the resulting complexes are expected to be strong complexes. Furthermore, retrodonation of π-electron density from the metal to the empty, relatively low-energy d orbital of the sulfur can contribute to the strength of the Pd−S bond. Two different strategies have been used: the catalytic transformation has been on one hand performed with C_2-symmetric ligands, resulting in catalytic systems with restricted numbers of diastereomeric transition states, thus facilitating the analysis of the interactions responsible for enantioselection. Another possibility arose from the use of mixed heterodonating ligands containing strong and weak donor heteroatom pairs, thus giving rise to different electronic properties associated with each metal-heteroatom. Due to the *trans*-effect,[25] the nucleophile would thus preferentially attack the allylic system on the carbon possessing a greater positive charge character, *i.e.*, on the carbon situated *trans* to the best π- acceptor. To evaluate the selectivity of a new chiral ligand for allylic substitutions, the reaction usually performed is the transformation of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate, in the presence of a base (Scheme 6). This reaction allows an easy comparison and analysis of the results due to the symmetry of the substrate.

The results in terms of activity and enantioselectivity given in the following sections refer mainly to this specific

Scheme 6



Scheme 7



L*	time (days)	conv (%)	ee (%)
21	7	74	27 (*R*)
22	1	100	42 (*S*)
23	7	100	81 (*S*)
24	6	80	76 (*S*)
25	2.5	95	70 (*R*)

transformation. To perform chiral discrimination during an asymmetric allylic substitution process, the use of heterodonor ligands that distinguish between both terminal allylic carbons in the intermediate species through their different electronic effects proved to be very efficient. A conceptually different approach is based on the use of homodonor ligands with backbone symmetry and rigidity. Trost, hence, prepared highly efficient *N*,*N*′,*P*,*P*′-ligands[26] possessing a C_2-symmetric structure acting as chiral pockets. The following sections of this article will deal with homodonor *S*,*S*-ligands and then with heterodonor *P*,*S*- and *N*,*S*-ligands. Some other examples will also be given in the last part, in which sulfur-containing (and not coordinating) ligands have been successfully used for promoting the Tsuji−Trost reaction.

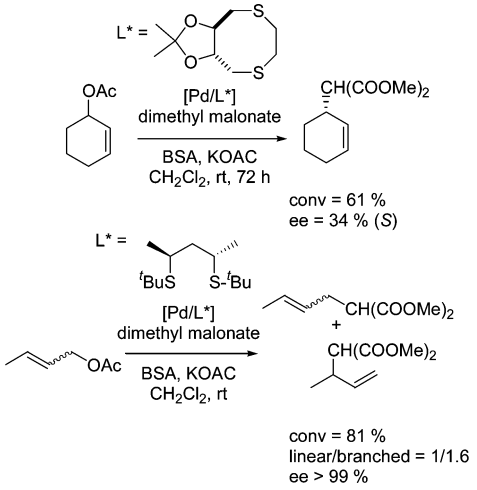
2.2.2. Chiral S,S-Ligands

Few *S*,*S*-coordinating ligands have been reported for their use in Pd-catalyzed allylic substitutions. Those chiral homodonor ligands generally gave only modest asymmetric induction for this transformation even if some of them were performing. Jansat *et al.*,[27] however, published efficient dithioether ligands with backbone rigidity. They prepared ligands containing a five-membered heterocycle core such as *O*-isopropylidene or pyrrolidine. Some representative examples leading to up to 81% ee in the test reaction are shown in Scheme 7.

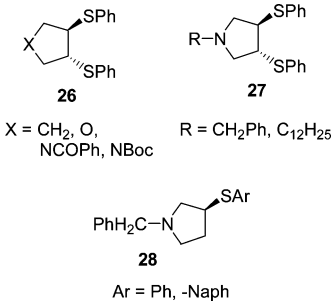
The highest enantioselectivities were obtained with ligands of type **23**−**25**, while bicyclic chiral ligands (butterfly-type, **22** in Scheme 7) proved to be the most active.[28] Solid structures of complexes and structural studies in solution provided the authors with proof of *S*,*S*-coordination in all cases. The corresponding palladium complexes were also tested for the transformation of cyclic allylic acetate (ee of the product up to 34%) and unsymmetrical allylic acetate (mainly toward the linear isomer). The authors obtained the branched isomer in up to 99% ee for the transformation of (*E*/*Z*)-1-acetoxy-2-butene (see Scheme 8).

Chiral pyrrolidine thioethers were also examined by Skarżewski and his group (Scheme 9).[29] The authors divided

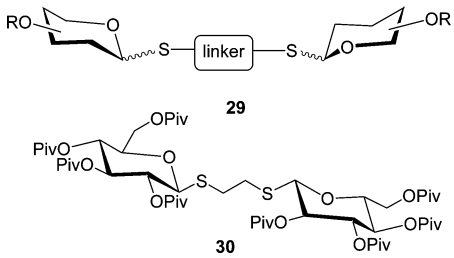
Scheme 8



Scheme 9



Scheme 10

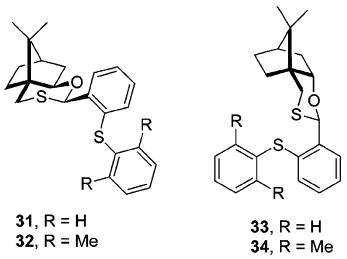


these ligands into two classes, purely *S*,*S*-coordinating ligands (see **26**) and *S*,*N*-chelates (see **27** and **28**).

The first class showed moderate activity and efficiency (up to 42% ee), whereas ligands **27** were much more effective (81−89% ee). By comparing the efficiency of the corresponding catalysts with regard to the *S*,*N*-chelates of type **28**, the authors assume ligands **27** to operate mainly as sp^3-nitrogen- and sulfur-donating ligands, contradicting the conclusion of Gómez and co-workers.[28]

Khiar *et al.*[30] aimed to prepare C_2-symmetric bis(thioglycosides) in which, upon coordination to the metal, the sulfur atom should become stereogenic. However, in these ligands, the sugar residue should provide a well-defined chiral environment. The authors argued that the presence of cheap carbohydrates and their various hydroxy groups in different orientations opens the possibility of a molecular platform by an easy tuning of steric or electronic effects. They developed a parallel synthesis varying the sugar residue, the linker, and the protective groups for preparing type **29** bis(thioglycosides) (see Scheme 10).

Scheme 11



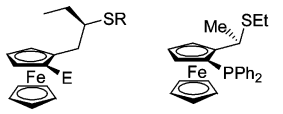
L*	t (h)	yield (%)	ee (%)
31	12	100	57 (*R*)
32	15	100	94 (*R*)
33	9	100	49 (*S*)
34	13	100	75 (*S*)

The authors chosed to screen one diversity element while fixing the others. The ability of the ligands to perform an efficient catalytic transformation was then evaluated and the best results for the test reaction were obtained with ligand **30** (90% ee at 0 °C). Both enantiomers of the targeted allylated product were obtained with 90% ee, by using inexpensive natural sulfur-modified D-sugars. The authors indeed successfully exploited the fact that α-D-arabinose is almost the mirror image of *β*-D-galactose, and they demonstrated that their sulfur derivatives behaved as pseudoenantiomers in the Pd-catalyzed allylic substitution.[31] The authors further succeeded in synthesizing the corresponding Pd(II) complex and observed by in depth NMR studies the formation of an unique *anti* diastereomer with C_2-symmetry in solution, thus indicating a real control of the sulfur configuration by the sugar backbone. X-ray analyses further indicated that the sugar residues were placed in a pseudoaxial orientation (in the *exo*-anomeric conformation).[32] This effect, as a result of n−*σ** hyperconjugative delocalization, is strong enough for an efficient stereochemical control over the sulfur configuration, as both atoms possess (*S*) absolute configurations.

Excellent results in terms of activity and selectivity for the test reaction were reported by Nakano, Kabuto, and coworkers via the preparation of chiral sulfideoxathiane.[33] They prepared *S*,*S*-ligands from the reactions of mercaptoisoborneol or mercaptoborneol with phenylthiobenzaldehydes with good yields (see Scheme 11).

Tested as ligands for the Pd-catalyzed allylic test alkylation, they allowed the preparation of the targeted product with up to 94% ee (see ligand **32**). The presence of the bulky linked 2,6-dimethylphenylthio moiety proved necessary for achieving such a high level of enantioselectivity (compare **31** and **32** in Scheme 11). The scope of the utilization of the catalyst obtained in **32** was examined for reactions involving bulkier nucleophiles. Hence, the use of methyl diethylmalonate led to the formation of the expected allylated product with a quantitative yield and near complete stereocontrol (99% ee). Semiempirical molecular orbital calculations were performed to propose an explanation for the high performance of ligand **32** compared to **31**. Geometry optimization and energy calculations were in accordance with a control of the catalyst conformation by the steric hindrance generated by the two methyl substituents of the phenyl ring.

Scheme 12



35 **36**

L*	R	E	t (h)	yield (%)	ee (%)
35a	^{i}Pr	STol	100	84	20 (*R*)
35b	^{i}Pr	SePh	100	65	44 (*R*)
35c	Me	PPh_2	0.16	99	90 (*R*)
35c	Me	PPh_2	24[a]	99	97 (*R*)
36			-	-	34

[a] -20°C

Enders *et al.*[34] reported the synthesis and use of ferrocenyl ligands with planar chirality and additional central chirality in the β-position of the side chain in Pd-catalyzed allylic substitutions. The authors used their SAMP/RAMP-hydrazone method to allow a highly diastereoselective alkylation in the α-position to the hydrazone functional group. Then, the regio- and diastereoselective metalation of the ferrocene ring *ortho* to the directing hydrazone moiety was successfully achieved by adding lithium perchlorate. Phosphorus, sulfur, or selenium derivatives were obtained by using the corresponding electrophiles. Subsequent reduction in hydrazines with catecholborane was followed by removal of the auxiliary under acidic conditions, to afford a large variety of asymmetric sulfur-containing ligands (*S*,*S*-, *S*,*Se*-, and also *S*,*P*-chelates, Scheme 12).

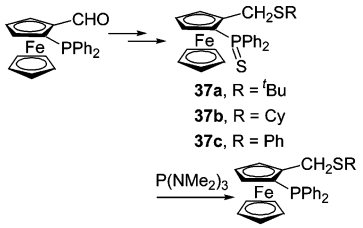
The authors observed that *S*,*S*- or *S*,*Se*-coordinating ligands displayed low activity and modest enantioselectivity in the Tsuji−Trost test reaction (respectively 20 and 44% ee). Replacing one coordinating atom by phosphorus as a strong π-acceptor allowed the reaction to be performed in quantitative yield and 90% ee (see **35c** in Scheme 12). At −20 °C the enantioselectivity could be raised up to 97%. For comparison, the authors tested a similar planar chiral ferrocene *S*,*P*-ligand **36**, bearing a stereogenic center in the α-position, that proved to be less efficient in terms of enantioselectivity for the transformation conducted under the same conditions. NMR studies and the X-ray crystal structure supported the assumption that this type of ligands allowed electronic differentiation of the allylic carbon termini and that a preferred configuration (*exo*−*syn*−*syn*) was strongly favored with these intermediates by intramolecular C−H/π interactions.

Manoury *et al.*[35] prepared various chiral ferrocenyl thiophosphine-thioethers with only planar chirality, starting from an enantiomerically pure aldehyde (Scheme 13).

Potentially, *S*,*S*-ligands of the series **37** proved efficient for the test reaction, yielding the substitution product in high yield (within 2 h at room temperature) and up to 93% ee. For comparison, the authors also tested the *S*,*P*-analogues of the series **38** that gave similar results. However, in this case, the best enantiomeric excess was obtained only with the ligand bearing a phenyl substituent on the sulfur atom.

Chiral sulfur-coordinating ligands have also been synthesized in which the asymmetry element is only present as an enantiopure sulfoxide functionality. To illustrate this class of compounds, Shibasaki *et al.*[36] reported a chiral bis(sulfoxide) ligand (*S*,*S*)-1,2-bis(*p*-tolylsulfinyl)benzene ((*S*,*S*)-**39** in Scheme 14) and studied its chelating ability for Pd, Rh, and Ru.

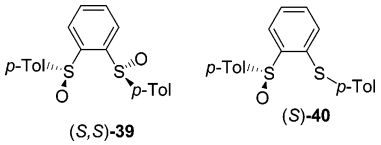
Scheme 13



L*	yield (%)	ee (%)
37a	90	93
37b	90	87
37c	93	88
38a	93	80
38b	93	80
38c	97	93

38a **38b** **38c**

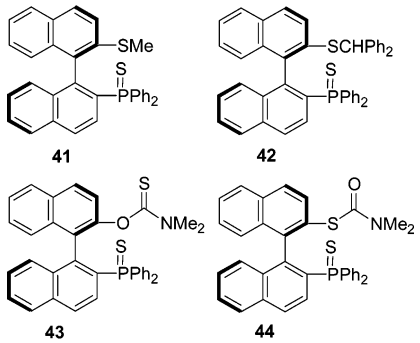
Scheme 14



(*S*,*S*)-**39** (*S*)-**40**

L*	yield (%)	ee (%)
(*S*,*S*)-**39**	40	64
(*S*)-**40**	82	49

Scheme 15



41 **42** **43** **44**

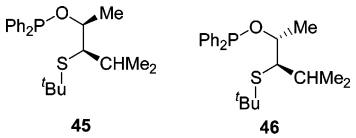
L*	Solvent	Yield	ee
41	Toluene	77	31 (*S*)
42	THF	80	74 (*R*)
43	THF	44	89 (*R*)
44	THF	31	9 (*R*)

X-ray crystal structure analyses of the palladium complex indicated that the ligand coordinated Pd(II) through the sulfur atom and that the complex had C_2-symmetry. Preliminary results in Pd-catalyzed allylic alkylations led to moderate asymmetric induction; however, ligand (*S*,*S*)-**39** gave higher enantioselectivities than the corresponding unsymmetric monosulfoxide ligand (*S*)-**40**.

Shi *et al.*[37] have recently described Pd-catalyzed asymmetric allylic substitutions by using axially chiral *S*,*S*- and *S*,*O*-heterodonor ligands based on the binaphthalene backbone. The symmetric allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate was performed in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as palladium precursor, BSA, and different additives (KOAc or LiOAc), in various solvents. The best results are summarized in Scheme 15.

Moderate to high enantiomeric excesses could be reached with the *S*,*S*-coordinating ligands **41**−**43**, depending on the

Scheme 16



45 **46**

L*	yield (%)	ee (%)
45	93	91
46	97	98

solvent and the additive used. The coordination of ligand **41** to Pd was studied by NMR analyses and suggested the formation of a *S*,*S*-heterodonor complex. No explanation was given concerning the differences observed in the product configuration. However, the corresponding *S*,*O*-chelate **44** proved to be less efficient in terms of both activity and selectivity for this reaction.

To conclude, *S*,*S*-coordinating ligands have been successfully used for Pd-catalyzed asymmetric allylic alkylation. In some cases, very high levels of enantioselectivity have been reached, favorably competing with the most efficient nitrogen- or phosphorus-containing ligands. However, very often those catalysts were proved poorly active, and mixed ligands (*S*,*P*- and mainly *S*,*N*-chelates) have been developed to obtain competitive catalytic species.

2.2.3. Chiral S,P-Ligands

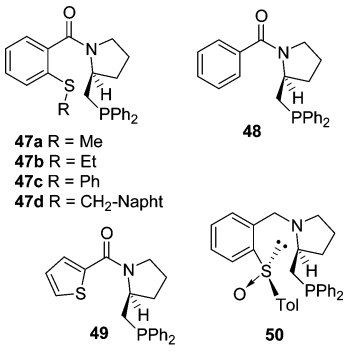
As could be foreseen from the example published by Enders,[34] many more examples are found in which hard−soft heterodonor ligands are used to perform asymmetric allylic substitution processes. Evans *et al.*[38,39] prepared a new class of mixed phosphorus/sulfur ligands incorporating a thioether as a chiral control element and a diarylphosphinite moiety as a strong donor heteroatom (see Scheme 16 for some examples).

Type **45** and **46** ligands possess two chelating subunits that may be independently substituted to prepare a large family containing sterically and electronically differentiated analogues. A systematic variation of the substituents at the sulfur, phosphorus, and backbone led to very efficient structures in terms of activity and enantioselectivity in the test reaction described in Scheme 6. Furthermore, the authors could prove the contribution of the sulfur in the coordination of the palladium atom by preparing crystals of these chiral organometallic complexes and performing X-ray studies. These structures also showed the relative electronic impact of the heteroatom *P*- and *S*-donors, since the Pd−C bond *trans* to the phosphinite functionality was longer than the Pd−C bond *trans* to the thioether group. Furthermore, these geometrical observations were in complete agreement with the product configuration.

The group of Hiroi[40] studied the synthesis and use of (*S*)-proline-derived phosphines bearing various organosulfur groups for the test Tsuji−Trost reaction (see Scheme 17). The authors observed an increase in the value of the enantiomeric excess by increasing the steric hindrance around the sulfur atom in the type **47** ligands, with a maximum of 88% for the ligand bearing a sterically hindered naphthyl group (see **47d** in Scheme 17).

Interesting results were obtained with ligand **47c**, substituted with a phenyl group. In this case, the substitution

Scheme 17



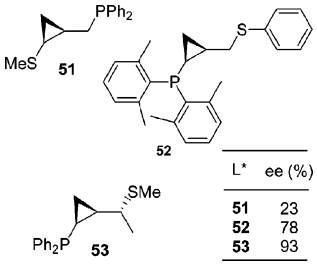
47a R = Me
47b R = Et
47c R = Ph
47d R = CH_2-Napht

48

49 **50**

L*	yield (%)	ee (%)
47a	65	62 (*S*)
47b	72	72 (*S*)
47c	42	41 (*R*)
47d	44	88 (*S*)
48	69	42 (*R*)
49	44	30 (*R*)
50	76	79 (*R*)

Scheme 18



51 **52** **53**

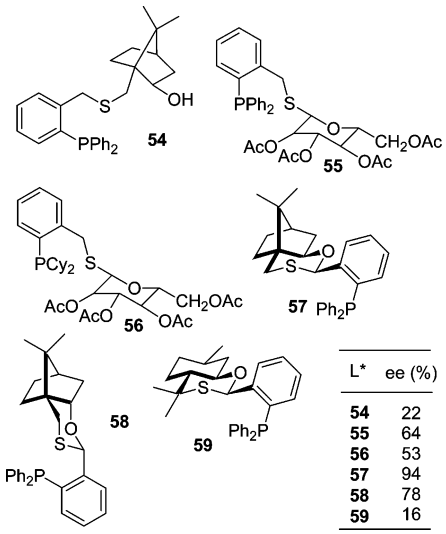
L*	ee (%)
51	23
52	78
53	93

product was obtained with an activity, enantioselectivity, and configuration similar to those obtained with ligands **48** and **49**. The authors proposed for these three ligands a *N*,*P*-coordination, referring to the low coordination ability of the aromatic sulfenyl groups compared with other alkyl sulfenyl functions.[41] In the other cases, the coordination to palladium should have given rise to nine-membered *S*,*P*-chelates, and the nucleophilic attack occurred *trans* to the better π-acceptor, here the sulfenyl groups. They explained the high level of asymmetry by the generation of another new chirality on the sulfenyl sulfur atoms in the formation of the intermediary nine-membered chelates. They finally prepared the corresponding diastereomeric sulfoxides, affording the substitution product with ee's up to 79% (see structure **50** in Scheme 17, for which there is a matched pair for the formation of the sterically favored chelate).

Very few examples are found in the literature where cyclopropane skeletons are used as a chiral ligand backbone. Molander *et al.*[42] described the synthesis of *S*,*P*-coordinating ligands by a modular approach where both heteroatoms were *cis* oriented to allow easy coordination. Some examples are reported in Scheme 18 with enantiomeric excesses reaching a maximum value of 78% for this type of ligands, depending on the substituent on the sulfur or on the phosphorus atom. The authors observed that a direct attachment of the phosphorus atom to the cyclopropyl ring led to better results (compare ligands **51** and **52** in Scheme 18).

Improvements in terms of enantioselectivity were obtained by preparing a second series of ligand with an additional stereocenter between the sulfide and the cyclopropane ring

Scheme 19



L*	ee (%)
54	22
55	64
56	53
57	94
58	78
59	16

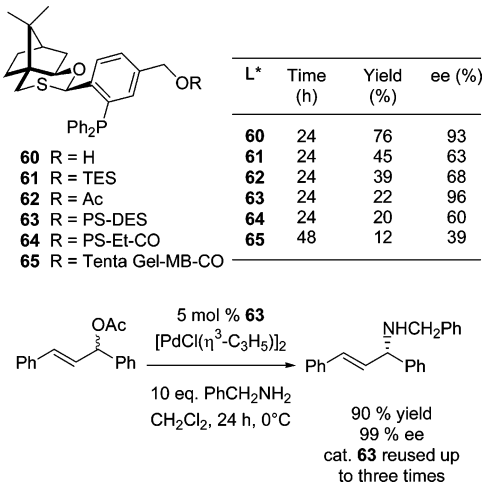
(structure **53**). In this case, an enantioselectivity of 93% was reached in the test reaction for the expected product obtained with >95% yield. X-ray crystallographic data and NMR measurements were performed, allowing a mechanistic proposition in accordance with the absolute stereochemistry of the products observed: the nucleophilic attack occurring at the carbon *trans* to the π-accepting phosphorus atom.

Pregosin *et al*.[43] prepared a new heterobidentate *S,P*-ligand in which the chirality was not associated with the phosphine backbone. They synthesized exo-8-((*o*-(diphenylphosphino)-benzyl)thio)borneol **54** (see Scheme 19) and expected some interesting secondary chemical control due to the presence of an additional OH group. However, in the nucleophilic allylic substitution process, the expected product was isolated with 93% yield after 4 days of reaction and only 22% ee. These results were optimized by the preparation of new ligands in which the chiral centers were placed nearer to the palladium coordination sphere, for a better transfer of the chiral information.[44] The two chiral bidentate *S,P*-ligands **55** and **56** in Scheme 19, based on β-D-thioglucose, were easily prepared from chloromethyl phosphine and the anion of β-D-thioglucose tetraacetate. This strategy proved to be efficient, since a higher enantioselectivity (64% and 53%, for **55** and **56**, respectively) could be obtained.

Oxathiane-type ligands have been rarely used for asymmetric catalysis, and Nakano and Hongo were the first to test the ability of such compounds to perform palladium-catalyzed allylic substitutions.[45] They synthesized norbornane-based phosphinooxathianes **57** and **58** in Scheme 19 (starting from (1*S*)-(−)-10-mercaptoisoborneol and (1*S*)-(−)-10-mercaptoborneol, respectively) and (+)-pulegone-based derivatives (see structure **59**). Compound **57** proved to be an efficient asymmetric ligand for palladium, since it led to the expected product of the test reaction in high yield (80% in 24 h at −30 °C) and high enantiomeric excess (up to 94%). Analogous structures **58** and **59** were both less efficient and selective. The authors explained the low stereodifferentiation, particularly for ligand **59**, by sterical effects from the *gem*-dimethyl group in the oxathiane ring, hindering the formation of a stable π-allyl complex. The palladium catalyst prepared from **57** also proved very active and enantioselective (up to 90% ee) in the analogous allylic amination with either benzylamine or potassium phthalimide as the nucleophile.[46]

Nakano *et al*. reported recently the first heterogeneous Pd-catalyzed asymmetric allylic alkylations by supporting ligand

Scheme 20

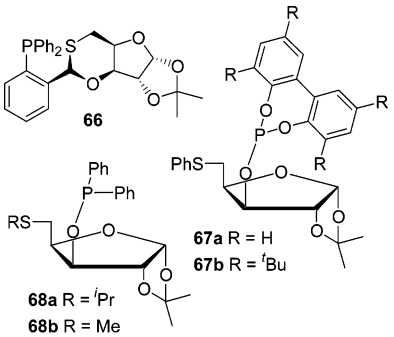


L*	Time (h)	Yield (%)	ee (%)
60	24	76	93
61	24	45	63
62	24	39	68
63	24	22	96
64	24	20	60
65	48	12	39

57 on various organic polymers.[47] Ligand **60**, analogous to **57** in Scheme 20, was prepared, bearing an hydroxyl functionality allowing the anchoring of this *S,P*-chelate on an organic support such as polystyrene-diethylsilyl (structure **63**), polystyrene-ethyl (**64**), or TentaGEL (**65**) via either an ether or an ester link. Corresponding ligands **61** and **62** were also prepared to compare the results obtained under homogeneous and heterogeneous conditions. Very good results in terms of enantioselectivity were obtained by using the PS-DES supported catalytic system, since 96% ee was obtained for the product of the test reaction, though with a poor chemical yield. The other heterogeneous catalysts proved far less enantioselective, probably for steric reasons or because of the presence of poisoning oxygen functional groups in ligand **65**, according to the authors. Heterogeneous catalyst **63** was further successfully examined in the palladium-catalyzed allylic amination depicted in Scheme 20. The product was obtained with an excellent enantioselectivity (99%), and the catalyst could be recovered and reused up to three times, albeit with significant loss of activity and enantioselectivity (79% ee at the third cycle). Nevertheless, this first polymer-supported *S,P*-type ligand proved efficient associated to palladium for allylic substitutions and opened the way to the preparation of other heterogeneous sulfur-containing catalysts showing a better stability for efficient recycling.

Nakano *et al*.[48] prepared a xylofuranose-based phosphino-oxathiane ligand illustrating the concept of heterodonor chelates with a rigid backbone. The ligand was easily obtained from commercially available 1,2-*O*-isopropylidene-D-xylofuranose in five steps (see structure **66**, in Scheme 21). The asymmetric palladium-catalyzed test allylic alkylation with this ligand afforded the desired product in up to 91% ee and high yield. Surprisingly, a decrease in temperature led to a decrease of ee. The absolute configuration of the product was in total accordance with a nucleophilic attack occurring at the allyl terminus *trans* to the better π-acceptor (the phosphorus atom). This ligand also proved to be very efficient for the corresponding allylic amination. However, a very low enantiomeric excess (4%) was obtained using this ligand for the palladium-catalyzed asymmetric tandem allylic allylation of 1,4-diacetoxy-*cis*-2-butene with 2-(benzylamino)ethanol. Corresponding *N,P*-chelates, the phosphinooxazinane ligands, gave the targeted 2-vinylmorpholine in up to 94% ee.[49]

Scheme 21

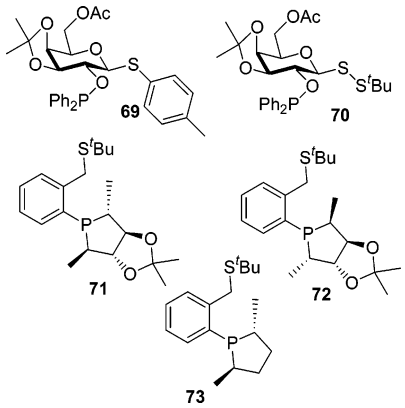


L*	Conv (%)	ee (%)
66	91	91
67a	100	3
67b	58	58
68a	100	88
68b	91	61
68c	90	47

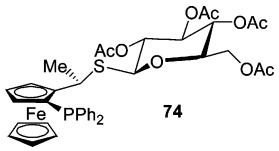
Starting from carbohydrates as an inexpensive and versatile chiral source for preparing ligands, Claver, van Leeuwen, *et al*.[50] reported the synthesis of various type **67** furanoside thioether-phosphites ligands (Scheme 21) and compared their efficiency in terms of both activity and enantioselectivity to analogous diphosphite or phosphine-phosphite ligands. The authors observed that the *S*,*P*-coordinating ligands were generally less enantioselective than their diphosphite counterparts. By preparing ligands with various substituents on the thioether moiety, they concluded that these modifications had no significant influence on the enantioselectivity. However, the steric bulk on the phosphite backbone proved to be of major importance, since the unsubstituted biphenol ligand led to a racemic compound (compare ligands **67a** and **67b** in Scheme 21). Analogous thioether-phosphinite derivatives were prepared by Diéguez *et al*.[51] (see ligands **68** in Scheme 21) in a few steps from inexpensive D-(+)-xylose. The authors performed the Pd-catalyzed allylic test reaction in dichloromethane with potassium acetate as the base and obtained good results in terms of activity and enantioselectivity. Ligand **68a** led to the best enantioselectivity for this transformation (88% ee at room temperature and 93% ee at 0 °C) whereas the use of ligand **68b** with a smaller steric hindrance around the sulfur atom gave higher activities (91% conversion in 5 min) but lower asymmetric induction. Interestingly, similar trends were observed when these catalytic systems were used for the corresponding Pd-catalyzed allylic amination. This new family of thioether-phosphinite ligands led to catalysts that showed better performances than the corresponding thioether-phosphite ligands. In this case, however, the effect of the substitution of the phophinite backbone on the catalyst efficiency has not yet been studied.

Apart from the synthesis of C_2-symmetric bis(thioglycosides) (see Scheme 10), Khiar *et al*. also prepared some thioglycosides having a phosphinite moiety at the 2-position of the pyranose ring for preparing heterodonor ligands with different donor−acceptor properties.[52] Starting from commercially available galactose pentaacetate, the authors synthesized four phosphinite thioglycosides, as tunable ligands, by varying the sulfur substituent (see for example structures **69** and **70** in Scheme 22). Associated to palladium, these ligands catalyzed the test reaction in high chemical yield, and high enantiomeric excesses (up to 96% ee) were achieved

Scheme 22



Scheme 23



by using the more sterically hindered compound **70**. The importance of the stereochemistry at the anomeric center was noted, since the analogous α-thioglycoside led to the racemic product. Dynamic and NOE NMR studies were conducted, which revealed that the complex formed between **70** and the palladium precatalyst was obtained as a single isomer, showing an efficient control of the sulfur configuration. The authors used the same strategy, as previously described, for their *S*,*S*-chelating[31] ligands to afford the opposite enantiomer for the reaction product. They synthesized 2-phosphinite *tert*-butyl-thioarabinoside, which behaved as a pseudoenantiomer to **70** and yielded the expected Tsuji−Trost product with the opposite configuration and 96% ee.

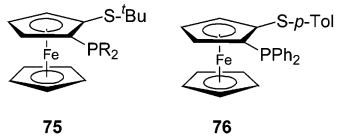
RajanBabu *et al*.[53] reported the synthesis of mono- and bis(phospholanes) from D-mannitol, with the latter affording excellent catalysts, associated to palladium for performing the Tsuji−Trost reaction. The corresponding monophospholanes **71**, **72**, and **73** (see Scheme 22), bearing a pendant S-*tert*-butyl group, proved as active but less enantioselective for the same transformation (up to 60% ee for ligand **72**).

Another class of *S*,*P*-containing ligands has been used in palladium-catalyzed allylic substitutions, with an additional element of chirality being introduced here via the planar chirality of the ferrocene derivatives. An example has been described by Albinati and Pregosin,[54] who prepared a ferrocene based chiral auxiliary substituted with a thioglucose functionality (see **74**, in Scheme 23).

This ligand allowed the formation of the Tsuji−Trost product with 88% ee. This result not only came from the planar chirality of the ligand but also from the sugar moiety, since changing the carbohydrate substituent with a cyclohexyl or an ethyl group resulted in a dramatic decrease in the reaction selectivity (67% ee and 34% ee, respectively). Thus, thioglucose plays an important role and the combination of the two stereogenic fragments afforded an improved result.

The planar chirality of the ferrocene core has also been associated with numerous other sulfur-containing ligands. Carretero *et al*.[55] prepared 1-phosphino-2-sulfenylferrocenes (Scheme 24) starting from sulfinyl ferrocene, by diastereocontrolled *ortho*-lithiation followed by phosphination. Subsequent reduction of the sulfoxide moiety to sulfide led to enantiopure planar chiral ferrocenes.

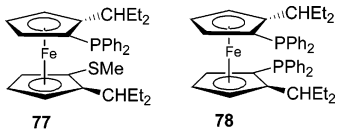
Scheme 24



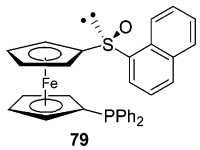
75 **76**

L*	R	yield (%)	ee (%)
75a	Ph	92	93
75b	(*p*-F)C_6H_4	94	92
75c	(*p*-CF_3)C_6H_4	90	92
75d	2-Furyl	60	90
76	-	92	40

Scheme 25



77 **78**



79

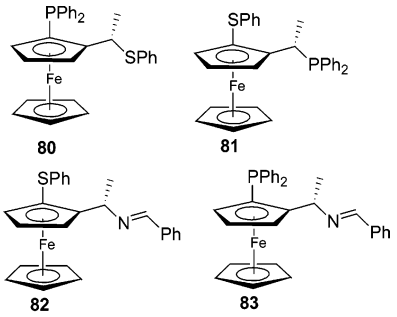
L*	yield (%)	ee (%)
77	> 99	38.5
78	> 99	5.5
79	96	68

These ligands provided the expected product in the test reaction with good to excellent yields and enantioselectivities. The reaction was completed in 4 h using **75a** and could be accelerated by the addition of Bu_4NCl, which also allowed the reaction to be carried out at −20 °C.[56] Electron-withdrawing groups on the phosphorus atom (see ligand **75b** and **75c** in Scheme 24) afforded the desired product with high enantioselectivity, and the reaction rate was significantly shortened to 20 min. On the contrary, ligands bearing electron-rich phosphines (see ligand **75d**) were slightly less efficient. Ligand **76**, in which the sulfur atom is less sterically hindered, led to an important decrease in asymmetric induction. This family of *S,P*-bidentate ferrocenes possessing exclusively a planar chirality was also successfully used for the Pd-allylic substitution with nitrogen nucleophiles. The authors performed X-ray diffraction analyses and solution NMR studies. They proved the formation of a *S,P*-bidentate ligand, giving a five-membered palladacycle, and proposed a mechanistic course for explaining the observed selectivity, taking into account the major intermediates between the four possible complexes coming from the chirality of the coordinated sulfur and the W/M configuration of the allyl group.

Kang *et al*.[57] prepared a pseudo-C_2-symmetric *S,P*-hybrid ferrocenyl ligand **77** to compare the activity and enantioselectivity of this new heterodonor ligand with its C_2-symmetric biphosphine counterpart **78** (Scheme 25). This *S,P*-bidentate ligand containing planar chirality was obtained in 55% yield in a multistep reaction starting from 1,1′-ferrocenedicarboxaldehyde.

These ligands were tested for their ability to form efficient Pd complexes for the asymmetric allylic alkylation and asymmetric Heck reaction (see section 2.4.) For the usual Tsuji−Trost transformation test reaction, the resulting *S,P*-chelating complex proved to be very active, leading to the expected product in quantitative yield (after 20 min) with 38.5% ee. Even if this value is moderate, it is much higher than that obtained using the symmetric diphosphine analogue **78** (5.5% ee).

Scheme 26



80 **81**

82 **83**

L*	yield (%)	ee (%)
80	90	93.8 (*S*)
81	93	75.3 (*R*)
82	90	86.3 (*R*)
83	83	71.0 (*R*)

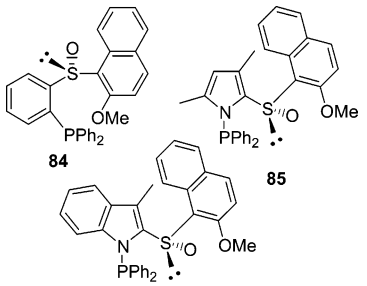
Toru and co-workers prepared and tested chiral ferrocenyl ligands possessing chiral sulfinyl and phosphinyl groups under similar conditions.[58] These ligands proved more efficient, since the best result (68% ee) was obtained for a catalyst derived from **79** (Scheme 25). The stereochemical course of the reaction was rationalized by assuming the addition of the nucleophile *trans* to the phosphorus atom.

Hou and Dai[59] prepared several chiral ferrocene ligands possessing the same planar and central chiralities (*S*,R_p configuration) as bidentate chelates with different donor atoms. These compounds are depicted in Scheme 26. The authors aimed to study the *trans* effects of these different coordination atoms, by a direct comparison of their efficiency as catalysts. The four ligands led indeed to the desired product with high yield and enantioselectivity but different absolute configurations. The *S,P*-ligand **80** furnished the highest enantioselectivity for the synthesis of the (*S*) product, whereas all other chelates led to the opposite enantiomer. From these results, X-ray diffraction studies of the corresponding Pd complexes, and NMR studies, the authors concluded that the different orientations of the allyl moiety were due to the different *trans* effects of coordinating atoms and proposed a C═N > P > S sequence.

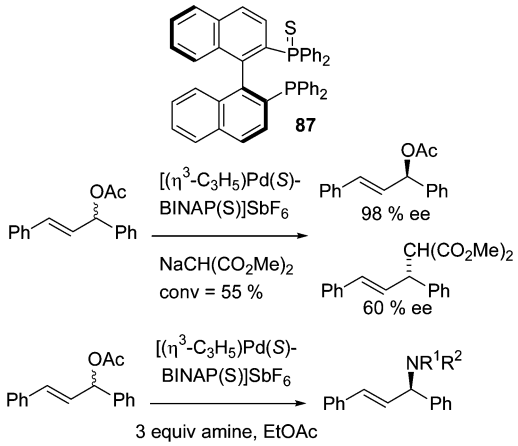
An interesting example has been reported by Hiroi *et al*.,[60] who prepared chiral *β*-phosphino sulfoxides as ligands for the Tsuji−Trost reaction, with the chirality being solely introduced by the chiral sulfoxide moiety. The authors prepared chiral *o*-phosphinophenyl sulfoxides from 2-fluoroiodobenzene and readily available sulfinates. The chiral sulfoxide **84** depicted in Scheme 27 was proven to be stable at room temperature, whereas a complete conversion in the corresponding phosphine oxide could be observed under refluxing THF. Performing the palladium-catalyzed asymmetric allylic alkylation with this ligand at low temperature allowed the formation of the dimethylmalonate derivative with high enantioselectivity (up to 82% ee) and good yield (71%).

Once again, X-ray analyses proved the formation of a five-membered chelated palladium complex with coordination between the phosphino function and the sulfinyl group. It is then assumed that the nucleophile attacks the allyl substrate *trans* to the best *π*-acceptor (here the phosphine group) on

Scheme 27



Scheme 28

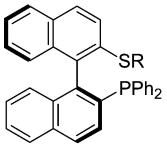


the preferred conformer, obtained by lowering the steric hindrance. This proposed mechanism is in complete agreement with the observed asymmetric induction provided by the use of this ligand. The same group[61] prepared later *N*-diphenylphosphano nitrogen-containing five-membered aromatic ligands with chiral sulfinyl groups as the unique chiral source (see structures **85** and **86** in Scheme 27). The coordination of the sulfur atom and the phosphano group was proven by X-ray crystallographic analyses. Ligand **85** led to an active catalyst in THF at −45 °C, since the expected product was formed with 96% yield and 80% ee. The introduction of a methyl-substituted indole ring (ligand **86**) provided the highest enantioselectivity (93%), probably thanks to the steric hindrance controlling the vicinal chiral sulfinyl group.

Faller *et al*. reported the use of the axially chiral (*S*)-BINAP(S) ligand **87** in Scheme 28 for the kinetic resolution of acyclic allylic acetates.[62] Alkylation of racemic 1,3-diphenylallyl acetate proceeded with 72% ee in the expected product at complete conversion. By adjusting the addition of the nucleophile, the authors were also able to recover the substrate with more than 98% ee at 55% conversion. Interestingly, this catalytic system, applied to the transformation of nonsymmetrical compounds, led to high ratios of branched *vs* linear species whereas Pd catalysis usually led mainly to the linear product. The electronic asymmetry of the ligand was assumed to be responsible for this unusual regioselectivity.

The same group reported more recently[63,64] that the Pd/(*S*)-BINAP(S) system catalyzed efficiently the asymmetric allylic amination of acyclic carbonates. A wide range of amines were tested (primary, secondary, cyclic, or acyclic reagents), leading to enantiomeric excesses of up to 97%. Unsymmetrically substituted substrates were also tested,

Scheme 29



88a R = Me
88b R = $CHMe_2$
88c R = CH_2Ph
88d R = $CHPh_2$

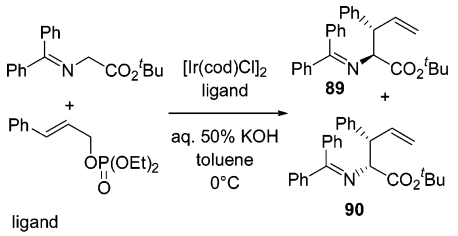
L*	ee
88a	91
88b	60
88c	77
88d	33

leading in these cases to predominantly branched substitution products. X-ray structure analyses of the corresponding palladium complexes were performed, indicating a *S*,*P*-coordination with a narrow angle compared to the P−O−Pd angle observed in the corresponding BINAP(O) complex, probably responsible for the observed regioselectivity.

Axially chiral *S*,*P*-heterodonor ligands BINAPS have been reported by Kang,[65] Gladiali,[66] and Shi[67] with different alkyl groups on the sulfur atom. The structures **88** depicted in Scheme 29 have been synthesized from enantiopure BINOL as the starting material. Kang and co-workers reported 91% ee for the product of the usual allylic alkylation test by using ligand **88a**. Gladiali tested the corresponding isopropyl derivative **88b**, which led to the expected compound in quantitative yield within minutes in 60% ee. Shi obtained 77% ee and 33% ee, respectively, by using ligands **88c** and **88d**. They interestingly obtained a reversal of enantioselectivity between ligands **88a**, **88c** and **88b**, **88d**. According to X-ray analyses and NMR spectroscopic studies, the authors assumed in each case a *S*,*P*-coordination as a metallacycle in a pseudo-boat-seven-membered arrangement. The steric bulkiness of alkyl groups on the sulfur atom seems responsible for the observed reversal of enantioselectivity by favoring one or the other diastereomeric π-allyl complex.

The asymmetric allylic substitution can also be catalyzed by iridium complexes, as reported by Takemoto. Iridium precatalysts proved efficient in the presence of chiral bidentate phosphites bearing thioalkyl groups for this transformation.[68] The authors aimed to control the reaction between 3-substituted allylic alcohol derivatives with unsymmetrical C-nucleophiles for the synthesis of β-substituted α-amino acids. In this case, catalysis in the presence of other transition metals such as iridium led to the product issued from the alkylation at the more substituted terminus of the allylic substrate. The iridium-catalyzed allylic substitution of diphenylimino glycinate was examined in the presence of various allylic alcohol derivatives, and the best results in terms of isolated yield of the expected products were obtained with the phosphate compound, as a more hydrolysis-resistant substrate. Only the branched products **89** and **90** (Scheme 30) were produced with **89** as major diastereomer with the *S*,*P*-chelates **91a**−**c**. The best results in terms of activity and enantioselectivity were obtained with ligand **91a**, which led to a six-membered chelate in the presence of iridium and, thus, to an enhanced nucleophilicity of the catalyst. Interestingly, the choice of the base, and especially the effect of countercations of the resulting enolate, dramatically affected the **89**/**90** diastereoselectivity. Isomer **90** was obtained as the major compound (and up to 97% ee) if the enolate was prepared in the presence of a lithiated base. The use of various substituted phosphate derivatives was considered as a versatile tool toward asymmetric synthesis of both diastereomers. This methodology was applied to the asymmetric synthesis of quaternary α-amino acids starting from an imino

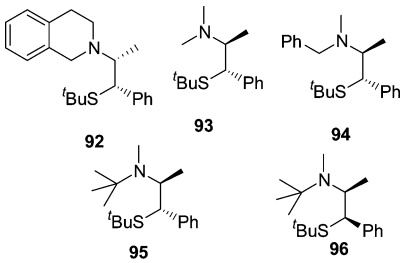
Scheme 30



L*	yield (%) 89+90	ratio 89/90	ee 89
91a	82	82/18	97
91b	43	65/35	29
91c	4	72/25	41

91a R = $(CH_2)_2SEt$
91b R = $(CH_2)_3SMe$
91c R = $(CH_2)_4SMe$

Scheme 31



L*	yield (%)	ee (%)
92	99	72 (*R*)
93	7	87 (*S*)
94	35	78 (*S*)
95	98	89 (*S*)
96	nd	60 (*R*)

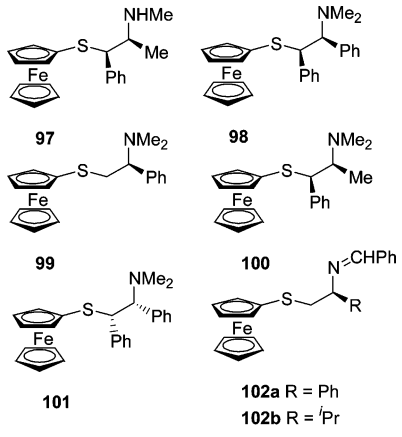
alaninate compound.

2.2.4. Chiral S,N-Ligands

S,N-Chelates, among sulfur-coordinating ligands, have been the most widely studied to promote Tsuji−Trost reactions. As for the analogous aminoalcohols, aminothioethers have been developed and tested in this reaction with the chirality placed mainly on the carbon skeleton but also on an additional ferrocene backbone. Various iminothioethers have been synthesized and successfully used as palladium chelates, and also different pyridine sulfide chelates. However, most examples are found in the sulfur oxazoline series, probably due to the greater ability of the bis(oxazoline) counterparts to lead to very active catalysts for performing carbon−carbon bond formations.

In particular, Page *et al*. synthesized heterobidentate *S,N*-ligands as aminothioethers for achieving this reaction. They first prepared ligand **92** (see Scheme 31) from (*1S,2R*)-norephedrine and 2-(2-bromoethyl)benzylaldehyde.[69] The corresponding palladium catalyst remained inactive by using the usual procedure for the nucleophilic allylic substitution involving BSA and a catalytic amount of potassium acetate. However, the use of cesium carbonate as base allowed the reaction to be performed with total conversion in less than 2 h. Poor enantioselectivities were obtained when the sulfur atom was substituted with an aromatic group, but they increased up to 72% ee for R = ^{t}Bu. The authors explained these results by steric and not electronic considerations.

Scheme 32



L*	t (h)	yield (%)	ee (%)
97	20	87	43 (*S*)
98	20	88	99 (*S*)
99	20	99	79 (*S*)
100	20	96	77 (*R*)
101	20	96	99 (*S*)
102a	90	90	78 (*R*)
102b	90	85	99 (*R*)

Analogous ligands were further synthesized[70] from optically active (*1S,2S*)-pseudoephedrine and various substituents on the nitrogen atom.

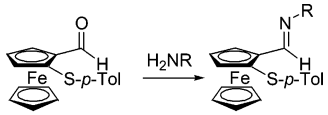
The enantioselectivity of the transformation did not depend to a great extent on the bulkiness of the substituent on the nitrogen atom (compare **93** and **95**, for example, in Scheme 31). However, the absolute stereochemistry of the obtained product differed from that obtained with the first generation of ligands (compare **92** and **93** in Scheme 31, for example) that possess the opposite configuration at the C-2 (norephedrine) methyl group. The synthesis and use of ligand **96** also led to the isolation of the product with (*R*)-configuration, indicating that the stereochemistry of the phenyl group was also decisive in this series.

Bonini *et al*.[71] synthesized and tested, in the Tsuji−Trost reaction, β-aminoalkyl and β-iminoalkyl ferrocenyl sulfides. The stereoselective synthesis of these ferrocenyl sulfides was performed via either regio- and stereoselective ring-opening of aziridines or substitution of mesylated β-aminoalcohols by mercaptoferrocene.

All these ligands were highly efficient and selective for the allylic nucleophilic substitution. The β-dimethylamino derivatives were the most selective. Furthermore, increasing the steric bulk on the backbone chiral centers did not afford better selectivities (compare **99** and **101** in Scheme 32). The imino derivatives led to catalysts as selective but less active. The obtained absolute configuration in the reaction product is in total accordance with an attack of the nucleophile *trans* to the better π-acceptor, *i.e.*, the sulfide (in the case of aminoalkyl ferrocene sulfides) or the imino functionality (for the iminoalkyl ferrocene sulfides **102b**). More recently, the authors used (S_{Fc})-(2-*p*-tolylthio)ferrocenecarboxaldehyde as the key compound for the synthesis of new sulfur-containing ligands and especially 2-(iminoalkyl)ferrocenyl *p*-tolylsulfides **103** (see Scheme 33), possessing a unique planar chirality.[72]

The ferrocenyl imines **103a**−**e** were tested in the palladium-catalyzed allylic substitution, and the aromatic imines afforded the targeted product with ee up to 72%. Imines

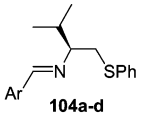
Scheme 33



103 a-e

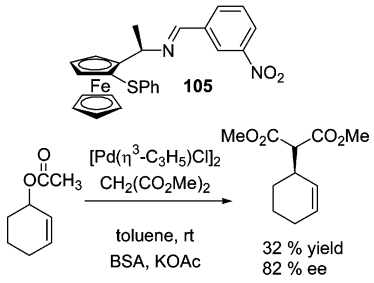
L*	R	ee (%)
103a	*p*-$Me_2NC_6H_4$	72 (*R*)
103b	*p*-$MeOC_6H_4$	70 (*R*)
103c	*o*-ClC_6H_4	32 (*R*)
103d	Mes	15 (*S*)
103e	CH_2Ph	60 (*R*)

Scheme 34



104a-d

L*	Ar =	yield (%)	ee (%)
104a	Ph	86	89
104b	(*p*-NO_2)C_6H_4	77	82
104c	(*p*-MeO)C_6H_4	85	88
104d	(*o*-Cl)C_6H_4	87	94



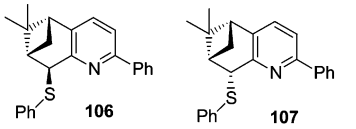
bearing donating substituents in the *para*-position of the aromatic ring gave the best results in this series.

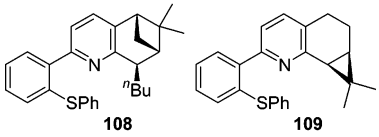
The iminosulfide chelates have been studied in detail by Anderson and co-workers.[73,74] The authors performed this nucleophilic allylic substitution efficiently with palladium complexes containing chiral imine-sulfide chelate ligands derived from aminoacids (**104a**−**d**, Scheme 34).

The ligands **104a**−**d**, obtained easily in two steps from commercially available amino alcohols, were chosen as new mixed donor ligands in which the ligating sulfur atom, instead of the hydroxyl group derived from the amino acid, had a high affinity toward most metals useful in catalytic reactions, and particularly palladium. Up to 94% enantiomeric excess was obtained in the Tsuji−Trost transformation by using ligand **104d**. The authors were able to isolate and characterize a Pd-allyl intermediate by X-ray diffraction. They proposed a possible mechanism for the chirality transfer, controlled by the steric environment of the chiral imine-sulfur chelate ligand, with the reaction occurring *trans* to the imine donor.

Zheng *et al*. later published the synthesis of a chiral ferrocene-based sulfur-imine ligand (**105** in Scheme 34) and tested its efficiency as a palladium chelate for the asymmetric allylic alkylation of cycloalkenyl esters.[75] However, this catalyst was not very active, since only a 32% yield of expected product was obtained after 7 days of reaction, albeit with a good enantioselectivity of 82%. The authors prepared various corresponding ferrocene-based phosphine-imine ligands

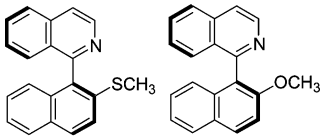
Scheme 35





L*	yield (%)	ee (%)
106	90	83 (*R*)
107	85	78 (*S*)
108	61	32 (*R*)
109	72	63 (*R*)

Scheme 36



that proved both more active and enantioselective for this reaction.

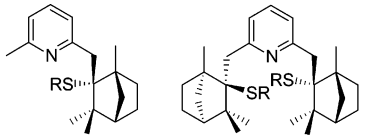
Chelucci *et al*.[76] made a significant contribution to the development of chiral pyridine-type ligands for applications in asymmetric catalysis. They prepared sulfur-containing pyridine ligands and studied their efficiency to chelate palladium for catalyzed allylic substitution (Scheme 35).

Ligands **106** and **107** were readily obtained in a two-step procedure starting from (+)-pinocarvone. By using 2 molar equiv of ligands compared to the palladium precursor, the test Tsuji−Trost reaction was performed with good yields and high levels of asymmetric induction. Both epimeric ligands **106** and **107** gave a similar enantioselectivity, but dimethyl 1,3-diphenylprop-2-enylmalonate was obtained with the opposite configuration, indicating that the stereodifferentiation was highly sensitive to the stereogenic center bonded to the sulfur. Chelucci also reported the synthesis of an analogous class of *S*,*N*-coordinating ligands, namely chiral 2-(2-phenylthiophenyl)-5,6,7,8-tetrahydroquinolines.[77] Their preparation was based on the Kröhnke methodology involving the reaction of α,*β*-unsaturated ketones (from naturally occurring compounds) with a pyridinium salt. Two ligands are drawn in Scheme 35 (structures **108** and **109**), which gave poorer performances in terms of both activity and enantioselectivity compared to the analogous pyridine derivatives.

Chelucci *et al*.[78] described another *S*,*N*-ligand, in which the nitrogen atom is part of an aromatic ring, the 1-(2-methylthio-1-naphthyl)isoquinoline **110** in Scheme 36. The synthesis involved a Suzuki-type coupling, and the formation of Pd-diastereomeric complexes was used for the resolution step.

Unfortunately, the corresponding Pd catalyst tested in the Tsuji−Trost test reaction showed almost no enantioselectivity. The corresponding *N*,*O*-chelate **111** was not a very reactive complex either. After 2 weeks, the expected product could be isolated in 75−80% yield, with 68% ee, when **111** was used.

Scheme 37



(+)-112a, R = H
(+)-112b, R = Me
(+)-112c, R = Et
(-)-112d, R = CH_2Ph

113a, R = Me
113b, R = Et
113c, R = CH_2Ph

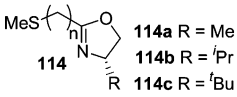
L*	yield (%)	ee (%)
(+)-112a	10	81 (*S*)
(+)-112b	80	53 (*R*)
(+)-112c	84	91 (*R*)
(-)-112d	96	92 (*R*)
113a	83	78 (*R*)
113b	80	84 (*R*)
113c	90	85 (*R*)

Other examples of pyridine sulfide ligands useful in the Pd-catalyzed allylic substitution have been described by Kellogg and co-workers.[79] They prepared pyridine thiols and dithiols by base-induced addition of 2,6-lutidine to thiofenchone. As can be seen from Scheme 37 and the results summarized for ligand **112a**, the catalysts issued from the thiols ligands were not very active, probably due to a deprotonation of the chiral ligand by the base present in the reaction mixture. The authors thus prepared various thioether derivatives by alkylation of the mono- and dithiol adducts and also studied their efficiency in the Tsuji−Trost reaction.

Generally, higher selectivities and activities were observed for all ligands when BSA/KOAc was used as a base, compared to NaH. The best results were obtained by coordination with the benzyl monothioether (−)-**112d**, as can be seen from the results in Scheme 37, and results were further improved (up to 98% ee and 96% yield) when the reaction was performed in acetonitrile (instead of dichloromethane) at 0 °C. The authors obtained an X-ray structure of a palladium complex from **112a**, indicating that the sulfur was coordinated in a rigid six-membered ring, in a single absolute configuration due to the steric hindrance generated by the fenchyl methyl groups. C_2-symmetrical dithioethers **113** also led to high chemical yields and enantioselectivities. However, attempts to obtain structures of the corresponding Pd-allylic intermediates failed.

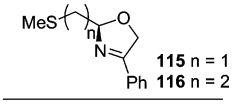
Among *S*,*N*-chelates, sulfur-oxazoline ligands have been the most studied for their potential use in Tsuji−Trost reactions. Williams and co-workers were the first to prepare various *S*,*N*-ligands[80] (structures **114**−**116**, Scheme 38) containing oxazoline functionalities and sulfur as an auxiliary donor ligand, in which the sulfur group was an alkyl sulfide,[81] an aryl sulfide,[81,82] and a sulfide within a thiophene ring.[83] The authors prepared these various ligands to control the stereochemical course of the reaction via the properties of both the oxazoline and the secondary donor atom. The different sulfur groups showed modified binding properties, different steric environments, and different electronic behavior. The ligands depicted in Scheme 38 were obtained in good yields by reacting the appropriate nitriles with homochiral aminoalcohols. All the sulfanylmethyl-oxazolines (see structures **114**, Scheme 38) were efficient ligands for the palladium-catalyzed allylic substitution. Up to 66% ee could be obtained, and this was increased to 75% ee by using an excess of ligand **114c** compared to palladium (4:1). This result suggested that the ligand did not coordinate to the palladium very strongly.

Scheme 38



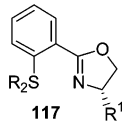
114 **114a** R = Me, **114b** R = ^{i}Pr, **114c** R = ^{t}Bu

L*	yield (%)	ee (%)
114a	68	51
114b	74	70
114c	71	66



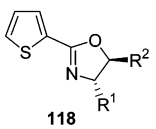
115 n = 1, **116** n = 2

L*	yield (%)	ee (%)
115	86	56
116	79	88



117 **117a** R^1 = Me, R^2 = Me; **117b** R^1 = ^{t}Bu, R^2 = Me; **117c** R^1 = ^{t}Bu, R^2 = Ph

L*	yield (%)	ee (%)
117a	91	40
117b	86	80
117c	92	96



118 **118a** R^1 = Me, R^2 = Ph; **118b** R^1 = CH_2Ph, R^2 = H; **118c** R^1 = ^{i}Pr, R^2 = H

L*	yield (%)	ee (%)
118a	56	6
118b	68	24
118c	63	68

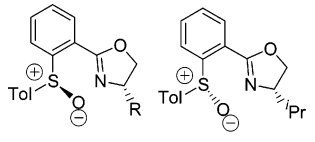
Interestingly, oxazolines **115** and **116** prepared from the aminoalcohol possessing the same relative configuration led to the product with the opposite configuration as the major enantiomer compared to the ligands of series **114**.[84] The authors explained the enhanced enantioselectivity obtained with ligand **116** compared to **115** by the placement of the allyl unit closer to the chiral environment. The longer tether ($n = 2$) in this ligand should allow the formation of a six-membered chelate between the bidentate ligand and the metal.

The use of diarylsulfides[85] (**117c**, Scheme 38) afforded the expected product with the highest enantioselectivity level (96% ee) for this series. Only small changes in enantioselectivity were observed by modifying the nature of the aryl group R_2 on the sulfur atom in **117c**. At the same time and independently, Helmchen *et al.*[86] described an analogous ligand to **117c** (R_1 = ^{i}Pr and R_2 = Ph) and compared its performance in this transformation with the corresponding *P*,*N*- or *Se*,*N*-chelate. They found that the steric course of the reaction was insensitive toward the nature of the soft chelating atom, but the reactivity varied considerably as follows: P > Se > S.

Thiophene-oxazoline ligands were also synthesized and tested (see **118** in Scheme 38) but led to less efficient catalysts for both the activity and the enantioselectivity of the transformation. However, modifying the ligand **118c** to Pd ratio increased both the yield and enantioselectivity of the reaction. The use of a 10-fold excess of **118c** compared to palladium afforded the expected product in 89% yield and 81% ee, suggesting once again that this type of ligand does not bind strongly to the palladium allyl complexes.

Corresponding oxazolines tethered to sulfoxides were also prepared[85] by ortholithiation of the parent 2-phenyl oxazoline with buthyllithium and the addition of either (*S*)- or (*R*)-*p*-tolylmenthylsulfinate (Scheme 39). The diastereomeric ligands **119a** and **120** were tested and led to very different results, demonstrating the importance of the stereochemistry at the sulfur center for determining the stereochemical outcome of the reaction.

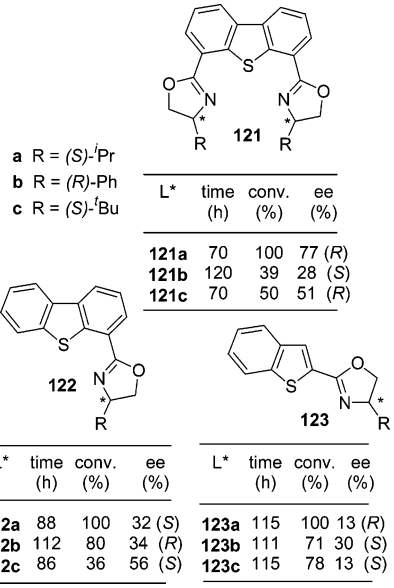
Scheme 39



119a R = *i*Pr **120**
119b R = H

L*	ee (%)	yield (%)
119a	88	96
119b	56	92
120	55	42

Scheme 40



a R = (*S*)-*i*Pr
b R = (*R*)-Ph
c R = (*S*)-*t*Bu

121

L*	time (h)	conv. (%)	ee (%)
121a	70	100	77 (*R*)
121b	120	39	28 (*S*)
121c	70	50	51 (*R*)

122

L*	time (h)	conv. (%)	ee (%)
122a	88	100	32 (*S*)
122b	112	80	34 (*R*)
122c	86	36	56 (*S*)

123

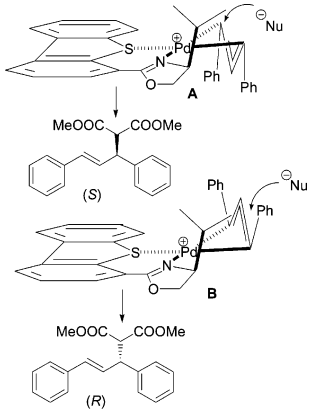
L*	time (h)	conv. (%)	ee (%)
123a	115	100	13 (*R*)
123b	111	71	30 (*S*)
123c	115	78	13 (*S*)

Ligand **119b**, in which the oxazolinyl moiety is achiral, also led to an enantioenriched product. The authors prepared a similar sulfone derivative, but the corresponding palladium catalyst was not reactive for the same transformation. The authors concluded from these results that the sulfoxide ligand was more likely to bind through the sulfur atom than through the oxygen atom.

In view of all these results, we attempted to introduce new sulfur-containing oxazoline compounds.[87,88] We chose dibenzothiophene and benzothiophene as backbones, where the sulfur atom is part of a strong π-donor structure. These skeletons are of particular interest, since their aromatic structure opens the door to a great variety of synthetic transformations, on various positions of the aromatic rings, depending on the procedure used.

Furthermore, different possible sites of chelation are offered by these ligands, *i.e.*, *N*,*N*′- or *S*,*N*-type ligation. C_2-symmetric bis(oxazolines) based on the dibenzothiophene structure (DBT-BOx **121**, Scheme 40) have also been synthesized to allow potential *trans*-chelating tridentate ligands. DBT-MOx **122** and BT-MOx (**123**, Scheme 40) provided different possibilities: the former can afford a six-membered chelate with the metal, whereas the latter may yield a five-membered chelate. All these new sulfur-oxazoline ligands have been prepared in overall good yields starting from the corresponding dibenzothiophene- or benzothiophene- (mono- or di-) carboxylic acids and commercially available amino alcohols.

Scheme 41



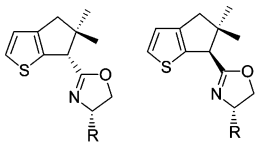
Allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate was investigated first under various reaction conditions with DBT-BOx(*i*Pr) **121a** as the chiral ligand. A high level of enantioselectivity (77% ee, Scheme 40) and activity in the transformation was achieved when the nucleophile was prepared from a BSA/KOAC system in refluxing dichloromethane using allylpalladiumchloride dimer as the catalyst precursor. Analogous ligands **121b** and **121c** were both less efficient and selective when the transformation was performed under these optimized conditions. Furthermore, we observed that DBT-BOx **121a** containing chiral fragments with (*S*)-configuration led to the substitution product with (*R*)-configuration as the major isomer. This is in contrast with results obtained using other C_2-symmetric bis(oxazolines),[89−91] where the (*S*)-configuration in the chiral ligand led to the (*S*)-product as the major compound. Compared with the inefficiency of the dibenzofuran analogue to perform this palladium-catalyzed reaction,[92] we assume a probable participation of the sulfur atom in stabilizing the complex involved in the selective transformation.

DBT-MOx compounds were then used as ligands for the test reaction and the corresponding catalysts allowed the preparation of the desired product, albeit with a lower activity and enantioselectivity than those of the analogous bis-(oxazolines) system **121**. Furthermore, it was observed that, contrary to DBT-BOx(*i*Pr) **121a**, the monooxazoline **122a** led principally to the (*S*)-enantiomer with 32% ee (Scheme 40). This stereochemical outcome of the reaction can be explained as depicted in Scheme 41. The intermediate **A** would be favored compared to **B**, where the steric hindrance is greater between the substituent of the oxazoline ring and the phenyl group of the substrate.

The incoming nucleophile is supposed to attack on the opposite face of the π-allyl system, *i.e.*, on the less sterically hindered face. It is assumed that this electronic information would be transferred, with dibenzothiophene acting as a π-donor, via the *trans* effect to the allyl moiety. In our particular case, the nucleophile would thus preferentially attack the allylic system on the carbon possessing a greater positive charge character, *i.e.*, on the carbon situated *trans* to the nitrogen atom of the oxazoline moiety (see Scheme 41, for DBT-MOx **122a**).

Finally, the Tsuji−Trost reaction was tested in the presence of BT-MOx ligands **123**, as sulfur−nitrogen chelates leading to a five-membered ring with the palladium atom, in an attempt at selectivity control by narrowing the chelating ring size. The results are summarized in Scheme 40, leading, however, generally to catalysts less active than DBT-MOx derivatives.

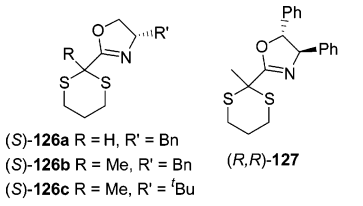
Scheme 42



(*R*)-**124** R = ^{i}Pr (*S*)-**124** R = ^{i}Pr
(*R*)-**125** R = Bn (*S*)-**125** R = Bn

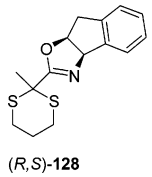
L*	t (h)	yield (%)	ee (%)
(*R*)-**124**	136	95	66 (*S*)
(*S*)-**124**	70	91	70 (*S*)
(*R*)-**125**	96	92	62 (*S*)
(*S*)-**125**	30	93	73 (*S*)
(*R*)-**124**/(*S*)-**124**	112	96	69 (*S*)

Scheme 43



(*S*)-**126a** R = H, R' = Bn
(*S*)-**126b** R = Me, R' = Bn
(*S*)-**126c** R = Me, R' = ^{t}Bu

(*R*,*R*)-**127**



(*R*,*S*)-**128**

L*	yield (%)	ee (%)
(*S*)-**126a**	94	50 (*S*)
(*S*)-**126b**	96	54 (*S*)
(*S*)-**126c**	96	90 (*S*)
(*R*,*R*)-**127**	98	74 (*R*)
(*R*,*S*)-**128**	94	72 (*R*)

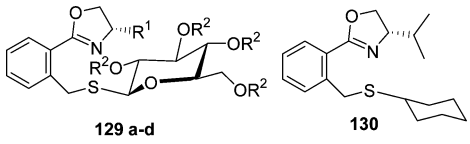
Recently, Ricci *et al.*[93] reported another example of a *S*,*N*-containing ligand where the sulfur atom is part of a thiophene ring and the nitrogen comes from an oxazoline functionality. They thus developed the synthesis of cyclopenta[*b*]thiophene-alkyloxazolines with two chiral carbon atoms as sources of chirality (Scheme 42).

All the complexes formed from 2 equiv of each ligand and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as the palladium precursor proved to be active for the allylic substitution performed in dichloromethane. Good levels of enantioselectivity were obtained with these ligands, leading to products with the same stereochemistry, whatever the configuration of the cyclopentanyl chiral carbon. This result was explained by the authors by the classical *trans* effect for the attack of the nucleophile, leading to the same stable Pd-allyl intermediate in each case. Furthermore, they tested a mixture of two diastereomers ((*R*)-**124** and (*S*)-**124**) to obtain the expected product (same configuration) with a comparable yield and enantioselectivity. Interestingly, it was concluded that in this case the resolution of the diastereoisomeric mixture was not necessary to obtain good enantioselectivity in the catalytic process. The chiral center located in the oxazoline core thus seemed of major importance for inducing high enantioselectivity, as had already been observed by Williams and coworkers in the preceding examples.

The same group later reported the synthesis of new nitrogen−sulfur-donating ligands, containing a chiral oxazoline moiety and the 1,3-dithianyl motif.[94] The ligands depicted in Scheme 43 were tested as palladium chelates for performing the test reaction under standard conditions.

The corresponding palladium complexes were found active for this transformation, since the expected substitution product was isolated in very high yield after a 4 h reaction

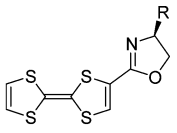
Scheme 44



129 a-d **130**

L*	R^1	R^2	t (h)	yield (%)	ee (%)
129a	^{i}Pr	C(O)Me	72	99	93 (*S*)
129b	^{i}Pr	C(O)^{t}Bu	96	40	97 (*S*)
129c	Ph	C(O)Me	7	99	90 (*S*)
129d	Ph	C(O)^{t}Bu	6	62	96 (*S*)
130	-		23	75	75 (*S*)

Scheme 45



131 a-c

L*	R	yield (%)	ee (%)
131a	^{i}Pr	29	21
131b	Ph	28	17
131c	^{t}Bu	trace	-

time at ambient temperature. The presence of a methyl substituent on the dithianyl ring (compare **126a** and **126b** in Scheme 43) did not seem crucial for the enantioselectivity of the transformation. However, good enantioselectivity was achieved when the oxazoline ring was functionalized with bulky substituents. The best ee for this series of ligand was obtained with compound **126c** (90% ee), bearing a *tert*-butyl group.

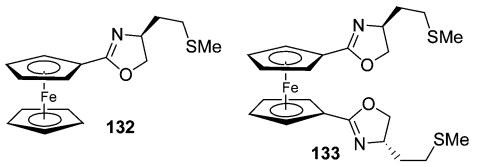
As already mentioned in the previous section, Pregosin *et al*. published the use of combined phosphino-thioether mixed ligands and their use in palladium-catalyzed enantioselective allylic alkylation.[44] These authors then prepared analogous *S*,*N*-chelates, with the nitrogen function arising from an oxazoline group and the *S*-coordinating atom from a thiosugar moiety.[95] They thus prepared the series of ligands **129** (see Scheme 44) with various substituents on the oxazoline or thioglucose part.

All ligands contained stereogenic centers both on the oxazoline core and on the sugar moiety. Their use in enantioselective allylic alkylation afforded very high enantiomeric excesses (see Scheme 44), whereas in ligand **130**, in which the thioglucose function was replaced by a cyclohexyl ring for comparison, the selectivity was significantly lowered. Furthermore, better results were obtained when the thiosugar moiety was substituted by bulky substituents (pivaloyl derivatives compared with acetate derivatives).

Bryce synthesized chiral oxazolines linked to tetrathiafulvalene[96] for their use as redox-active ligands. The authors aimed at the synthesis of a chiral ligand capable of performing an enantioselective transformation with the subsequent loss of the metallo-intermediate upon electrochemical oxidation, to improve the catalytic cycle. Tetrathiafulvalene-modified oxazolines were synthesized for this purpose and tested, as depicted in Scheme 45.

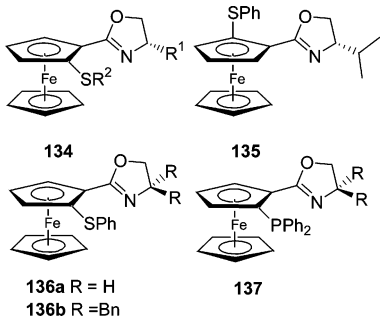
Low enantiomeric excesses were measured for these catalytic systems. However, a quasi-reversible interaction between the palladium source and **131a** was proven by cyclic

Scheme 46



L*	yield (%)	ee (%)
132	98	93
133	93	91

Scheme 47



136a R = H
136b R =Bn

voltammetric measurements, indicating that the binding of the palladium to this ligand should be electrochemically controlled. These authors later improved the activity, the enantioselectivity, and electrochemical stability of this type of complex via the synthesis of chiral ferrocenyl-oxazolines incorporating thioether units (Scheme 46).[97]

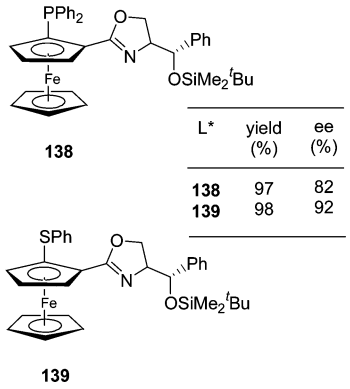
These redox-active liganding systems were successfully used in palladium-catalyzed allylic substitution reactions (up to 93% ee). The binding of palladium to these ligands was studied by cyclic voltammetry and proved to be reversible. This electrochemical behavior seemed promising for an application of analogous catalysts in reactions where electrochemical recycling is the main step in the catalytic cycle.

Numerous ferrocenyl-based sulfur-coordinating ligands have been synthesized and tested to study the influence of the planar chirality on the stereochemical course of the Tsuji−Trost reaction. A series of chiral thioether derivatives of ferrocenyl oxazolines were prepared by You *et al.*[98] by diastereoselective lithiation followed by electrophilic quenching of the oxazoline ferrocene. The authors varied the R^1 group on ligand **134** using commercially available aminoalcohols and the R^2 group (Me, Ph, Tol) on the sulfur atom (Scheme 47).

Up to 98% ee and a nearly quantitative yield could be obtained with **134** (R^1= ^{t}Bu, R^2 = Ph), in only 1 h of reaction time. The use of a diastereomeric ligand to **134** (see **135** in Scheme 47) led to a similar enantioselectivity and absolute configuration, indicating that the central chirality of the oxazoline ring played a major role in controlling the enantiodifferentiation. The authors proved this assumption by synthesizing the single planar thioether **136a** and obtained the Tsuji−Trost product with only 8.5% ee.

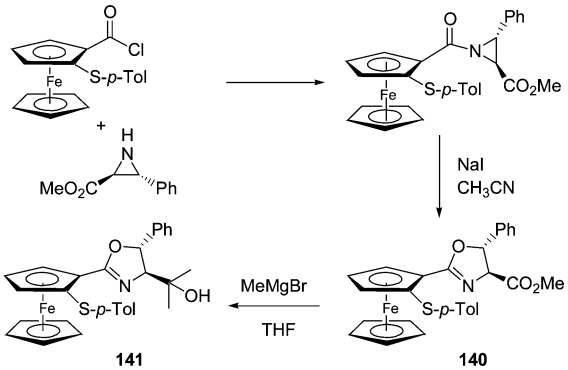
The same group also studied the precise role of planar chirality in ferrocene systems on the enantioselectivity in the Tsuji−Trost reaction.[99] Indeed, ligands **134** (*S*,*Sp*) and **135** (*R*,*Rp*), as diastereoisomers, led to the product with the same configuration, but the ee obtained with **135** (90%, mismatched chirality) is lower than the ee obtained with ligand **134** (98%, matched chirality). Therefore, the authors

Scheme 48



L*	yield (%)	ee (%)
138	97	82
139	98	92

Scheme 49



assumed that the effect of planar chirality should not be overlooked. Interestingly, the type **136b** ligand modified on the oxazoline ring by two Bn groups afforded the substitution product in 72% ee. This result was explained by the creation of a new chirality on the sulfur atom by coordination to palladium, dependent on the steric hindrance. Conversely, when the bis(oxazoline) in **136** was not substituted (*i.e.*, **136a**), there was no diastereoselectivity in the coordination process and the chirality on the sulfur atom was easily racemized, leading to poor enantioselectivity in the catalytic transformation. The authors prepared analogous *P*,*N*-ligands with only planar chiralities (see **137** in Scheme 47): they led to higher enantiocontrol, since such a disturbance could not occur on the phosphorus atom.

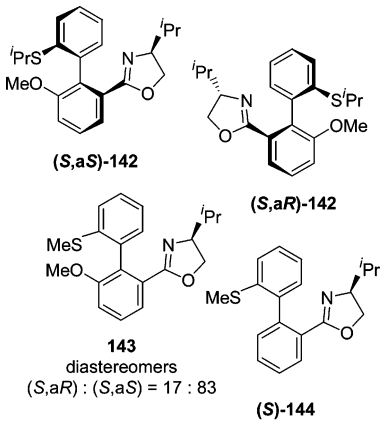
Aït-Haddou *et al.*[100] also prepared ferrocenyloxazolines with two stereogenic centers starting from asymmetric 2-amino-3-phenyl-1,3-propanediol. They further modified them into ferrocenes with planar chirality by introducing a phosphine and/or a phenylsulfenyl functional group diastereoselectively in the *ortho*-position, due to a nitrogen-directed lithiation (Scheme 48).

The catalytic results are very good, and they are especially high for the *S*,*N*-chelate in terms of both activity and enantioselectivity.

More recently, a new synthesis of ferrocenyl oxazolines was described by Bonini and Zwanenburg.[101] Their synthesis is based on an iodide-mediated ring expansion of *N*-ferrocenoyl-aziridine-2-carboxylic esters as depicted in Scheme 49.

The ligands **140** and **141** were successfully used as palladium chelates for the allylic substitution of 1,3-diphenyl-prop-2-enyl acetate, since they led to a total conversion within a few hours, with respectively 68 and 90% ee. However, the additional chiral center (compared with other analogous ligands) present in the oxazoline backbone did

Scheme 50



L*	time (h)	yield (%)	ee (%)
(S,aS)-142	96	trace	-
(S,aR)-142	48	92	20 (*S*)
143	72	90	74 (*S*)
(S)-144	48	93	82 (*S*)

not seem to be of major importance for the ee and the activity of the corresponding catalysts.

Chiral sulfur-oxazoline ligands in which the presence of a biphenylbackbone brought additional axial chirality were introduced by Ikeda and co-workers.[102] Chiral ligands with an axis-fixed (see **142** and **143** in Scheme 50) and an axis-unfixed (see **144**) biphenyl backbone were obtained in good yields by coupling reactions of methoxybenzene derivatives, substituted with a chiral oxazoline, and a sulfur-containing Grignard reagent.

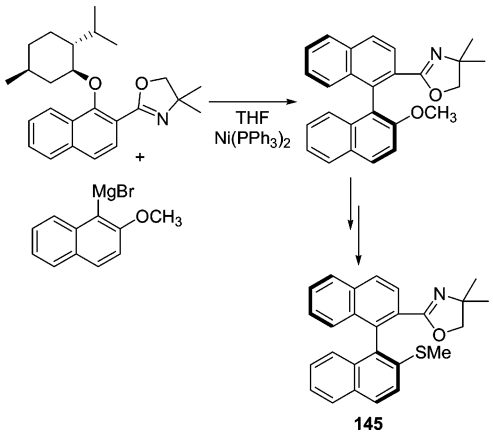
The axial chiral ligands were tested in the palladium-catalyzed asymmetric allylic alkylation, and (a*R*)-axial structures proved to be interestingly more active than (a*S*)-axial ones, although they both led to poor enantioselectivities. The catalyst derived from ligand **143**, present as a diastereomeric mixture, afforded good yields and 74% ee. Ligand (*S*)-**144**, having a free rotation biphenyl axis, was proven to adopt only one of the two possible diastereoisomers, as determined by ^{1}H NMR, on coordination with bis(acetonitrile)−dichloropalladium(II). Consequently, the corresponding complex showed the highest catalytic activity (93% yield) and enantioselectivity (82%) for the test reaction. As a comparison, Gladiali prepared a novel binaphthalene-templated *S*,*N*-ligand possessing axial chirality as the unique chiral source and an achiral oxazoline unit.[103] The ligand was obtained in 85% ee and high chemical yield via a Ni-catalyzed asymmetric coupling between disubstituted naphthalene derivatives (Scheme 51).

In the Pd-catalyzed allylic alkylation, ligand **145** led to the expected product with complete conversion of the substrate and up to 66% ee.

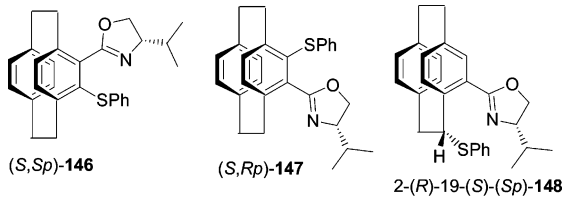
Another type of *S*,*N*-ligands possessing planar chirality was developed by Hou *et al.*[104] from [2.2]paracyclophane. There are few reports concerning the use of chiral [2.2]-paracyclophane in asymmetric catalysis. The authors reported the preparation of *S*,*N*-ligands possessing planar and central chirality by modifying the paracyclophane backbone with oxazoline moieties (Scheme 52).

These new ligands catalyzed the Tsuji−Trost reaction to afford the substitution product in almost quantitative yield. Ligand **148**, in Scheme 52, with substituents at both benzylic and benzene ring positions, gave the highest ee value and

Scheme 51

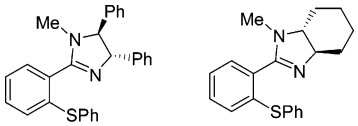


Scheme 52



L*	time (h)	conv (%)	ee (%)
146	32	98	54 (*R*)
147	21.5	98	63 (*S*)
148	1.5	98	94 (*S*)

Scheme 53



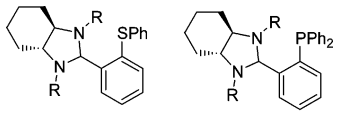
L*	yield (%)	ee (%)
149	78	96
150	59	48

the highest reactivity. The authors assumed that the longer tether between the donor atoms that coordinate the palladium one brought the asymmetric environment closer to the allyl species during the reaction.

As developed above, and among *S*,*N*-ligands, chiral oxazolines bearing various organosulfur substituents have been often synthesized and used with great success for the nucleophilic allylic substitution. In this context, Morimoto *et al.*[105] prepared chiral thioimidazoline ligands assuming that the more electron-rich imino groups (amidines) could beneficially affect the corresponding Pd catalyst in terms of both activity and enantioselectivity, compared to the imidate group in oxazolines. The preparation of ligands **149** and **150** (Scheme 53), starting from 2-bromobenzonitrile and the corresponding chiral diamines, was achieved in 4 steps with 13% and 8% global yield, respectively.

Although the enantioselectivity and activity for **150** were modest, very good results were obtained with **149** (see Scheme 53), which are comparable with those obtained by the sulfur oxazoline chelates developed by Williams (see results obtained by ligand **117c** in Scheme 38).

Scheme 54



151 R = Me
152 R = Et

153 R = Me
154 R = Et

L*	t (h)	conv (%)	ee (%)
151	24	29	45
152	24	24	35
153	4	> 99	97
154	4	> 99	95

Kim *et al.*[106] were interested in testing analogous chiral imidazolidine ligands in this Pd-catalyzed asymmetric allylic alkylation. They prepared thioimidazolidines (**151** and **152** in Scheme 54) and the corresponding phosphinoimidazolidines (**153** and **154**, in Scheme 54), starting from (*R*,*R*)-1,2-diaminocyclohexane, converted into its *N*,*N*′-dialkyl analogues.

The authors performed the reaction in each case in the presence of BSA and LiOAc as base, in THF at room temperature with a ligand/catalyst ratio of 4/1. The phosphinoimidazolidine ligands were both efficient and selective for this transformation, whereas the corresponding *S*-containing ligands where much less active and enantioselective.

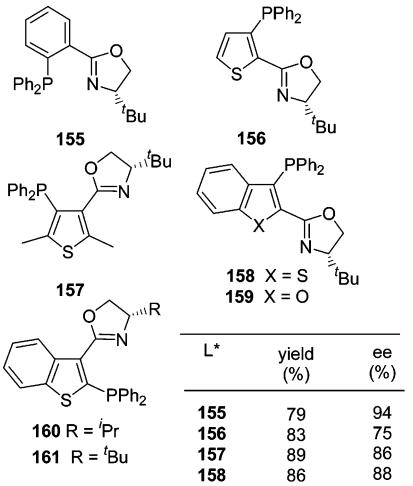
To conclude this section, numerous *S*,*N*-chelates have been efficiently synthesized and tested as palladium ligands to perform nucleophilic allylic substitutions. Due mostly to their rapid synthesis and their high stability, these structures have attracted much attention. However, apart from very few exceptions, the corresponding catalysts remained generally both less active and less enantioselective than the analogous *N*,*P*-counterparts.

2.2.5. Ligands with an S-Noncoordinating Atom

A last class of ligands has to be mentioned in this article, even if their sulfur atom is not directly concerned with the coordination to the transition metal. Hence, sulfur-containing but not coordinating compounds have been synthesized and tested as ligands for performing the Tsuji−Trost reaction. We have chosen to summarize some examples in which the sulfur atom is part of an aromatic ring (in diphosphine chelates, for instance) or of a thiazoline ring, thus modifying the electronic properties of the coordinating atom. The results obtained in terms of activity and selectivity of the corresponding catalysts are compared with those from the more usual structures. To conclude this section, sulfoxide- and sulfoximine-containing ligands are presented, capable of performing enantioselective Tsuji−Trost reactions, with the asymmetry being solely introduced through the chiral sulfur atom.

In order to prepare large-scale, easily accessible ligands, Tietze *et al.*[107] synthesized various chiral thiophene-, benzothiophene-, and benzofuran-oxazoline/phosphine-containing ligands. The authors described a simple introduction of the substituents on the heteroaromatic backbone by metalation (or bromination followed by halogen−metal exchange) and subsequent introduction of an aldehyde function (precursor of the oxazoline moiety) or reaction with PPh_2Cl (to introduce the diphenylphosphine group). The sulfur atom in these ligands is not a chelating atom but influences the course of the reaction by modifying the electronic distribution on the aromatic core.

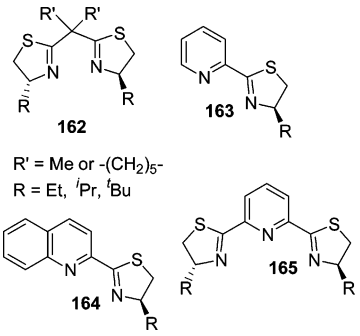
Scheme 55



160 R = ^{i}Pr
161 R = ^{t}Bu

L*	yield (%)	ee (%)
155	79	94
156	83	75
157	89	86
158	86	88
159	89	86
160	92	97
161	91	94

Scheme 56



R′ = Me or -$(CH_2)_5$-
R = Et, ^{i}Pr, ^{t}Bu

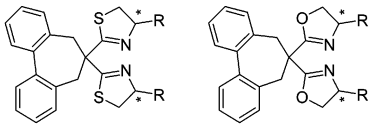
The highest enantioselectivity (97%) and yield (92%) were achieved with ligand **160** within 2 h at 0 °C. The position of the substituents at the heterocyclic skeleton of the ligand was important for the enantiomeric excess (compare ligands **156** and **157** or **158** and **161**; Scheme 55). However, replacement of the sulfur atom by an oxygen atom in the benzofuran ligand **159** did not have a strong effect on the results. These values compare well with those obtained from the well-known analogous phosphino-oxazoline **155**. A similar study was latter published by Cozzi and co-workers.[108]

Masson *et al.*[109] prepared sulfur analogues of the well-known chiral mono- and bis(oxazolines) (*i.e.*, thiazoline derivatives) to study the influence (both steric and electronic properties) of the sulfur atom, replacing the oxygen atom, on the enantioselectivity and activity observed in the Tsuji−Trost reaction. Once again, this example illustrates the role of sulfur-containing (and not coordinating) ligands for the performance of this reaction.

The authors developed an easily accessible procedure to synthesize these ligands by using dithioesters as sulfur sources and commercially available aminoalcohols. Their method thus allowed the preparation of various ligands as structures **162** (see Scheme 56) with about 75% overall yield for five steps.

Furthermore, they prepared 2-pyridyl **163** and 2-quinolyl thiazolines **164** and a tridentate thiazoline derivative **165** analogous to the well-known PyBox. A preliminary test to evaluate these ligands as Pd chelates in the Tsuji−Trost reaction was performed only with structure **162** (R = Et, R′

Scheme 57



166a R = $CH_2CH(CH_3)_2$
166b R = $CH(CH_3)_2$
166c R = CH_2Ph
166d R = Ph

167a R = $CH_2CH(CH_3)_2$
167b R = $CH(CH_3)_2$
167c R = CH_2Ph
167d R = Ph

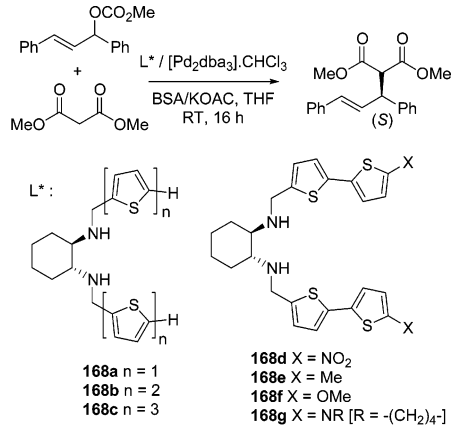
L*	Temp (°C)	yield (%)	ee (%)	config
166a	0	87	16	*S*
167a	20	88	74	*R*
166b	0	89	56	*S*
167b	20	86	75	*R*
166c	0	84	14	*R*
167c	20	83	73	*R*
166d	0	86	19	*S*
167d	20	90	86	*R*

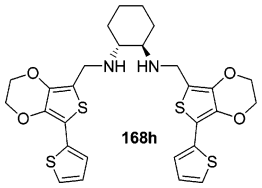
= Me) to yield the desired substitution product with 87% ee and 90% yield. The reaction mixture was stirred in toluene at room temperature over 3 days. As a comparison, an analogous bis(oxazoline) (R = CH_2Ph, R′ = Me) afforded the same product (and same configuration) in 88% ee and 97% yield (in dichloromethane at room temperature also in nearly 3 days of reaction).[110] In this case, the presence of the sulfur atom replacing the oxygen atom, did not seem to strongly modify the course of the catalytic transformation. The authors reported recently a more detailed study[111] with a direct comparison with the known oxazolines analogues. Ligands of type **162**, with Et, ^{i}Pr, or ^{t}Bu substituents on the thiazoline rings, led to the preparation of more active and enantioselective catalysts by palladium coordination, compared to the analogous oxazolines. The authors observed an inversion in the product configuration by using the ^{t}Bu-substituted ligand and suspected a possible competition between sulfur and nitrogen for the palladium chelation, leading to the coexistence of three π-allylic palladium complexes as intermediates in the reaction mixture. However, they were able to isolate crystals suitable for X-ray analyses that showed a *N*,*N*-coordination in the solid state. Pyridyl thiazolines of type **163** proved to be less active but slightly more enantioselective than their parent oxazolines whereas the sulfur-containing pyridine bis(thiazoline) **165** was completely inefficient.

Recently, Du *et al.*[112] prepared another series of C_2-symmetric bis(thiazoline) ligands bridged by a dibenzo[*a*,*c*]-cycloheptadiene backbone. The synthesis of their new ligands involved the standard preparation of the corresponding dihydroxy diamides followed by a new cyclization method with P_2S_5 and triethylamine in refluxing toluene.

To understand the effect of the presence of a sulfur atom in the structure, the authors also synthesized the corresponding bis(oxazolines) and tested both families of ligands in the allylic alkylation test reaction. In all cases, bis(oxazolines) proved to be better ligands in terms of selectivity (up to 86% ee, compared to 56% ee for the bis(thiazoline) **166b** (Scheme 57), but the sulfur-containing ligands led to more active catalysts. Similar yields were indeed obtained in a comparable reaction time (72 h) when the reaction was performed at 0 °C with the series of ligands **166** (or 20 °C with the oxygen-containing chelates). Interestingly, (*S*)-bis(oxazolines) led to the major product with (*R*) configuration, whereas the corresponding (*S*)-bis(thiazolines) led to the reversed configuration (except for ligand **166c**). The authors proposed that both series of ligands may have a different coordination

Scheme 58





L*	yield (%)	ee (%)
168a	65	45
168b	96	99
168c	99	99
168d	75	60
168e	96	99
168f	98	99
168g	98	99
168h	98	98

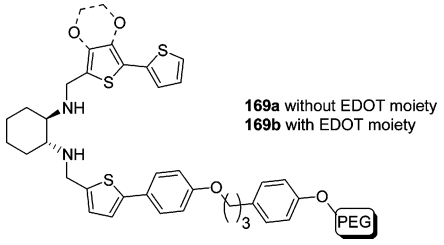
configuration in the transition states, since sulfur, as a better liganding atom than oxygen, may compete for chelation with nitrogen in the thiazoline structure. Since the steric effect near the sulfur atom is less large than that near the nitrogen atom, the enantioselection is much weaker. Unfortunately, the authors did not succeed in preparing palladium crystals suitable for X-ray analyses from the thiazoline series.

Very recently, Bandini, Umani-Ronchi, *et al.*[113] described the synthesis of new *N*,*N*-palladium chelates as chiral diamino oligothiophenes. X-ray diffraction studies of palladium complexes of ligand **168b** (see Scheme 58) clearly showed a five-membered palladacycle through the nitrogen atoms but also a significant van der Waals interaction between the sulfur atom of one inner thiophene ring and palladium.

These ligands were thus tested as Pd chelates for catalyzing the reaction depicted in Scheme 58, and **168b** or **168c** proved particularly efficient, since the targeted product was synthesized in nearly quantitative yield with excellent enantiomeric excess. The reaction between the same carbonate and dimethyl methylmalonate as a more challenging nucleophile also led to the desired product with 99% ee in the presence of **168b**. Under optimized conditions, 1,3-dimethylallyl carbonate reacted with dimethyl methylmalonate in the presence of this ligand, leading to the substitution product in up to 90% ee. The important role played by the inner thiophene ring was proven by preparing analogous ligands to **168b** bearing one or two phenyl rings replacing one or two thiophene rings. High enantioselectivities were obtained when only the thiophene ring was maintained close to the nitrogen-chelating unit. The authors concluded that the weak Pd/S interaction, as a noncovalent secondary interaction, was crucial for a very efficient enantiofacial discrimination around the metal center. The fine-tuning of the catalyst efficiency was further optimized using the presence of this easy functionalizable thiophene ring as an additional ancillary ligand. This approach was named by the authors: molecular remote control (MRC).[114]

Since oligothiophenes are renowned for their easy charges shuttling along the organic backbone, the modification of

Scheme 59



their skeleton, even in positions away from the metal center, should affect the efficiency of the corresponding catalyst. Ligands **168d**−**g** were synthesized possessing various electron-donating or electron-withdrawing substituents at the α-position of the bithienyl group (see Scheme 58). All new ligands led to the targeted compound with very high enantioselectivities except ligand **168d**, possessing the nitro group. It should also be noted that the stronger the electron-donating character of the thiophene substituent is, the greater the initial reaction rate. The synthesis of ligand **168h**, possessing the strongly electron-donating 3,4-ethylenedioxythiophene (EDOT), led to excellent results, confirming the conclusion that the sulfur−palladium interaction observed in the solid state was also present in solution.

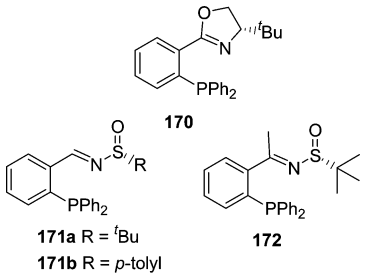
With this catalytic system, the authors reported one of the rare examples of asymmetric heterogeneous catalysis conducted in the presence of sulfur-containing ligands.[115] The diamino-oligothiophene was modified for easy grafting on a soluble polymeric support (MeOPEG). The ligands **169** (see Scheme 59) associated to palladium could catalyze the Tsuji−Trost reaction depicted in Scheme 58 either as homogeneous or heterogeneous catalysts, depending on the transformation solvent.

In dichloromethane, *i.e.*, under homogeneous conditions and after an optimization of the reaction conditions, no loss of activity or selectivity was observed using ligand **169a** (Scheme 59) instead of its nonsupported analogue **168b** (Scheme 58). In THF, in which the polymer is insoluble, similar results were obtained. Hence, the same polymer was interestingly used either as homogeneous or heterogeneous catalyst, leading in both cases to high results in terms of both activity and selectivity. Under those conditions, however, ligand **169b** proved less efficient. The recovery and reuse of catalyst issued from **169a** were also studied. Even if an efficient procedure for the recovery of the ligand is described, the catalysts reuse attempts (without the addition of Pd salt) were accompanied by a significant loss in both activity and enantioselectivity over three cycles.

Ellman *et al.*[116] developed a new type of ligands with *S*-containing atoms, with the chirality being solely introduced on this heteroatom. They thus prepared sulfinyl imines, through condensation of commercially available *tert*-butanesulfinamide with aldehydes or ketones, such as structures **171a** for a comparison of their chelating abilities with those of phosphinooxazolines **170** in Scheme 60.

The catalytic test transformation was performed in CH_2Cl_2 in the presence of a slight excess of palladium relative to the ligand. The authors observed a decrease in the enantiomeric excess when the ligand was present in excess and assumed in this case the displacement of the chiral sulfinylimine moiety from the palladium by the -PPh_2 group of another ligand, leading to a less selective catalyst. The good activity and selectivity of ligand **171a** compared to **171b** was explained by the positive effect of the steric hindrance and

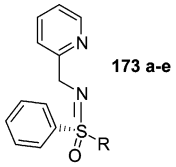
Scheme 60



L*	t (h)[a]	ee(%)
170	nd	94
171a	8.5	93
171b	> 25	0
172	5	56

[a] for 100% conv

Scheme 61



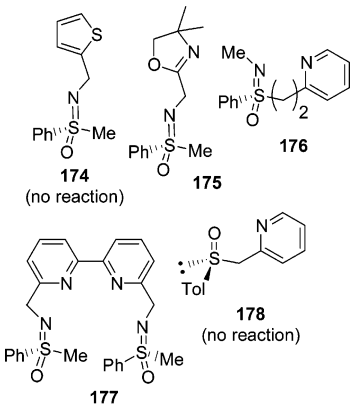
L*	R	Solvent	yield (%)	ee (%)
173a	CH_3	CH_2Cl_2	89	39
173b	$CHMe_2$	CH_2Cl_2	65	39
173c	$(CH_2)_2C_6H_5$	CH_2Cl_2	80	52
173d	$(CH_2)_2$-*o*-$(CH_3O)C_6H_4$	CH_2Cl_2	73	51
		toluene	82	54
173e	$(CH_2)_2$-*o*-$(HO)C_6H_4$	toluene	50	65
		toluene (-5°C)	77	73

the donating ability arising from the *tert*-butyl group. A π-allyl−Pd(II) complex of ligand **171a** was isolated, and its X-ray crystal structure confirmed a *P*,*N*-chelating ligand with the formation of a six-membered ring. All the catalytic results described above were obtained with high catalyst loading (30 mol %), and the reduction of this concentration led to slow transformations and to selectivities highly dependent on the substrate concentration. By increasing the steric hindrance on the phosphorus atom in **171a** (*o*-tol instead of Ph), the authors obtained a more active catalyst (even at low catalyst loading, *i.e.*, 5 mol %, 4 h reaction time), approaching the best results obtained with the more usual phosphinooxazoline **170**. Ketimine ligand **172** provided an increase in the reaction rate but did not improve the enantioselectivity of the transformation.

Bolm *et al.*[117] prepared *N*,*N*-chelating ligands, with the chirality being provided by the presence of a sulfoximine functionality, such as structures **173a**−**e** in Scheme 61.

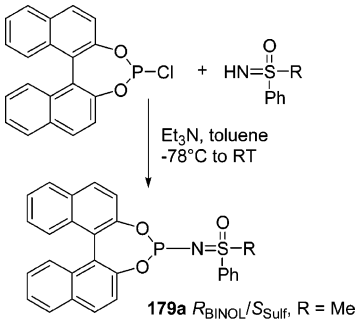
Corresponding Pd(II)−π-allyl complexes could be isolated and studied by X-ray crystal analyses to prove a *N*,*N*-coordination. These ligands were tested in the Tsuji−Trost reaction (2 mol % of the Pd(II)−π-allyl dimer, BSA, KOAc in either CH_2Cl_2 or toluene, at room temperature) to afford the desired product in good yield, but with moderate enantioselectivity depending on the R substituent at the sulfur atom. An alkyl group led to low ee, whereas a phenethyl functionality improved the selectivity. Changing CH_2Cl_2 to toluene also enhanced the yield and the enantioselectivity of the reaction. The presence of a hydroxyl group on the aryl substituent increased the ee, and so did a lower reaction temperature (−5 °C). The best result was achieved using

Scheme 62



L*	yield (%)	ee (%)
175	99	35
176	11	13
177	56	13

Scheme 63



179a R_{BINOL}/S_{Sulf}, R = Me
179b S_{BINOL}/S_{Sulf}, R = Me
179c R_{BINOL}/S_{Sulf}, R = ^{t}Bu
179d S_{BINOL}/S_{Sulf}, R = ^{t}Bu

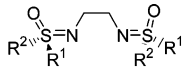
L*	yield (%)	ee (%)
179a	93	57 (*R*)
179b	95	35 (*S*)
179c	90	63 (*R*)
179d	89	58 (*S*)

ligand **173e** (77% yield and 73% ee). The authors attempted to further vary the structure of the chelates and proposed other *N*,*N*-sulfur-containing ligands (see Scheme 62) but without encouraging results.

Recently, Reetz and Gais[118] prepared BINOL-derived *N*-phosphino sulfoximines (see Scheme 63) through a high yield, one-step phosphorylation of the corresponding sulfoximines. These ligands were tested in the presence of Pd to perform the usual Tsuji−Trost reaction. Although currently it is unclear whether these compounds act in a monodentate manner or if they are *P*,*O*-chelates, they catalyzed the reaction in high yield and up to 63% ee. The authors observed that the ligand/Pd ratio greatly influenced the selectivity of the reaction, with the best results mainly obtained with a 1/1 ratio. The matched versus mismatched combinations led to important variations in the ee values (compare **179a** and **179b** in Scheme 63), and the more sterically hindered ligand **179c** led to the highest ee.

Bolm *et al.*[119] also described the synthesis and use of C_2-symmetric bis(sulfoximines) as ligands in palladium-

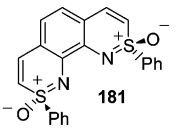
Scheme 64



180 a-d

L*	R^1	R^2	t	yield (%)	ee (%)
180a	Me	Ph	5 d	73	72
180b	^{i}Pr	Ph	5 d	78	76
180c	^{c}Pent	Ph	5 d	78	90
180d	2-MeO-Ph	Me	2 h	99	8

Scheme 65



181

Solvent	t (h)	yield (%)	ee (%)
THF	5	80	80
benzene	3	90	82
toluene	3.5	85	78
CH_2Cl_2	4	30	0
CH_3CN	5	45	0

catalyzed allylic alkylations. Both nitrogen atoms, in this case as *N*,*N*-chelates, came from the sulfoximine moieties which were coupled through reaction with oxalyl chloride and subsequent borane reduction of the carbonyl groups. The authors prepared ligands bearing aliphatic and aromatic substituents at the sulfur atom and observed (see Scheme 64) that steric bulk allowed an increase in the enantiomeric excess of the expected substitution product. However, the corresponding catalysts were poorly active, since good conversions (*i.e.*, 70−80% yield) could only be obtained after 5 days of reaction at room temperature. However, only ligand **180d** proved to be much more active (99% yield in 2 h) with complete loss of selectivity (8% ee). They also used ligand **180c** as the most selective ligand of this series to perform nucleophilic substitution with substituted malonates. The product corresponding to the substitution with the acetamido-derived diethylmalonate was obtained in 98% ee and isolated in 89% yield after 96 h of reaction in refluxing dichloromethane.

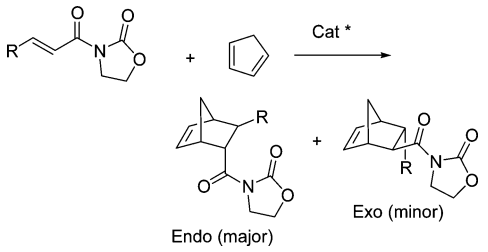
Harmata *et al.*[120] described a chiral bis(benzothiazine) **181** from the reaction of a sulfoximine with a dialdehyde and prepared both enantiomers in good yield (68%, Scheme 65). The authors studied, in particular, different reaction conditions to perform the Tsuji−Trost allylic alkylation and proved that good conversions and enantiomeric excesses were obtained in relatively nonpolar solvents whereas the reaction remained racemic in dichloromethane or acetonitrile. They also evaluated their ligand in the reaction with cyclohexenyl acetate, but the corresponding catalyst proved moderately active and enantioselective (60% ee).

2.2.6. Conclusion

Since the pioneering works of James *et al*. and Kellogg *et al*. devoted to the use of chiral sulfur-coordinating ligands in asymmetric catalysis, numerous articles have been pub-

lished dealing with the successful application of these ligands in enantioselective catalytic C−C bond formations. The Tsuji−Trost reaction has been hence successfully performed using various *S*,*S*-, *S*,*P*-, or *S*,*N*-chelates to achieve the test reaction. Key advantages of these new types of ligands are their easy synthesis, mostly starting from readily available commercial compounds, and their stability, which facilitates the catalytic procedures. Chiral homodonor *S*,*S*-ligands afforded generally dimethyl 1,3-diphenylprop-2-enylmalonate as the test reaction product with moderate activity and enantioselectivity. Noteworthy, however, are the excellent results in terms of selectivity obtained by Gómez, Martin, *et al*. with type-DMPS chiral dithioethers as palladium chelates for the transformation of linear nonsymmetrical substrates as a probably very important base for the development of highly competitive catalytic systems. The seminal work of Enders' group for the preparation of very efficient *S*,*P*-ligands incorporating a thioether as a chiral control element and a diarylphosphinite moiety inspired a lot of research for the preparation of structurally different heterodonor ligands. Whereas *S*,*P*-ligands containing a carbohydrate skeleton were demonstrated to be efficient chirality inductors, the results were less impressive with ligands arising from a planar or axial chirality. *S*,*N*-Chelates were by far the most studied structures, generally leading, however, to less efficient catalysts than their analogous *P*,*N*-counterparts. Numerous sulfur-oxazoline ligands were intensively studied for the catalytic formation of C−C bonds. The enantioselectivities for the model reaction remained moderate to good, but the activity was by far lower than that of the analogous phosphorus-oxazoline catalysts. Some more interesting results may perhaps be found with those *S*,*N*-ligands in the transformation of other, structurally different, substrates. Other ligands have also been discussed in which the sulfur atom is not a coordinating one. Neither the introduction of the sulfur atom in the aromatic carbon skeleton of *P*,*N*-ligands (especially phosphine-oxazoline ones) nor the preparation of thiazoline derivatives led to any remarkable improvements. In the latter case, a *N*,*N*-coordination was mostly noted. Some promising results were interestingly obtained for chelates in which the sulfur atom was present as a sulfoximine moiety for introducing the chirality. Ellman *et al*. indeed prepared phosphorus-containing sulfinyl imines that proved in some cases as competitive as the more usual phosphinooxazolines. Moreover, bis(sulfoximines) prepared by Bolm *et al*. were proven to be promising ligands for the Tsuji−Trost reaction involving substituted malonate derivatives. To conclude, sulfur ligands were not demonstrated to be more efficient in terms of both activity and enantioselectivity than phosphorus ones but some interesting results may be expected for their use in transformations involving more "demanding" substrates. Furthermore, we want to emphasize that the catalytic enantioselective C−C bond formation is a reaction that still remains a challenge in terms of activity, enantioselectivity, catalyst loading, and recycling. We may imagine that chiral sulfur-containing ligands, as particularly robust compounds, have a future in the development of asymmetric heterogeneous or homogeneous-supported C−C bond formations. To the best of our knowledge, only two groups have reported their results concerning the test of sulfur-containing catalysts under heterogeneous conditions for the Tsuji−Trost reaction.

Scheme 66



2.3. Asymmetric Diels–Alder and Hetero-Diels–Alder Reactions

2.3.1. Introduction

Catalytic asymmetric cycloaddition reactions have been intensively developed as powerful atom economical ways to prepare optically active carbocyclic and heterocyclic compounds. These transformations are normally efficiently promoted by Lewis-acid catalysts[121,122] with oxygen-chelating ligands but also phosphorus-containing chelates.[123] More recently, numerous studies have focused on the use of chiral *N*-containing ligands based on the excellent results described by Evans[124,125] using bis(oxazoline) derivatives associated with copper salts.

The usual test reaction developed to evaluate the activity and enantioselectivity of the studied chiral complex is the cycloaddition performed between cyclopentadiene and *N*-alkenoyl-1,3-oxazolidin-2-ones (Scheme 66). In this case, a square-planar catalyst−substrate complex can be considered between the two points binding *N*-acyl-imine dienophiles and the metal, leading thus to more rigid intermediates in order to attain high enantioselectivities.

For R = H, and without catalyst, the reaction can be performed at room or even lower temperature and affords the products in good yield, with the endo product as the major isomer. In the presence of a chiral catalyst, the reactions are usually tested at very low temperatures.

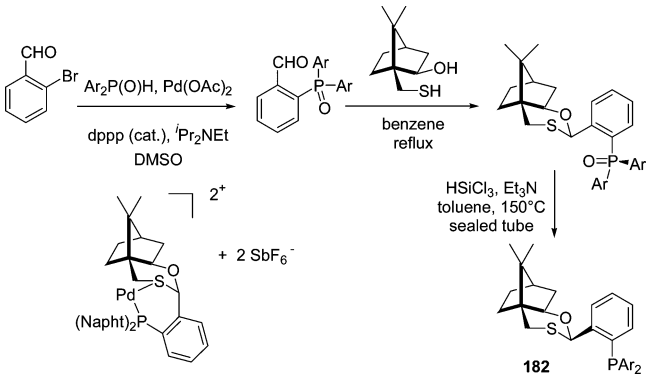
The Diels−Alder transformation has been performed with various Lewis acids. Copper derivatives have been mainly used with success, but examples are to be found in which iron, magnesium, palladium, nickel, or ytterbium proved efficient for this transformation. To the best of our knowledge, very few sulfur-coordinating ligands have been used for the preparation of catalysts aimed at promoting this reaction. Accordingly, numerous examples exist with sulfur-containing chelates as efficient ligands for this reaction, where the sulfur atom is part of a sulfoxide functionality, sometimes present as a unique asymmetric center or associated with another chiral group.

2.3.2. Ligands with an S-Coordinating Atom

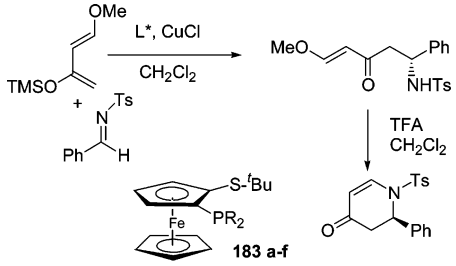
As far as we know, Nakano *et al*. were the first to describe the use of *S*,*P*-coordinating ligands useful for the Diels−Alder reaction.[126] They prepared phosphinooxathiane in a three-step procedure involving a palladium cross-coupling reaction and a condensation with commercially available (1*S*)-(−)-10-mercaptoisoborneol (Scheme 67).

The authors prepared the corresponding palladium and platinum halide complexes with these ligands, which, however, proved poorly active. Changing the counterion of the complex from chloride to SbF_6 allowed the formation of the endo product of the test reaction (R = H in Scheme 66) with 85% ee, with the ligand substituted by phenyl

Scheme 67



Scheme 68



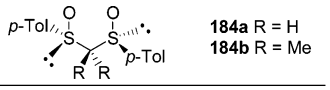
L*	R	yield (%)	ee (%)
183a	Ph	79	80
183b	(*p*-F)C_6H_4	70	71
183c	2-Furyl	58	71
183d	Cy	60	55
183e	*o*-Tol	66	57
183f	1-Naph	96	80

groups on the phosphorus atom. This ee could be raised up to 93% ee by using an analogous conformationally constrained Pd catalyst with 1-naphthyl moieties on the phosphine. The catalysts were very active, since the reaction could be performed at −78 °C and completed within a few hours. The structure of a palladium species coordinated with a phosphinooxathiane ligand was determined by X-ray analyses, proving a phosphorus and sulfur coordination in a square-planar geometry.

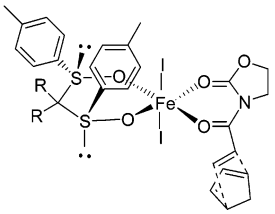
Another of the few Diels−Alder-type reactions in which sulfur-coordinating ligands have been used was recently described by Carretero and co-workers. They prepared chiral phosphino sulfenyl ferrocenes and tested them as copper chelates for enantioselective formal aza-Diels−Alder[127] reactions of *N*-sulfonyl imines.[128] This reaction (see Scheme 68) was rarely performed as a catalytic asymmetric process and allowed the synthesis of six-membered heterocycles as key intermediates for the preparation of biologically active compounds.

The model reaction was performed between Danishefsky's diene and the *N*-tosylimine of benzaldehyde in the presence of chiral phosphino sulfenyl ferrocenes and copper(I) salts as catalysts. Under those conditions, the acyclic Mannich-type addition product was obtained and was transformed into the Diels−Alder adduct by treatment with TFA. The *S*,*P*-bidentate character of the ligands was proven by isolation of one complex and X-ray analyses. Complexes prepared with CuCl afforded the expected product in up to 80% ee, and this value increased to 97% by performing the reaction at −20 °C and by using CuBr as catalytic precursor with ligand **183f**. High values, in terms of both activity and

Scheme 69



L*	yield (%)	endo / exo	ee (endo) (%)
184a	74	95 / 5	36 (*S*)
184b	78	96 / 4	56 (*S*)



enantioselectivity, were obtained with a wide range of substrates, including other *N*-sulfonyl imines and/or substituted dienes.

The authors proved more recently that these planar chiral phosphino sulfenylferrocene ligands were also suitable for the palladium-catalyzed Diels−Alder reaction.[129] They performed the test reaction between cyclopentadiene and acryloyl-1,3-oxazolidin-2-one in the presence of the dichloride metal complex and $AgBF_4$ as a chloride scavenger. The palladium catalyst was very active, since the reaction could be run at −78 °C. Ligand **183e**, bearing bulky groups at both sulfur and phosphorus atoms (Scheme 68), led to the best results with up to 95% ee for the expected major endo product. When this ligand was used as a copper-chelate for the same transformation, the product was obtained with lower (54% ee) and opposite enantioselectivity. This difference was explained by the geometry of the palladium (square-planar) and copper (tetrahedral) complexes.

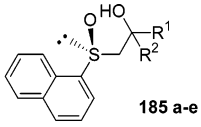
2.3.3. Ligands with an S-Noncoordinating Atom

Many more examples have been published in which this reaction was performed with sulfur-containing but not coordinating ligands. The chirality in these structures is very often solely introduced via sulfoxide functionalities, proving the important role of the sulfur atom for the enantioselectivity of the catalytic transformation.

As an illustration of this proposal, Khiar *et al.*[130] were interested in the preparation of C_2-symmetric ligands containing two oxygen-donor atoms. They thus synthesized and used bis(sulfoxides) as chelates for the iron(III)-catalyzed Diels−Alder reaction between 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadiene. Ligand **184a**, (*S*,*S*)-bis-*p*-tolylsulfinylmethane (Scheme 69), was synthesized in one step by reacting (*R*)-methyl-*p*-tolyl sulfoxide and commercially available menthyl (*S*)-*p*-toluene sulfinate. The dimethyl analogue **184b** was obtained by dimethylation of **184a** in a two-step procedure.

The corresponding iron catalysts were prepared *in situ* and afforded the desired diastereomers (*ca.* 90% de) in good yields by reacting for 5 h at −50 °C in CH_2Cl_2. The enantioselectivity of the transformation increased with the steric hindrance of the ligand (compare R = H and R = Me in Scheme 69), but the authors failed in preparing various derivatives by testing the same synthetic procedure with electrophiles other than MeI. They further explained the product configuration (endo product as major *S* enantiomer) by a transition state in which the ligand and the dienophile were chelated to the metal with octahedral geometry via the

Scheme 70



185 a-e

L*	R^1	R^2	yield (%)	de (%)	ee (endo) (%)
185a	Ph	Ph	95	> 96	88
185b	Me	Me	92	94	10
185c	^{i}Pr	^{i}Pr	89	92	20
185d	Ph	H	93	> 96	28 (*S*)
185e	H	Ph	94	86	6 (*R*)

equatorial site. The less hindered face for the approach of the cyclopentadiene is thus located on the side opposite to the sterically hindered *p*-tolyl groups of the ligand.

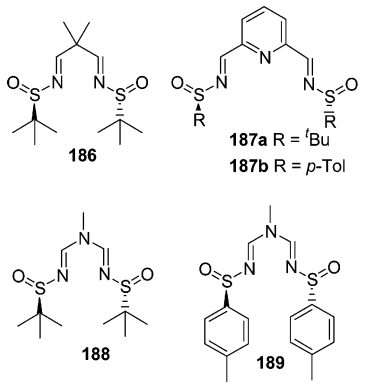
With the aim to control the asymmetric Diels−Alder reaction by a double chelation of the Lewis acid by hydroxyl groups vicinal to the sulfoxide moiety, Llera *et al*.[131] synthesized various enantiomerically pure hydroxysulfoxides (Scheme 70). Their synthesis involved the preparation of enantiomerically pure (*R*)- or (*S*)-methyl-1-naphthylsulfoxide (70% yield in two steps), the subsequent transformation in the corresponding anion with LDA, and a final reaction with various substituted ketones.

This series of ligands was used in the presence of MgI_2 as the Lewis acid in the Diels−Alder test transformation. All the catalysts proved to be active and diastereoselective to achieve this transformation, but only the ligand bearing two phenyl groups adjacent to the hydroxyl functionality was interestingly enantioselective (up to 88% ee). The authors ruled out a donor/acceptor interaction between the aromatic rings and the electron deficient double bond in the dienophile to be responsible of this enhanced selectivity compared to other ligands. Hydroxysulfoxides substituted in the *para* position of the phenyl rings with methoxy substituents, as better donors, did indeed not improve the selectivity. When only one phenyl group was present at the hydroxylic carbon, leading to the formation of an asymmetric carbon center, a reversal in the sense of the stereoselectivity was observed, when both diastereomeric ligands were used (with the configuration at the sulfur atom being maintained). The authors explained the observed sense of enantioselection of the asymmetric induction by proposing a 1:1:1 complex between the ligand, the metallic center, and the dienophile with a tetrahedral arrangement of the oxygen atoms around the metal.

Ellman *et al*.[132] reported another example of chiral ligands, in which the chirality was solely introduced by the presence of sulfoxide moieties. They thus prepared novel sulfinyl imines and a bis(sulfinyl)-iminoamidine from commercially available and optically stable chiral sulfinamides (Scheme 71).

These various donor ligands were involved in the Diels−Alder test reaction and displayed good catalytic activity but showed moderate enantioselectivity (up to 72% for **187a**). The authors demonstrated the important influence of the copper counterion on the activity by using noncoordinating hexafluoroantimonate for accelerating the reaction (see examples with ligand **187a**). To improve the enantioselectivity, the authors prepared **188**, a bis(sulfinyl)iminoamidine ligand containing more basic donor atoms that associated to $Cu(SbF_6)_2$, which led to the desired endo product with a very high yield and enantio- and diastereoselectivities. This

Scheme 71



186

187a R = ^{t}Bu
187b R = *p*-Tol

188

189

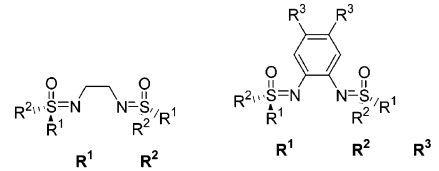
L*	Metal	conv (%)	de (%)	ee (endo) (%)
186	$Cu(OTf)_2$	100	80	6
187a	$Cu(OTf)_2$	60	88	72
187a	$Cu(SbF_6)_2$	100	88	39
187b	$Cu(OTf)_2$	50	88	37
188	$Cu(SbF_6)_2$	100	> 98	98
189	$Cu(SbF_6)_2$	-	88	32

catalytic system proved to be as efficient for the Diels−Alder reactions involving crotyl-, cinnamoyl-, or activated β-carboxy-substituted dienophiles with cyclopentadiene or cyclohexadiene. According to X-ray analyses, the authors demonstrated that this potentially effective *N*,*S*- or *O*-coordinating ligand led in fact to a complex existing as a M_2L_4 quadruple-stranded helicate in which both Cu atoms were coordinated to the sulfinyl oxygens in a square-pyramidal array. Infrared data obtained in solution also proved a binding mode via oxygen. The authors further tested the importance of the substitution on the sulfinyl imidoamidine (siam) framework.[133] The substitution of the internal nitrogen atom in **188** by different groups with various electronic properties did not lead to a noticeable modification in the catalysts efficiency. To investigate the importance of the substituent on the sulfur atom, the authors prepared ligand **189**, which led to a major decrease in the enantioselectivity. The authors further studied successfully the Diels−Alder reaction with a wide range of substrates, both substituted dienophiles and/or acyclic substrates, by using these copper catalysts.

Another class of sulfur-containing ligands was described by Bolm *et al*., who synthesized[134] and studied the liganding ability of salen-like bis(sulfoximines) (Scheme 72). The chirality is generally introduced via the use of chiral diamines in the salen series, whereas, in sulfoximines, the chirality is present via the sulfur atom at a position that is achiral in the original structure. Given that the stereogenic sulfur atom is located near the *N*-coordinating atom, these structures were assumed to be promising for asymmetric catalysis by the authors. They investigated the Diels−Alder cycloaddition between cyclopentadiene and acryloyl-2-oxazolidinones with various bis(sulfoximines) and $Cu(OTf)_2$ as the copper source.[135]

The authors observed that the reaction could be run using a 10 mol % 1/1 mixture of bis(sulfoximine) and $Cu(OTf)_2$ and give the expected product with an excellent yield and high enantioselectivity. This selectivity could be increased by diminishing the steric demand of the aliphatic substituent on the bis(sulfoximine) (compare **190a** and **190b** in Scheme 72) and introducing a 2-methoxy group on the aryl substituent (compare **191a** and **191b** or **191c** and **191d**). The authors

Scheme 72

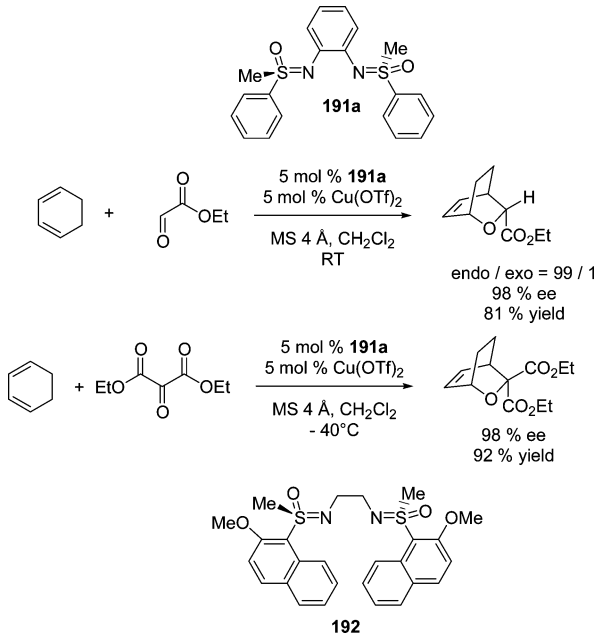


	R^1	R^2
190a	CH_3	Ph
190b	^{i}Pr	Ph
190c	2-MeO-Ph	Me

	R^1	R^2	R^3
191a	CH_3	Ph	H
191b	2-MeO-Ph	Me	H
191c	CH_3	Ph	Me
191d	2-MeO-Ph	Me	Me

L*	yield (%)	ee (endo) (%)	endo / exo
190a	98	66	93 / 7
190b	98	49	93 / 7
190c	98	76	93 / 7
190c (-50°C)	98	83	94 / 6
191a	98	75	93 / 7
191b	98	79	91 / 9
191c	98	81	93 / 7
191d	98	93	89 / 11

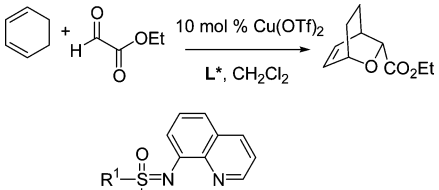
Scheme 73



exhaustively studied next the influence of other reaction parameters upon the selectivity. They proved that, by using less coordinating counterions (for instance perchlorate) and chloroform as the solvent, the ee increased considerably (up to 92% ee for ligand **191a**). The results given for ligand **191d** in Scheme 72 are obtained under those optimized conditions. Type **191** ligands were synthesized by palladium-catalyzed *N*-aryl imination from 1,2-dibromobenzene and (*S*)-*S*-methyl-*S*-phenylsulfoximine with Pd_2dba_3 in 70% yield. Ligand **191a** was further tested in an analogous catalytic transformation, namely the copper-catalyzed hetero-Diels−Alder reaction (Scheme 73).[136]

The 1,3-cyclohexadiene and ethylglyoxylate reaction catalyzed by the corresponding copper(II) triflate complex led to the expected product in high yield (81%) and high enantio- and diastereoselectivities. Furthermore, by using freshly prepared ethylglyoxylate, the authors succeeded in performing a similar enantioselective reaction with only 0.5 mol % chiral catalyst. The reaction between cyclohexadiene and diethyl mesoxalate similarly afforded the expected

Scheme 74



	R^1	R^2
(*R*)-**193a**	CH_3	Ph
(*S*)-**193b**	^{t}Bu	Ph
(*R*)-**193c**	CH_3	2-MeO-Ph
(*R*)-**193d**	^{t}Bu	2-MeO-Ph
(*S*)-**193e**	CH_3	2-MeO-Napht

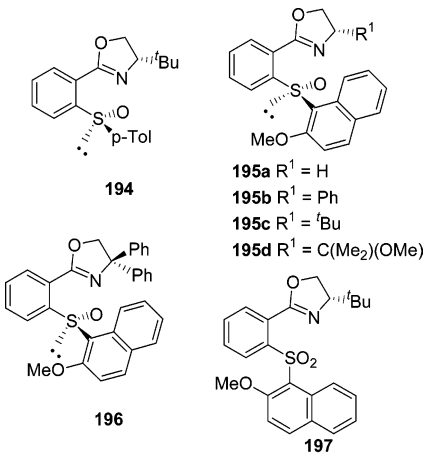
L*	yield (%)	ee (endo) (%)	de (%)
(*R*)-**193a**	97	75 (1*S*, 3*R*, 4*R*)	94
(*S*)-**193b**	18	0	76
(*R*)-**193c**	98	91(1*S*, 3*R*, 4*R*)	96
(*R*)-**193d**	41	0	84
(*S*)-**193e**	88	91(1*R*, 3*S*, 4*S*)	96

product in high yield and up to 98% ee by working at −40 °C. These reactions were later also studied in the presence of bis(sulfoximines) of type **190** (see in Scheme 72) with ethylene as the bridging unit, leading to more flexible ligands.[137] Copper(II) complexes of these ligands catalyzed the reaction between ethylgyloxylate and cyclohexadiene in up to 99% ee, in the presence of a very sterically hindered bis(sulfoximine), namely **192** in Scheme 73, bearing an *ortho*-methoxynaphthyl group as an aromatic substituent at sulfur.

Spectroscopic investigations were carried out using different techniques, including EXAFS, ESR, and UV−vis-spectroscopy,[138] to try to understand how the reactants, solvent, and concentration interact together with the catalytically active complex. The authors concluded that the chiral bis(sulfoximine) ligand was coordinated to the Cu(II) atom via the imine nitrogens and to the dienophile via the carbonyl oxygen atoms in a tetragonally distorted complex, affording a nonsymmetric square-pyramidal geometry. Since the two coordinating sulfoximine nitrogens were nonequivalent in such a coordination mode, the authors further studied the ability of monosulfoximine ligands to perform similar hetero-Diels−Alder reactions as C_1-symmetric chelates.[139] The targeted ligands were obtained by palladium-catalyzed *N*-arylations of enantiopure sulfoximines with 8-bromoquinoline derivatives, affording the quinoline-based C_1-symmetric sulfoximines in good yield. A large variety of ligands with different alkyl and aryl substituents at the sulfoximine moiety were thus synthesized and successfully tested in the hetero-Diels−Alder reaction between 1,3-cyclohexadiene and ethylglyoxylate or diethyl mesoxalate (see Scheme 74).

In Scheme 74, the yields and ee and de values are reported for the reaction with ethylglyoxylate and reach high values in general. The authors could obtain the desired product in up to 96% ee and 98% de by using ligand (*R*)-**193c** as the copper chelate and performing the reaction at −10 °C with as low as 1 mol % of complex. The steric hindrance generated by the alkyl substituent on the sulfoximine moiety

Scheme 75



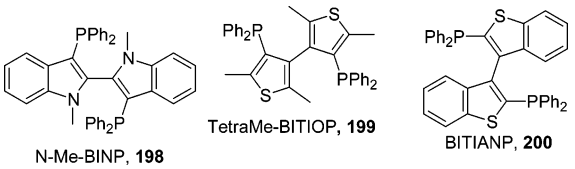
L*	yield (%)	endo / exo	ee (endo) (%)
194	86	94 / 6	46
195a	82	94 / 6	17
195b	83	94 / 6	50
195c	90	97 / 3	81
195d	90	94 / 6	92
196	96	84 / 16	36
197	62	92 / 8	6

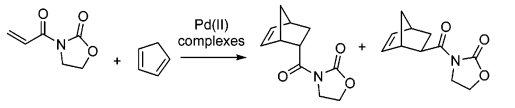
seemed to be of great importance for observing high selectivities, since ligands (*S*)-**193b** and (*R*)-**193d** bearing crowded ^{t}Bu groups led to poorly active complexes and racemic products. Similar results (with slightly lower values) were obtained in the reaction involving diethyl mesoxalate. An X-ray structure of the complex involving ligand (*R*)-**193c** and $CuCl_2$ was obtained, and the authors proposed a mechanistic model explaining the stereochemical outcome of the reaction. These ligands act as *N*,*N*-bidentate chelates, leading to a copper complex with a distorted tetrahedral coordination geometry. However, based on these results, better values in terms of activity and enantioselectivity were obtained with C_2-symmetrical bis(sulfoximines) compared to monosulfoximines. These studies clearly showed that C_2-symmetrical bis(sulfoximines) associated to copper precatalysts were very efficient systems for affording either Diels−Alder or hetero-Diels−Alder products in very high yield and excellent dia- and enantioselectivities.

Further optimization for the preparation of optically active sulfoxide-containing structures was proposed by Hiroi *et al.*,[140] who synthesized *N*,*O*-chiral chelates as sulfoxide-oxazoline liganding cores, for performing Diels−Alder reactions with Lewis acid catalysts. The authors synthesized a series of ligands with various substituents on the oxazoline ring or on the sulfinyl function, both being bridged by a phenyl group (Scheme 75). With ligand **195c**, the authors tested at first a variety of Lewis acids and found MgI_2 to be the best catalyst in terms of enantioselectivity for the reaction run at −78 °C in CH_2Cl_2. By varying the ligand structure and the preparation mode of the corresponding complex, they were able to obtain the expected product in the usual test reaction (Scheme 66, R = H), with up to 92% ee and 90% yield after 24 h of reaction.

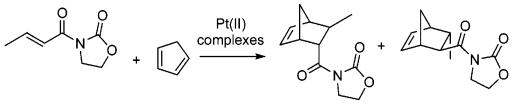
Their experiments proved that 2-methoxy-1-naphthyl sulfoxides provided higher enantioselectivities than other aryl sulfoxides (compare ligands **194** and **195c**, Scheme 75). The steric hindrance generated by bulky substituents on the oxazoline ring was also of major importance for the selectivity (see **195a**, **195b**, **195c**, and **195d**). Both chiral

Scheme 76





L*	E°(V)	T (°C)	conv (%)	de (%)	ee (endo) (%)
200	0.83	- 40	100	82	72
198	0.52	- 60	100	92	96
199	0.57	- 60	100	84	94
BINAP	0.63	- 60	100	90	99.7



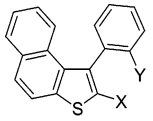
L*	conv (%)	de (%)	ee (endo) (%)
198	45	72	75
199	40	75	58
BINAP	40	71	73

centers were necessary, since the loss of one center led to a major decrease in ee (**195a**, **196**, and **197**). The authors assumed that the reaction occurred via a seven-membered magnesium chelate (as a tetrahedral complex coordinated by nitrogen, sulfinyl oxygen, and two carbonyl oxygens from the substrate). They proposed a preferential attack from the *Re* face side opposite to the bulky substituents. The MeO functionality in the sulfoxide naphthyl derivative is of the utmost importance for orienting the substituent, due to dipole−dipole repulsion from the sulfinyl group.

Another example of Diels−Alder cycloadditions promoted by sulfur-containing but not coordinating ligands has been described by Sannicolò and co-workers.[141] However, in this case, the sulfur atom is no longer present as a sulfoxide moiety to introduce chirality but is part of an aromatic cycle to modify its electronic properties. They prepared several C_2-symmetric biheteroaromatic diphosphines (Scheme 76) and tested their abilities to promote the [4+2]-cycloaddition of cyclopentadiene with *N*-2-alkenoyl-1,3-oxazolidin-2-ones as Pd(II) or Pt(II) ligands in comparison to the recent results obtained by Ghosh, who used BINAP as ligand associated to the same metals.[142] The authors assumed that the variation in the electronic properties at phosphorus resulting from the presence of the heteroaromatic backbone should allow a control of the stereoselection.

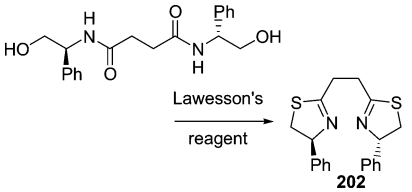
From the results summarized in Scheme 76 concerning the palladium-promoted catalysis, the authors proposed that the more electron-rich is the diphosphine, the more stereoselective and the faster the corresponding reaction. The electronic availability of each diphosphine was measured by electrochemical experiments to determine their oxidation potential (*vs* Ag/Ag^+). The same observations were made by performing the Diels−Alder reaction between cyclopentadiene and *N*-(2-butenoyl)-2-oxazolidinone in the presence of Pt(II). The authors concluded that the ligand should possess large electronic availability at phosphorus in order to efficiently carry out [4+2] cycloaddition reactions.

Scheme 77

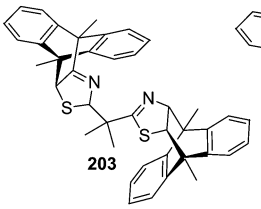


201a X=Y=PPh_2
201b X = PPh_2, Y = H

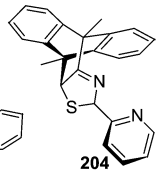
Scheme 78



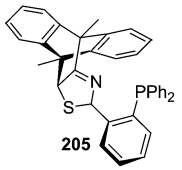
202



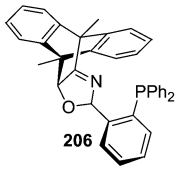
203



204



205



206

L*	Temp (0°C)	Time (h)	yield (%)	ee (endo) (%)
203	0	3	97	2 (*R*)
204	0	24	88	16 (*S*)
205	0	1	92	76 (*R*)
205	- 60	36	81	92 (*R*)
206	- 60	24	94	73 (*R*)

The same authors also prepared another ligand lacking the C_2-symmetry, as depicted in Scheme 77, and thus bearing electronically different phosphorus atoms.[143] The electrochemical oxidative potential was obtained by cyclic voltammetry. The oxidation potential of the phosphine group located on the phenyl ring was found to be 0.74 V (*vs* Ag/Ag^+) and the authors attributed a value of 0.91 V to the phosphine attached to the thiophene moiety (by comparison with ligand **201b**). This second functionality is a rather electron-poor phosphine.

Tested as palladium ligand for the Diels−Alder cycloaddition of cyclopentadiene and *N*-acryloyloxazolidin-2-one, the authors obtained the endo adduct with 90% de and 75% ee by using ligand **201a** and $Pd(ClO_4)_2$ as a palladium source in dichloromethane at −60 °C.

Since chiral oxazolines proved efficient ligands for various catalytic asymmetric C−C bond formations, and particularly for Diels−Alder cycloadditions, Nishio *et al*. reported the ability of corresponding thiazolines to perform this transformation.[144] The ligands were synthesized by treating bis(*N*-acylamino alcohols) with Lawesson's reagent (see, for example, **202** in Scheme 78). This ligand was only tested in the presence of zinc triflate as the catalyst for the test Diels−Alder reaction. The targeted endo product was obtained with 88% diastereoselectivity and 92% ee.

Kunieda and co-workers[145] prepared sterically congested "roofed" 2-thiazolines by thermal [4+2] cycloadditions of 2-thiazolone and cyclic dienes, subsequent hydrolytic ring cleavage with $Ba(OH)_2$, and final thiazoline ring formation following the general procedure for the preparation of oxazoline ligands. They thus synthesized a bis(thiazoline) derivative, a pyridylthiazoline, and a (2-diphenylphosphino)-phenylthiazoline (together with its oxazoline analogue for comparison) with high yield (see structures **203**−**206**, in Scheme 78).

The test Diels−Alder reaction was performed with these ligands in the presence of copper(II) triflate in dichloromethane, affording the endo product as the major isomer within a few hours. The bis(thiazoline) **203** and the pyridylthiazoline **204** gave low enantioselectivities (see Scheme 78) whereas the corresponding phosphino-thiazoline **205** led to the formation of the product with 76% ee by performing the reaction at 0 °C. Lowering the temperature to −60 °C allowed a significant increase in the enantioselectivity of the transformation, since the product was isolated with 92% ee. The analogous phosphinooxazoline ligand **206** remained less enantioselective under similar reaction conditions, proving the beneficial effect of the presence of the sulfur atom in the heterocyclic ring on the *N*,*P*-chelating behavior to the copper center.

2.3.4. Conclusion

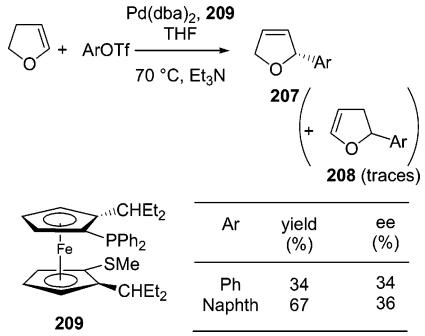
The great versatility of the Diels−Alder reaction has certainly been demonstrated here by numerous examples covering very different catalytic systems. Although very few reactions were successfully performed with sulfur-coordinating chelates, a great amount of interesting results in terms of activity and enantioselectivity were obtained with sulfur-containing ligands. Ligands containing sulfoxide moieties as the unique source of chirality afforded the expected product with high enantioselectivity, acting as *O*,*O*-chelates for iron, magnesium, or copper metals. The bis(sulfoximine) ligand series developed by Bolm and co-workers possessing *N*-coordinating atoms were even more efficient with copper(II) triflate as Lewis acid, allowing Diels−Alder and hetero-Diels−Alder reactions to be carried out with excellent yields and enantioselectivities. Chiral sulfoxide-oxazoline ligands were developed with less success, whereas bis(thiophene)- and bis(benzothiophene)-diphosphine BINAP analogues allowed the test reaction to be performed in the presence of palladium or platinum salts. Bis(oxazolines) associated with copper salts have been reported to lead to selective reactions with various substrates. Few thiazoline analogues have been tested, but a conformationally rigid and sterically bulky "roofed" bis(2-thiazoline) afforded the racemic product with high yield. The analogous phosphino-thiazoline led to the expected product with excellent enantiomeric excess.

2.4. Asymmetric Heck-type Reactions

2.4.1. Introduction

The Pd(0)-catalyzed coupling of alkenes with an aryl or alkenyl halide or triflate, the well-known Heck reaction, has been only quite recently studied in its asymmetric version. This reaction is an efficient method of carbon−carbon bond formation that tolerates several functional groups. However, interest in this transformation has varied, probably due to the difficulties encountered in controlling the regioselectivity in the case of unsymmetrical alkenes. The first successful reports of asymmetric Heck reactions (AHRs)[146] were independently published in 1989 by the groups of Shiba-

Scheme 79



Ar	yield (%)	ee (%)
Ph	34	34
Naphth	67	36

saki[147] and Overman,[148] who used chelating bis(phosphines) (*i.e.*, BINAP and DIOP, respectively) to reach around 45% ee in intramolecular versions of the AHR. Since then, numerous examples have been found for asymmetric ring closure by Heck reactions, mainly performed with *P*,*P*-containing enantiopure ligands and applied to the preparation of naturally occurring products.[149] The intermolecular version has been less developed and is very often limited to reactive substrates such as *O*- and *N*-heterocycles to ensure quite high reaction rates. However, in this case, the unselective formation of double bond regioisomers remains a difficulty that needs to be overcome. The use of sulfur-coordinating ligands to perform this reaction is very rare, and only two very recent examples will be described here. Chelating diphosphines have been, however, prepared with sulfur-containing heteroaromatic rings, showing promising results in terms of activity and selectivity for this reaction, with the heteroatom acting as a phosphine basicity modulator. These examples will also be reviewed here.

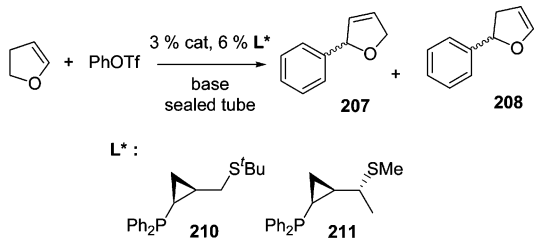
2.4.2. Ligands with an S-Coordinating Atom

As already presented in the nucleophilic allylic substitution section, pseudo-C_2-symmetric *S*,*P*-hybrid ferrocenyl ligands possessing only planar chirality have been synthesized by Kang and co-workers.[57] Corresponding palladium complexes have been tested in the intermolecular asymmetric Heck reaction of 2,3-dihydrofuran with aryltriflates.

The authors interestingly noticed the high regioselectivity of the catalytic transformation favoring the 2,5-dihydrofuran derivative **207** over the regioisomeric 2,3-dihydrofuran **208**, that was the product usually obtained as the major compound in the Pd(BINAP)-catalyzed reactions.[150] Despite changes in numerous parameters (in particular the temperature and the solvent), the best enantioselectivity did not exceed 36% (see Scheme 79).

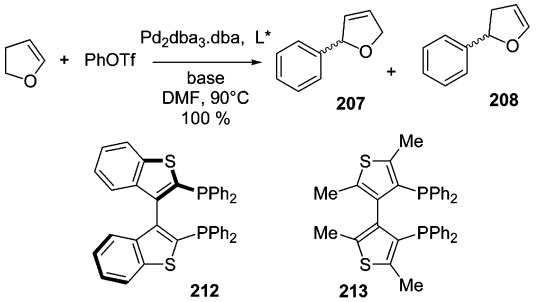
Molander *et al.*[42] have evaluated their new cyclopropane-based phosphorus/sulfur palladium complexes not only in the allylic alkylation but also in the intermolecular Heck reaction. A large series of ligands was described, and some of them were selected according to their ability to perform the Tsuji−Trost reaction with the best enantioselectivities (see section 2.2.3). The test transformation again involved the reaction between phenyltriflate and 2,3-dihydrofuran in the presence of the palladium catalyst (1.5 mol %) and a base, leading in most cases to a mixture of the desired product together with its isomerized analogue (see Scheme 80 for the best results). The catalysts were active in benzene at high temperature, affording compound **207** as the major isomer with a maximum value of 63% for the ee.

Scheme 80



L*	cat	base	conv (%)	207/208	ee 207 (%)	ee 208 (%)
210	$Pd(OAc)_2$	$^iPr_2NEt$	93	10.6	63	43
211	$Pd_2(dba)_3$	Et_3N	99	9.7	50	19

Scheme 81



L*	base	t	207/208	ee 207 (%)	ee 208 (%)
212	PS	18 h	<1/100	-	91
213	$^iPr_2NEt$	3 d	2/1	2	4
BINAP	PS	18 h	1/3	33	42

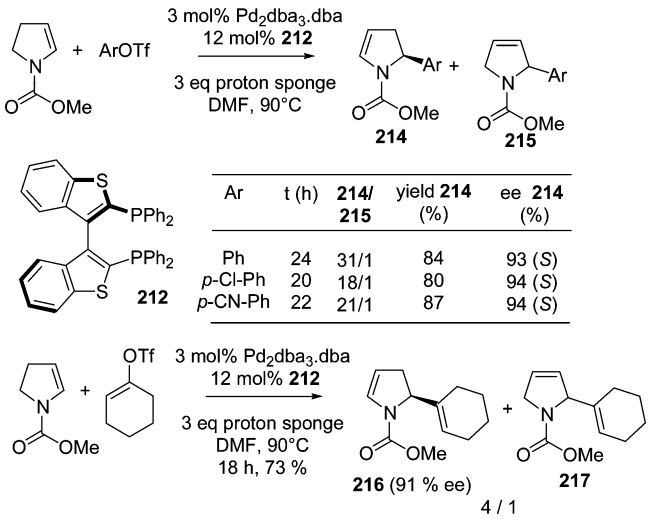
2.4.3. Ligands with an S-Noncoordinating Atom

Diphosphines based on thiophene or benzothiophene backbones developed by Sannicolò were tested in the enantioselective Heck reaction with dihydrofuran.[151] In the presence of proton sponge (1,8-bis(dimethylamino)naphthalene) as a base in DMF, the use of ligand (*R*)-BITIANP [(*R*)-(+)-2,2′-bis(diphenylphosphino)-3,3′-bi(benzo[*b*]-thiophene)] **212** as a palladium chelate interestingly led exclusively to regioisomer **208** with a high enantiomeric excess of 91% (see Scheme 81). The authors proved that the reaction was extremely solvent dependent, since the use of THF led to a much slower transformation with **207** as the major product. The use of (+)-4,4′-bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene **213** [(+)-TMB-TP] did not lead to noticeable results. The use of BINAP under the optimized conditions for **212** led to worse results, in terms of both regio- and enantioselectivity.

Tietze *et al.* also applied this methodology to the intermolecular Heck reaction of *N*-substituted 2-pyrrolines.[152] Under the optimized conditions described in Scheme 82 using BITIANP **212** as chiral ligand, they performed this transformation with various aryl triflates as alkylating agents to give one major isomer **214** with good yield, excellent regioselectivity (31/1), and up to 94% ee (see Scheme 82).

Alkenyl triflates were also successfully used in the presence of BITIANP, and the 5-cyclohexenyl-2-pyrroline derivative **216** was obtained, albeit with a moderate regi-

Scheme 82



Ar	t (h)	214/215	yield 214 (%)	ee 214 (%)
Ph	24	31/1	84	93 (*S*)
p-Cl-Ph	20	18/1	80	94 (*S*)
p-CN-Ph	22	21/1	87	94 (*S*)

oselectivity (**216**/**217** = 4/1) but a high enantioselectivity. Steric and electronic reasons were mentioned to explain the difference observed between BINAP and BITIANP in terms of both activity and selectivity. As a more electron-rich ligand, BITIANP may cause a higher electron density at the phosphorus atom, enhancing the reaction rate by favoring the oxidative addition of the aryl triflate. Furthermore, the binding between the phosphorus and the palladium atom is much stronger, allowing reactions to be run at higher temperature without partial or complete dissociation of the ligand.

Tietze and his co-workers described the preparation of tetrahydroisoquinoline and benzazepine derivatives by silane-terminated intramolecular Heck reactions as an application of this methodology for the synthesis of natural products.[153] The authors argued that one main disadvantage of the Heck reaction remains the low selectivity observed for the formation of the double bond by the last elimination step of the L_nPd-H species in the catalytic cycle. They thus prepared (*E*)- and (*Z*)-allyl silanes as substrates for a better control of the formation of the different side chains in the products.

This Heck transformation was performed with ligand **213** (see structure in Scheme 81) in the presence of the (Z)-allyl silane derivative (see Scheme 83), leading to the unique formation of the corresponding benzazepine with 71% yield and 92% enantiomeric excess. Interestingly, the analogous (*E*)-allylsilane was transformed in the presence of ligand **212** into two products, with the benzazepine containing the trimethylsilylvinyl side chain as the major compound (66% yield and up to 91% ee). Similarly, vinyl-substituted tetrahydroisoquinoline derivatives were prepared, starting from (Z)-adducts with up to 86% ee. Although ligands **212** and **213** are not sulfur-coordinating ligands for a specific chelation to the palladium atom, they proved very efficient in terms of activity, enantioselectivity, and regioselectivity, especially for the Heck transformation, compared to the analogous chiral diphosphine derivatives. The authors argued that this superiority was due to electronic factors (high electronic density) coming from the sulfur transferred to the phosphorus atom for a stronger coordination.

Not only *P*,*P*-coordinating but also *P*,*N*-chelating ligands proved efficient for performing the enantioselective intermolecular Heck reaction. Pfaltz[154] used a phosphinooxazoline **220** as Pd chelate for the arylation and cyclohexenylation of 2,3-dihydrofuran, interestingly leading exclusively to the kinetic product **207** (see Scheme 84) with 97% ee. Guiry *et al.*[155] synthesized analogous ligands called HETPHOX, in which the aromatic ring bearing the chelating phosphine group was replaced by a thiophene or a benzothiophene moiety for studying the influence of the modified electronic density of the phosphorus atom on the course of the catalytic transformation.

Results obtained with these catalytic systems are summarized in Scheme 84, in which only the highest values in terms of yield and enantiomeric excess have been reported. The nature of the base has been optimized in each case to afford the best conditions. In the benzothiophene series, the highest yields were obtained using ligand **218**, leading mainly to the kinetic isomer **207**. Compound **218a** afforded the best enantioselectivity (89% ee) whereas ligand **218b**, as the bulkiest compound of this series, produced isomer **208** with opposite regioselectivity as the major product, albeit with a low enantioselectivity (16%). The thiophene-containing phosphinooxazoline ligand **219b** gave rise to the synthesis of **207** as the major product with moderate yield (57%) and quite high enantioselectivity (78%). Ligand **219a**, bearing a ^{t}Bu-substituted oxazoline ring, proved to be the optimal ligand of this series, since isomer **207** was obtained with very high yield (97%) and enantioselectivity (95%), with these results being independent of the base used. The values obtained by this catalytic system are comparable in both activity and selectivity to the results obtained by Pfaltz with the analogous, non-sulfur-containing diphenylphosphinooxazoline. All these ligands behaved similarly in the analogous cyclohexenylation of 2,3-dihydrofuran. The best result was again obtained with ligand **219a** in the presence of triethylamine as the base, affording (*R*)-2-cyclohex-1′-en-1′-yl-2,5-dihydrofuran in 96% yield and 97% ee, but after a long reaction time of 7 days (see Scheme 85).

The authors further studied the asymmetric Heck reactions with 2,2-dialkyl-2,3-dihydrofuran[156] and tested the full range of ligands previously applied in reactions with 2,3-dihydrofuran. Ligand **219a** also proved to be the most efficient in terms of both enantioselectivity and activity and led, for example, to the phenylation of 2,2-dimethyl-2,3-dihydrofuran with up to 91% ee and high yield.

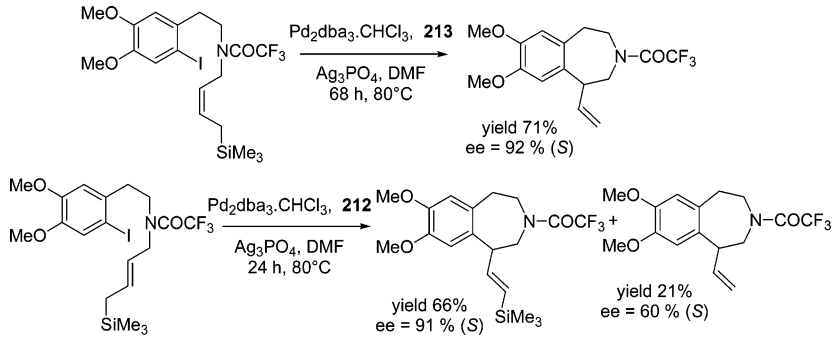
As successful palladium chelates for intermolecular Heck reactions, these ligands were further tested for performing the asymmetric intramolecular version of this transformation.[157] The test reaction, depicted in Scheme 86, is the Heck cyclization between an enamide and an aryl triflate, giving regioisomers **221** and **222**. The transformation had to be performed at high temperature (110 °C in toluene) and for 7 days to afford the expected products in moderate yield (up to 67% conversion by using ligand **223b**). Product **221** was the major compound obtained in each case with a very high regioselectivity, and ligands **223b** and **223c** led to the highest enantioselectivity (up to 68% ee). However, these modest results compete well with those obtained in the presence of the analogous phosphinooxazoline described by Pfaltz.

The influence of the nature of the base was then examined, showing that a proton sponge interestingly afforded the major product **221** with an analogous high regioselectivity and an improved enantioselectivity (up to 76% ee with ligand **223b**).

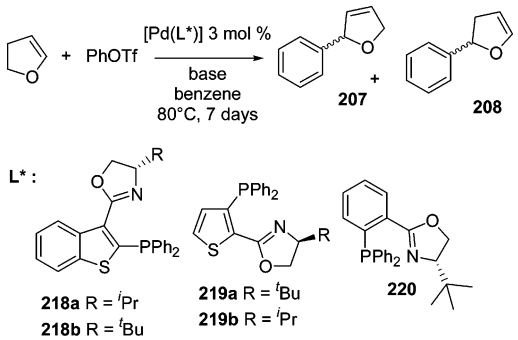
2.4.4. Conclusion

As a highly versatile procedure for C−C bond formation, the Heck reaction has been extensively studied in both

Scheme 83

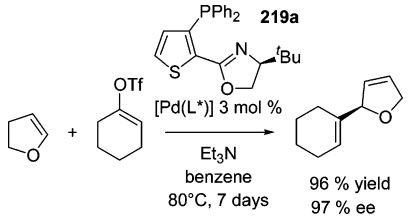


Scheme 84



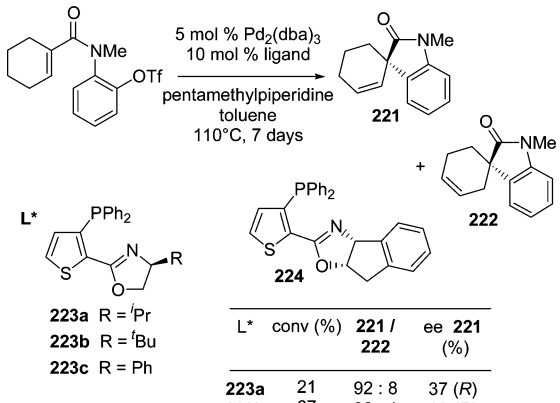
L*	base	yield (%) **207** (**208**)	ee **207** (%)	ee **208** (%)
218a	PS	23 (6)	89	nd
218b	Et_3N	8 (19)	43	16
218c	$^iPr_2NH$	66 (8)	77	nd
219a	$^iPr_2NH$	97 (2)	95	nd
219b	$^iPr_2NH$	57 (6)	78	nd
220	$^iPr_2NEt$	87 (nd)	97	nd

Scheme 85



intramolecular and intermolecular versions and the asymmetric variant has been applied in natural product total synthesis. Various asymmetric ligands have been developed to solve the regioisomer problem often encountered that resulted in the formation of both kinetic and thermodynamic products. There are relatively few examples in which sulfur-coordinating ligands have been successfully employed for this reaction, and the ligands presented in this section, albeit leading to active complexes, only lead to modest results in terms of enantioselectivity. The sulfur-containing analogous ligands to the phosphinooxazoline developed by Pfaltz led to similar results, allowing the formation of the kinetic isomer as major product. Interestingly, the benzothiophene analogous to BINAP, BITIANP, led to spectacular improvements, especially concerning the regioselectivity of the reaction, since, contrary to what occurs with the use of BINAP, only the thermodynamic isomer was produced with high yield and excellent ee.

Scheme 86



L*	conv (%)	**221** / **222**	ee **221** (%)
223a	21	92 : 8	37 (*R*)
223b	67	99 : 1	68 (*R*)
223c	54	98 : 2	68 (*R*)
224	13	92 : 8	20 (*R*)

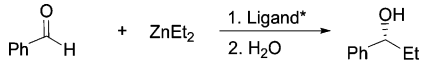
2.5. Enantioselective Addition of Organometallic Compounds to Aldehydes

2.5.1. Introduction

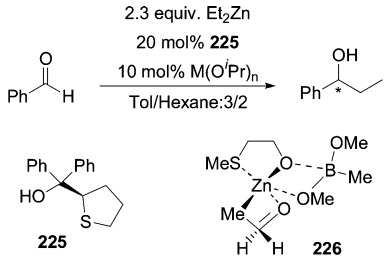
The asymmetric addition of diethylzinc to aldehydes in the presence of catalytic amounts of chiral ligands is a convenient method for the preparation of enantiomerically pure secondary alcohols. Even if this transformation requires stoichiometric quantities of metal, this addition reaction (involving catalytic amounts of ligands) has been widely studied and allows the synthesis of numerous chiral secondary alcohols, which are very useful synthons in the total synthesis of more complex molecules. The asymmetric induction was first achieved with high enantiomeric excesses using chiral β-amino alcohol derivatives as ligands.[158] Since these prelimilary results, numerous chiral sulfur-containing ligands have been synthesized and tested for their efficiency in this transformation. Amino thiols, as amino alcohol analogues, have been mainly studied and were found to be powerful sulfur-containing ligands to prepare active catalysts for achieving this reaction efficiently. The zinc thiolate derivatives often led to better yields and selectivities than the corresponding zinc alcoholates. This superior catalytic activity can be explained by at least three reasons: (1) Sulfur is more polarizable than oxygen in alcohols. (2) Thiols and thiolates have a higher affinity toward metals, especially zinc. (3) Metal thiolates are less inclined to decrease the Lewis acidity of the metal compared to metal alcoholates.

In this reaction, the usual asymmetric test is the addition of diethylzinc to benzaldehyde (Scheme 87). This section will be separated by class of ligands, (*S*,*O*)-, (*S*,*N*)-, and *S*-noncoordinating ligands, with the (*S*,*N*)-ligands being the most frequently used ligand in this reaction.

Scheme 87

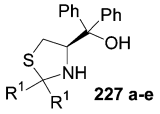


Scheme 88



$M(O^iPr)_n$ (mol%)	Yield (%)	ee (%)
none	69	22 (*S*)
$B(O^iPr)_3$ (10)	52	92 (*R*)
$Sc(O^iPr)_3$ (20)	58	89 (*R*)
$Ge(O^iPr)_4$ (20)	44	90 (*R*)
$Sn(O^iPr)_4$ (20)	42	90 (*R*)
$Ti(O^iPr)_4$ (10)	41	74 (*R*)
$Zr(O^iPr)_4$ (10)	68	90 (*R*)

Scheme 89



Ligand	R^1,R^1	Yield (%)	ee (%)
227a	H,H	30	15
227b	Me,Me	99	81
227c	Et,Et	84	64
227d	$-(CH_2)_4-$	99	69
227e	$-(CH_2)_5-$	90	67

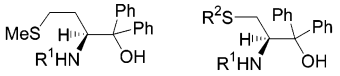
2.5.2. Chiral S,O-Ligands

Shiina *et al.*[159] synthesized ((*R*)-thiolan-2-yl)diphenylmethanol **225** and used its corresponding metal alkoxides in the enantioselective alkylation of benzaldehyde with diethylzinc. In the presence of 20 mol % of **225**, the authors obtained the desired 1-phenylpropanol with 22% ee. Then, they planned that one of the two zinc atoms involved in the transition state could be replaced with different metal alkoxides. Adding 10 mol % of $B(O^iPr)_3$ increased the enantioselectivity to 92% ee (52% yield). This catalytic system was applied to other aldehydes, albeit with lower enantioselectivities (for example 72% ee with nonanal). Transition states for this reaction were calculated for the transformation of formaldehyde with dimethylzinc in the presence of boron alkoxide generated from a simplified ligand derived from **225** and $B(OMe)_3$. The authors assumed that the boron atom was coordinated with oxygen one in the zinc alkoxide of **225** to form a stable four-membered ring structure **226** with two oxygens and two metallic species (Scheme 88).

Liu *et al.*[160] synthesized chiral 2,2-disubstituted thiaprolinol derivatives as ligands for the diethylzinc addition to aldehydes. In the utilization of benzaldehyde as substrate, the ligand **227b** proved to be the best (Scheme 89).

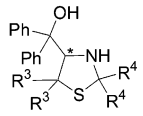
Martens *et al.*[161,162] prepared different sulfur-containing β-amino alcohols and tested them in the catalytic enantioselective addition of diethylzinc to benzaldehyde (Scheme 90). The optical purity of the obtained chiral secondary

Scheme 90



Ligand	R^1	R^2	ee[a] (%)
228a	H	-	5 (*R*)
Li-228a	H	-	48 (*S*)
228b	Et	-	76 (*S*)
Li-228b	Et	-	79 (*S*)
228c	^{n}Pr	-	91 (*S*)
Li-228c	^{n}Pr	-	89 (*S*)
228d	^{n}Bu	-	63 (*S*)
Li-228d	^{n}Bu	-	78 (*S*)
229a	H	^{i}Pr	45 (*R*)
Li-229a	H	^{i}Pr	62 (*R*)
229b	Et	^{i}Pr	74 (*R*)
Li-229b	Et	^{i}Pr	82 (*S*)
229c	^{n}Pr	^{i}Pr	79 (*S*)
Li-229c	^{n}Pr	^{i}Pr	68 (*S*)
Li-229c	^{n}Pr	^{i}Pr	94[b] (*S*)

a. Chemical yield 70-90%, 10 mol% of ligand
b. Utilisation of 5 mol% of ligand



Ligand	R^3	R^4	Conf. Ligand	ee (%)
230a	H	H	*R*	93 (*S*)
Li-230a	H	H	*R*	6 (*S*)
230b	$-(CH_2)_4-$	H	*R*	84 (*S*)
230c	$-(CH_2)_5-$	H	*R*	80 (*S*)
230d	H	Me	*S*	86 (*R*)

alcohol (calculated from the maximum rotation for the (*S*)-1-phenyl-1-propanol) increased with the bulkiness of the *N*-substituent of the catalyst (compare ligands **228a**, **228b**, and **228c**). The use of the lithiated analogues led to better enantioselectivities. This observation was attributed to the stronger hard acid character of the lithium cation compared to the zinc. The authors proposed that the lithium cation may coordinate more easily with the oxygen atom of the approaching aldehyde than zinc. This coordination should restrict the number of possible stereochemical courses of the reaction to afford high optical purities. The low stability of cyclic ligand **230a** in the presence of *n*-BuLi could explain the low selectivity observed with Li−**230a**.

N,*O*-Heterocycles derived from readily available and inexpensive (*R*)-cysteine have been synthesized by Martens, Brunet, *et al.*,[163,164] leading to β-amino alcohol ligands such as **231** and **232** with a sulfur atom in the backbone (Scheme 91).

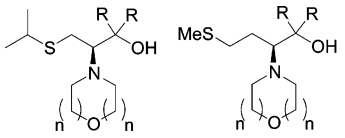
In the enantioselective addition of diethylzinc to benzaldehyde, the authors found up to 94% ee with **232c**. Furthermore, no correlation could be made between the ring size and the enantioselectivity.

2.5.3. Chiral S,N-Ligands

Kellogg *et al.*[165,166] synthesized chiral amino thiol **233** and disulfides **234a**−**c**, derived from ephedra alkaloïds, and thiazolidine **235**. These sulfur derivatives of ephedrine were used in the 1,2-addition of diethylzinc to benzaldehyde and afforded high enantiomeric excesses (Scheme 92).

The enantiomeric excesses generally exceeded those obtained with the corresponding β-amino alcohols. For ligand **233**, the HCl salt was used to prevent disulfide oxidation. The lower results in terms of enantioselectivity for the

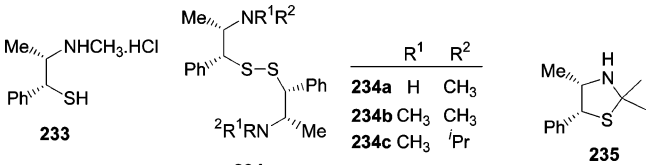
Scheme 91



231 a-c **232 a-g**

Ligand	R	n	Yield (%)	ee
231a	H	1	65	26(*R*)
231b	Et	1	84	92(*R*)
231c	-$(CH_2)_4$-	1	81	71(*R*)
232a	H	1	47	8(*R*)
232b	Et	1	79	83(*R*)
232c	Et	2	81	94(*S*)
232d	Et	3	89	93(*S*)
232e	Et	4	94	91(*S*)
232f	Et	5	85	72(*S*)
232g	Ph	1	85	53(*R*)

Scheme 92

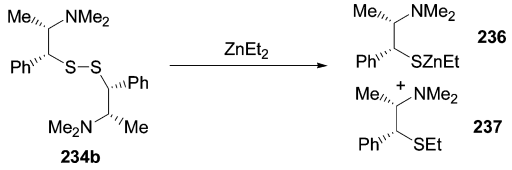


233 **234 a-c** **235**

	R^1	R^2
234a	H	CH_3
234b	CH_3	CH_3
234c	CH_3	^{i}Pr

Ligand	Conversion (%)	ee (%)
233	95	80 (*R*)
234a	75	86 (*R*)
234b	96	90 (*R*)
234c	97	89 (*R*)
235	>99	80 (*R*)

Scheme 93



234b **236** **237**

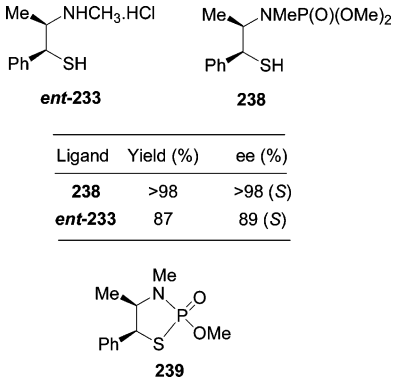
targeted product using **233** compared to **234** were explained by the presence of chloride ions, which have already been reported to lower enantioselection in the corresponding asymmetric Grignard reactions. Furthermore, the authors observed positive nonlinear effects for both ligands **233** and **234b**. Considering the mechanistic aspects on the activation of **234b**, they suggested that the alkylation of the disulfide moiety occurred to generate thioether **237** and thiolate **236**, with the latter being the active catalyst in this diethyzinc addition to aldehydes reaction (Scheme 93).[167]

Later, these authors[168] also compared the reactivity and the selectivity of thiol ephedrine ***ent*-233** and the corresponding phosphorylated thioephedrine **238** in the same transformation (Scheme 94).

In the Et_2Zn alkylation of benzaldehyde, structure **238** proved to be an excellent ligand. However, it was not possible to obtain ligand **238** as a completely pure compound, as it was always accompanied by a small amount of its cyclization product **239**. However, this did not seem to be detrimental to the activity and selectivity of the transformation.

Kang *et al.*[169,170] prepared highly enantioselective chiral cyclic aminothiol ligands **240a**−**i** for this transformation. In addition to the thio-ligands' advantages, the heterocyclic nature of the ligand series **240** acted as a face blocker (Scheme 95).

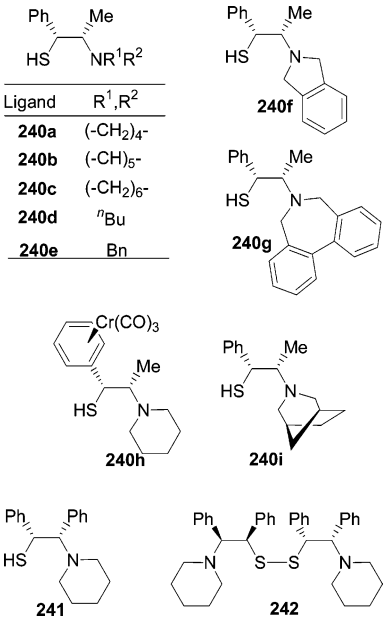
Scheme 94



***ent*-233** **238** **239**

Ligand	Yield (%)	ee (%)
238	>98	>98 (*S*)
***ent*-233**	87	89 (*S*)

Scheme 95



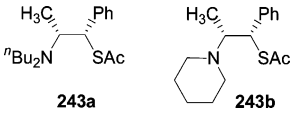
Ligand	R^1,R^2
240a	-$(CH_2)_4$-
240b	-$(CH)_5$-
240c	-$(CH_2)_6$-
240d	^{n}Bu
240e	Bn

240f **240g** **240h** **240i** **241** **242**

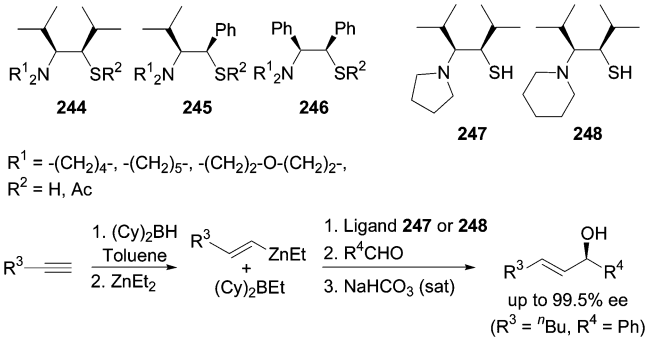
The best ligand in the addition of diethylzinc to α-branched aldehydes was (1*R*,2*S*)-1-phenyl-2-piperidinopropane-1-thiol **240b**. The authors obtained total enantioselectivity in favor of the (*R*)-enantiomer with this ligand. They found a very good yield (92−100%) and >99% ee with substituted benzaldehydes R−C_6H_4−CHO (R = H, 2-MeO, 4-MeO, 4-Cl, 4-F), *tert*-butylaldehyde, and cyclohexylaldehyde. A moderate ee was obtained with hexanal and *trans*-cinnamaldehyde (62 and 77% ee, respectively). The same group also compared the catalytic activity of the *β*-amino thiol **241** and the corresponding disulfide **242**[171] as ligands for this catalytic reaction (Scheme 95). Ligand **241** seemed as effective as **240b** in terms of reactivity and enantioselectivity. The disulfide **242** also showed a very high enantioselectivity (98%−100% ee for aromatic aldehydes). However, the reaction rate was slower than that observed with the corresponding thiol, while ligand **242** proved to be more chemically stable under all conditions.

Kang and co-workers also studied the influence of the sulfur substitution in chiral amino thiols on the enantioselective addition of organozinc reagents to aldehydes.[172,173] The catalytic reaction in the presence of chiral amino thiols was discussed and compared to the results obtained with their

Scheme 96



Scheme 97



chiral amino alcohol counterparts. Quantitative and thermodynamic aspects of the monomer−dimer equilibrium involved in thiazazincolidine and oxazazincolidine catalysts have also been reported. On the one hand, the authors proved the thiolate-catalyzed reaction was considerably faster than the corresponding alcoholate system. On the other hand, the racemic ligand systems were less reactive than the enantiopure ligands.

Chiral amino thioacetate ligands **243a**−**b** derived from (+)-norephedrine have been prepared by Jin *et al.*[174] (Scheme 96).

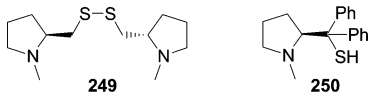
Ethylation of diverse aromatic aldehydes was successfully achieved, and the corresponding (*S*)-alcohols were obtained with excellent ee (97%−99% ee). Decreasing the amount of $ZnEt_2$ from 2.0 equiv (the usual quantity) to 1.1 equiv had only a small effect on the reactivity and enantioselectivity.

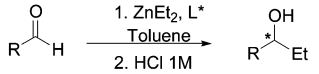
Yang *et al.*[175] synthesized chiral amino thiols and corresponding thioacetate ligands derived from (*S*)-(−)-valine. They applied them in the asymmetric diethylzinc addition to aldehydes with excellent enantioselectivities (up to 99.6% ee with aromatic aldehyde and 91.6% ee with *n*-octylaldehyde, with ligand **247**). These results were obtained with a catalytic loading as low as 0.02 mol %. The same ligand **247** was also used successfully in the enantioselective alkenylzinc addition to aldehyde (Scheme 97).[176] To prepare the alkenylzinc species, the terminal alkyne was first hydroborated to produce (*E*)-alkenylborane, which was then treated with diethylzinc to furnish the desired alkenylzinc reagent.

Gibson synthesized the new disulfide **249** and the β-amino tertiary thiol **250**[177,178] from L-proline (Scheme 98).

The results obtained for the enantioselective addition of diethylzinc to benzaldehyde were always better in terms of selectivity with the disulfide ligand **249**. However, this ligand gave moderate inductions with non-α-branched aldehydes (dihydrocinnamaldehyde and cinnamaldehyde, respectively, 69% ee and 70% ee), as already observed in the presence of the catalytic system described by Kang.[169] According to the authors, the decrease in enantioselectivity found with **250,** compared to **249**, was ascribed to the destabilization of the major intermediate in the transition state by a steric hindrance generated by the presence of the *gem*-diphenyl group.

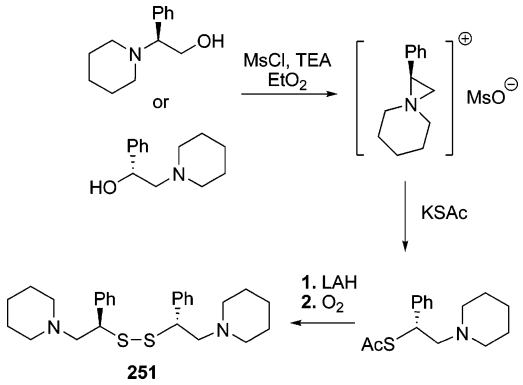
Scheme 98



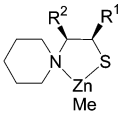


Ligand	R	Yield (%)	ee (%)
249	Ph	76	87 (*R*)
250	Ph	81	44 (*R*)
249	4-MeC_6H_4	83	99 (*R*)
250	4-MeC_6H_4	80	56 (*R*)
249	2-Naphthyl	88	90 (*R*)
250	2-Naphthyl	49	56 (*R*)
250	2-$MeOC_6H_4$	87	64 (*R*)

Scheme 99



Scheme 100

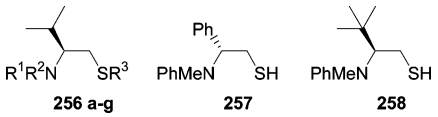


Active species	derived from the ligand	R^1	R^2	Distance between R^1 or R^2 and Zn
252	**251**	Ph	H	Zn-H(Ph) = 4.8 Å
253	**240**	Ph	Me	Zn-H(Me) = 2.8 Å
254	**241**	Ph	Ph	Zn-H(Ph) = 2.6 Å
255	-	H	Ph	Zn-H(Ph) = 2.4 Å

Gibson *et al.*[179] prepared another β-amino disulfide ligand **251**, which was synthesized from (*S*)-phenylglycine or (*R*)-styrene oxide (Scheme 99).

However, ligand **251** gave a lower enantioselectivity compared to **249** in the same reaction. In fact, the best result was found with 4-tolualdehyde (78% yield, 80% ee), as a moderate selectivity was obtained with benzaldehyde (61% ee). With nonaromatic aldehydes, the results were even worse. This decrease in enantioselectivity, compared with the disulfide ligand **249,** was probably due to the absence of a stereodifferentiating group at the carbon in the α-position to the amino group. In order to rationalize this result, a molecular mechanic analysis of the postulated active species was performed (Scheme 100). These calculations showed that the stereodifferentiating phenyl group in the methyzinc derivative **252** (derived from ligand **251**) was directed away from the zinc atom (4.8 Å). Since zinc was the key reacting center for the catalysis, it was expected that **252** would not

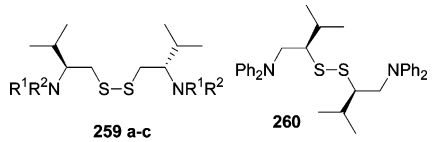
Scheme 101



256 a-g **257** **258**

	R^1	R^2	R^3	Yield (%)	ee (%)
256a	Ph	Ph	H	85	74 (*R*)
256b	Bn	Bn	H	91	58 (*R*)
256c	$-(CH_2)_5-$		H	78	66 (*R*)
256d	Ph	Me	H	89	82 (*R*)
256e	Ph	H	Ph	35	0
256f	Ts	Me	H	80	5 (*S*)
256g	^{i}Pr	Me	H	81	72 (*R*)
257	-	-	-	90	69 (*S*)
258	-	-	-	80	48 (*R*)

Scheme 102



259 a-c **260**

Ligand	R^1	R^2	Yield (%)	ee (%)
259a	Ph	Ph	67	59 (*R*)
259b	Ph	Me	85	80 (*R*)
259c	Bn	Bn	76	38 (*R*)
260	Ph	Ph	75	25 (*R*)

lead to an efficient enantiofacial discrimination, unlike catalyst **253** (derived from Kang's ligand **240**), in which the methyl group was close to the Zn (2.8 Å) and gave excellent enantioselectivity. The calculations concerning the nonsynthesized catalyst **255** showed that the phenyl in the C-2 position could act as a good blocking group (distance Zn−H(Ph) on C-2 = 2.4 Å), for a probably good enantioselective ligand.

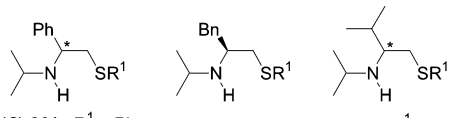
Anderson and co-workers[180] synthesized a new series of *S*,*N*-chelate ligands **256** derived from (*S*)-valine. The authors assumed the nitrogen substituents in the chiral ligands to be crucial for the asymmetric induction in the addition of diethylzinc to aromatic aldehydes. The best results in terms of enantioselectivity were always obtained with benzaldehyde (Scheme 101).

These results showed that nonsymmetrical Ph-substituted nitrogen donor atoms (**256d**) had a positive effect on the efficiency of these specific systems. Furthermore, by changing the steric bulk of the substituent on the nitrogen (Bn, ^{i}Pr, and Ph; see ligands **256b**, **256g**, and **256d**, respectively), the enantioselectivity of the reaction with benzaldehyde increased from 58 to 82% ee. The sulfur-substituted ligand **256e** gave the expected secondary alcohol in the racemic form with a low yield. The effect of the bulk of the chiral group on the ligand backbone (compare ligands **256d**, **257**, and **258**) has been studied. Ligands **257** and **258** led to a lower enantioselectivity than **256d**.

The authors further synthesized disulfide ligands **259a**−**c** and **260**. These chelates were prepared by oxidation of the corresponding monomers with oxygen (Scheme 102).

In the addition of diethylzinc to benzaldehyde, these disulfide analogues were generally less efficient when compared to the amino-thiol ligands[181] (compare, for example, ligand **256a**, Scheme 101 (74% ee) to ligand **259a**, Scheme 102 (59% ee)). This is in contradiction to the results reported by Kellogg[166] and Gibson,[177,179] where the disulfide analogues generally led to better catalysts when compared to amino-thiol complexes. On the other hand, the observations made by Kang[171] were more consistent with the results obtained by Anderson. Even if it is difficult to predict the enantioselectivity provided by the ligand (thiol or disulfide), disulfide ligands were more chemically stable, but the reaction time in their presence was always longer than that with the analogous thiol ligand.

Scheme 103



(*S*)-**261** R^1 = Ph
(*R*)-**261** R^1 = Ph
(*S*)-**262** R^1 = Et

263 R^1 = Ph
264 R^1 = Et

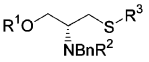
(*S*)-**265** R^1 = Ph
(*R*)-**265** R^1 = Ph
(*S*)-**266** R^1 = Et

Hilmersson *et al.*[182] have used similar chiral amino sulfide ligands for the enantioselective addition of methyllithium and butyllithium to aldehydes. They have synthesized eight chiral ligands from chiral amino acids (Scheme 103). The best results were found with ligand **261**. The addition products were obtained with good conversions and enantioselectivities up to 98.5% ee. It was important to note that these ligands were superior, with respect to the enantioselectivity, to their oxygen analogues in this reaction. The authors assumed that the Li−S bond (∼2.5 Å), which is longer than the Li−O bond (∼2.0 Å), could affect the geometry of the chelate and partially explain the difference in enantioselectivity.

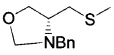
Chiral methyl-thioethers **267**, **268** and disulfides **269**, **270a**−**d** were prepared in few steps from L-cysteine by Braga and co-workers.[183] These new ligands were tested as catalysts for the diethylzinc addition to benzaldehyde. The best results were found with 2 mol % of **270a** at 0 °C (Scheme 104).

Ligand **270a** was also used in the addition of $ZnEt_2$ to different aldehydes: the authors found satisfactory yields and ee, especially at 0 °C: 4-tolualdehyde (86% ee), 4-anisaldehyde (70% ee), phenylacetaldehyde (92% ee). In the case of hexanal, between room temperature and 0 °C, the ee increased from 36% ee to >99% ee. The same trend was not observed in the case of decanal (34% ee *vs* 40% ee), but no explanations were given for these results. Interestingly, ligand **270c** also led to good yields (80−90% range) and excellent enantiomeric excesses (>94% ee) in the diethylzinc addition to aliphatic aldehydes (hexanal and decanal).[184] The authors suggested that the active catalyst did not maintain its C_2-symmetry during the reaction. The disulfide bond was probably cleaved *in situ* by $ZnEt_2$. However, these disulfide compounds proved to be easier to obtain and handle for synthetic applications. To have a better understanding of the relative importance of the various donor atoms (*N*,*O*,*S*) available in free or alkylated form as possible coordinating atoms resulting in covalent or dative bonds to the metal, Braga *et al.*[185] synthesized other chiral sulfides and disulfides from cysteine (Scheme 104). It was demonstrated that, for the diethylzinc addition to aldehydes, a covalent donor−Zn bond proved to be crucial and a thiolate−Zn bond was mandatory for good enantioselectivity. In fact, ligands **267e**−**g** were inefficient in terms of enantioselectivity in the $ZnEt_2$ addition to benzaldehyde. The alkylated sulfide ligands allowed the formation of the (*R*)-benzyl alcohol, albeit with decreased yields and selectivities in comparison with ligand

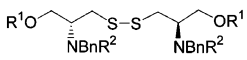
Scheme 104



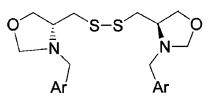
Ligand	R^1	R^2	R^3
267a	H	H	CH_3
267b	H	H	$(CH_2)_2CH_3$
267c	H	H	Bn
267d	H	H	CH_2SPh
267e	H	Me	CH_3, $(CH_2)_2CH_3$, Bn, CH_2SPh
267f	Me	H	CH_3, $(CH_2)_2CH_3$, Bn, CH_2SPh
267g	Me	Me	CH_3, $(CH_2)_2CH_3$, Bn, CH_2SPh
267h	H	H	
267i	Me	Me	



268



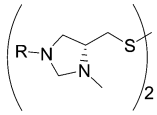
269 a-b



270 a-d

Ligand	Ar	Yield (%)	ee (%)
267a	-	67	41 (*R*)
268	-	57	40 (*S*)
267b	-	28	33 (*R*)
267c	-	29	30 (*R*)
267d	-	27	21 (*R*)
269a	-	56	0
269b	-	77	92 (*S*)
270a	Ph	98	80 (*S*)
270a	Ph	81	>99 (*S*)
270b	*p*-Tol	quant.	92 (*S*)
270c	*p*-$MeOC_6H_6$	83	84 (*S*)
270d	2-Fur	85	90 (*S*)

Scheme 105



Ligand	R
271 a	(*R*)-methylbenzyl
271 b	(*S*)-methylbenzyl
271 c	phenethyl
271 d	*n*-butyl

Ligand	R^2CHO	Yield (%)	ee (%)
271a	Ph	99	91
271b	Ph	99	86
271c	Ph	99	68
271d	Ph	92	66
271a	*p*-ClC_6H_4	92	89
271a	*o*-ClC_6H_4	93	89
271a	*o*-BrC_4H_6	94	90
271a	*p*-$MeOC_6H_4$	60	70
271a	*o*-$MeOC_6H_4$	62	76
271a	*p*-MeC_6H_4	94	84
271a	*n*-Nonyl	52	66
271a	*n*-Pentyl	59	76

269b, which permitted the synthesis of the (*S*)-benzyl alcohol with 77% yield and 92% ee.

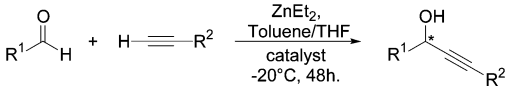
Other chiral disulfides derived from L-cysteine were synthesized by the same group[186] and used in the enantioselective addition of diethylzinc to aldehydes (Scheme 105).

The results shown in Scheme 105 suggested that the substituent at the nitrogen atom played an important role in the enantioselection of the addition reaction. Even if up to 91% ee was obtained with benzaldehyde, the presence of an electron-donating group on the aromatic ring of the substrate afforded lower ee (70 and 76% ee for *ortho*- and *para*-methoxybenzaldehyde). For aliphatic aldehydes, the enantioselectivity of the addition of diethylzinc remained moderate (66 and 76% ee, see Scheme 105).

These authors also used ligands **268**, **269**, and **270a** (Scheme 104) in the enantioselective synthesis of propargylic alcohols by direct addition of alkynes to aldehydes (Scheme 106).[187] Chiral amino alcohols are the most investigated ligands in this reaction;[188] however, this example represented the first generation of sulfur-based ligand used in this transformation.

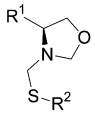
The enantioselective alkynylation reaction of aldehydes with diethyzinc, catalyzed with disulfide **270a**, provided different propargylic alcohols with good yield and moderate enantioselectivities, up to 58%.

Scheme 106



Ligand	R^1	R^2	Yield (%)	ee (%)
268	Ph	Ph	69	18
269	Ph	Ph	65	-
270a	Ph	Ph	67	56
270a	Ph	^{n}Bu	55	36
270a	4-MeC_6H_4	Ph	76	58
270a	2-ClC_6H_4	Ph	80	50
270a	4-$MeOC_6H_4$	^{n}Bu	81	52
270a	2-ClC_6H_4	^{n}Bu	72	58
270a	^{n}pent	^{n}Bu	73	43
270a	^{n}pent	Ph	82	51

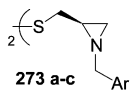
Scheme 107



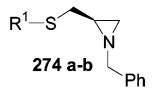
272 a-c

Ligand	R^1	R^2	Yield (%)	ee (%)
272 a	Bn	Ph	97	30
272 b	Bn	Bn	95	13
272 c	^{i}Pr	Bn	75	37

Scheme 108



273 a-c



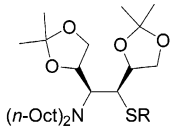
274 a-b

Ligand	Ar	R^1	Yield (%)	ee (%)
273 a	Ph	-	61	>99
273 b	*p*-Tol	-	60	>99
273 c	*p*-MeO-C_6H_4	-	58	56
274 a	-	Et	42	65
274 b	-	Bn	57	76

Braga *et al.*[189] synthesized chiral sulfide ligands containing oxazolidines. They tested them in the test reaction (Scheme 107) and obtained good yields and moderate enantioselectivities.

In 2004, Braga *et al.*[190] obtained aziridine sulfides and disulfides from (*R*)-cysteine for the enantioselective addition of diethylzinc to aldehydes. With these *S*,*N*-ligands in hand, they obtained up to 99% ee (61% yield) with 2 mol % of ligand **273a**, at 0 °C in toluene (Scheme 108). The disulfide ligands proved to be more efficient in this example than the sulfide ligands. Ligand **273a** was tested successfully in this

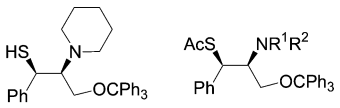
Scheme 109



275 a-b

Ligand	R	aldehyde	Yield (%)	ee (%)
275a	Ac	benzaldehyde	76	43 (*R*)
275b	H	benzaldehyde	97	82 (*R*)
275a	Ac	heptanal	76	45 (*R*)
275b	H	heptanal	80	73 (*R*)

Scheme 110



276 **277 a-b**

Ligand	R^1R^2	Yield (%)	ee (%)
276	-$(CH_2)_5$-	98	99 (*R*)
277a	-$(CH_2)_5$-	99	96 (*S*)
277b	^{t}Bu,^{t}Bu	62	95 (*R*)

reaction with aromatic or aliphatic aldehydes (ee from 75 to >99% and 40−92% yields).

The new β-amino thioacetate **275a** and the thiol **275b**, derived from D-mannitol, were synthesized by Cho and coworkers.[191] In the catalytic enantioselective addition of diethylzinc to benzaldehyde and heptanal, the best ligand was the β-amino thiol **275b** (Scheme 109).

However, the enantioselectivity observed with **275b** was lower than the enantioselectivities observed with the corresponding β-amino alcohol (87% yield, 92% ee at 0 °C). This is one of the rare examples in the literature in which the amino alcohol ligand proved better than the corresponding thiol derivative in terms of enantioselectivity, in the diethylzinc addition to aldehydes reaction.

Pericas *et al.*[192] synthesized thiols derived from norephedrine. These new β-aminothiols **276** and the (*S*)-acetyl derivatives **277a**−**b** were successfully tested in the addition of diethylzinc to benzaldehyde (Scheme 110).

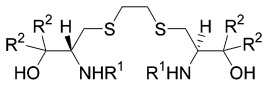
The results for this reaction were excellent, especially with ligand **276**, which also showed very high enantioselectivity for the transformation of other aromatic aldehydes: *para*- and *meta*-tolualdehyde (99% ee), 1-naphthylaldehyde (98% ee), and α,β-unsaturated aldehydes (up to 99% ee). With aliphatic aldehydes (*n*-heptanal), the enantioselectivity remained moderate (66% ee). The authors proposed a positive influence of the steric effect generated by the primary hydroxyl-protecting group on the catalytic activity.

Martens also synthesized C_2-symmetrical bis-β-amino alcohols from (*R*)-cysteine (Scheme 111).[193]

In the enantioselective addition of diethylzinc to benzaldehyde, the enantiomeric excesses of the 1-phenyl-1-propanol obtained ranged from 18% to 94% ee. The best ligand was **278f**, but the authors did not compare their new catalysts in terms of activity.

van Koten *et al.*[194] obtained new amino thiolate complexes. The air-stable bis(arenethiolate) complex **280** was easily synthesized via the reaction of $ZnCl_2$ with 2 equiv of the corresponding ligand **279** (Scheme 112).

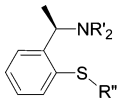
Scheme 111



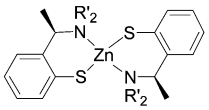
278 a-f

Ligand	R^1	R^2	ee (%)
278a	H	Et	18
278b	H	-$(CH_2)_4$-	29
278c	H	Ph	38
278d	Me	Et	21
278e	Me	-$(CH_2)_4$-	33
278f	Me	Ph	94

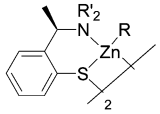
Scheme 112



279 a-c



280 a-c



R = Me, Et, ^{i}Pr

281 a-c

Ligand	R	cat. ratio (mol%)	Yield (%)	ee (%)
281a	Me	2	88	94 (*S*)
281c	Me	4	97	93 (*S*)
281a	Et	2	99	94 (*S*)
281c	Et	4	>99	96 (*S*)
281a	^{i}Pr	2	45	80 (*S*)
281c	^{i}Pr	4	68	91 (*S*)

	R'	R"
a	Me	$SiMe_3$
b	$(CH_2)_4$	H
c	$(CH_2)_5$	H

Complexes **280a**−**c** were tested in the enantioselective addition of diethylzinc to benzaldehyde, leading to the active species **281a**−**c**, which were formed from the reaction of **280** with ZnR_2 present in a large excess. By using **281a** in the addition of diethylzinc on different aldehydes, the conversion was almost always complete. The enantiomeric excess was excellent for aromatic aldehydes (94−99% ee), moderate for α,β-unsaturated and aliphatic aldehydes (75% and 69% respectively), and very good for heterocyclic 2-furylaldehyde (89% ee). The use of complexes **281b** and **281c** containing an heterorocyclic substituent enhanced both rates and enantioselectivities in the addition of diethylzinc to benzaldehyde. In the case of aliphatic aldehydes, the ee increased from 69% ee with **281a** to 80−82% with **281b,c**. In the application of other diorganozinc compounds, and particularly diisopropylzinc, the use of **281c** allowed the improvement of the yield and enantioselectivity in the addition to benzaldehyde.

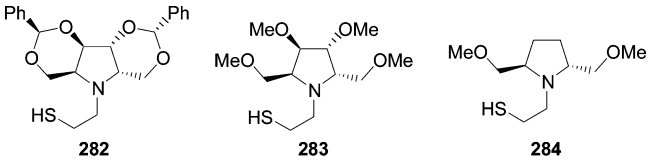
Mechanistic investigation and new details of the intermediates along the reaction coordinate of the zinc-catalyzed 1,2-addition of diorganozinc reagents to aldehydes are proposed by the authors.[195]

Mazaki *et al.*[196] synthesized three C_2-symmetric *N*-(β-mercaptoethyl)pyrrolidines **282**−**284** and used them in the diethylzinc addition to aldehydes. Up to 99% ee was obtained in the desired product with ligand **282** (Scheme 113).

Arai *et al.*[197] synthesized isoborneol-derived β-hydroxysulfide ligands **285** in asymmetric addition of diethylzinc to benzaldehyde. Up to 88% ee was obtained with ligand **285a** (Scheme 114). The authors found that the enantioselectivity of the reaction did not depend on the *S*-substituent of the ligand.

Hongo *et al.*[198] prepared new diastereoisomeric β-amino thiol ligands **286** and **287** with an isoquinuclidine skeleton.

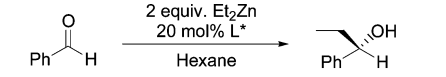
Scheme 113



282 **283** **284**

Ligand	RCHO	Yield (%)	ee (%)
282	Ph	94	96 (*S*)
282	*p*-MeC_6H_4	96	99 (*S*)
282	*o*-BrC_6H_4	89	99 (*S*)
282	*p*-ClC_6H_4	70	81 (*S*)
282	*p*-$MeOC_6H_4$	88	82 (*S*)
282	*o*-$MeOC_6H_4$	93	86 (*S*)
282	1-Naphthyl	85	86 (*S*)
282	trans-PhCH=CH	94	77 (*S*)
282	$PhCH_2CH_2$	90	85 (S)
282	$CH_3(CH_2)_7$	91	88 (*S*)
283	Ph	78	5 (*R*)
284	Ph	81	11 (*R*)

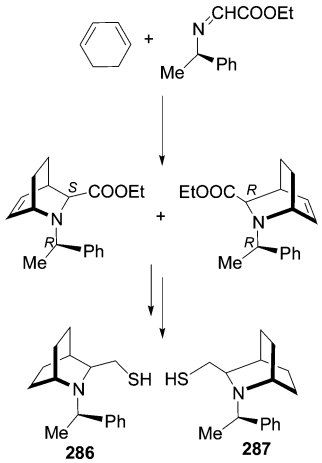
Scheme 114



285 a-c

Ligand	R^1	Yield (%)	ee (%)
285a	Bn	94	88
285b	Me	98	85
285c	^{i}Pr	94	86

Scheme 115



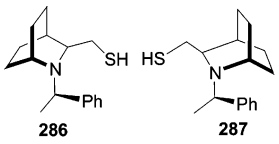
These compounds were easily synthesized from the corresponding amino esters, which were obtained by an imino-Diels−Alder reaction (Scheme 115).

These ligands were used to perform the zinc-catalyzed asymmetric addition to aldehydes (Scheme 116). Ligand **287** afforded the expected product with a high ee (94%). The approach of the attacking species to one of the enantiopic faces of the aldehyde was more efficient using ligand **287** compared to **286**. Other secondary alcohols were obtained with high ee, starting from substituted and sterically hindered aromatic aldehydes but also from aliphatic aldehydes.

Another β-amino thiol was synthesized by the same group.[199] This ligand **288** contained a bicyclo[2.2.1] ring system, the 2-azanorbornylmethanethiol, and was easily prepared from the corresponding β-amino alcohol **289** (Scheme 117).

The catalytic ability of these ligands was examined in the enantioselective addition of diethylzinc to aldehydes. The

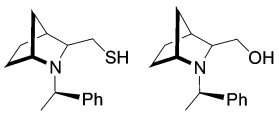
Scheme 116



286 **287**

Ligand	aldehyde	Yield (%)	ee (%)
286	benzaldehyde	38	71 (*R*)
287	benzaldehyde	68	94 (*S*)
287	2-naphthylaldehyde	49	94 (*S*)
287	2-Br-benzaldehyde	98	94 (*S*)
287	2-EtO-benzaldehyde	79	79 (*S*)
287	cyclohexane-carboxaldehyde	34	94 (*S*)

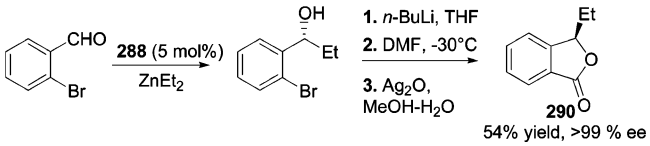
Scheme 117



288 **289**

Ligand	aldehyde	Yield (%)	ee (%)
289	benzaldehyde	53	22 (*R*)
288	benzaldehyde	95	97 (*R*)
288	2-naphthylaldehyde	95	98 (*R*)
288	2-EtO-benzaldehyde	100	97 (*R*)
288	cyclohexane-carboxaldehyde	97	>99 (*R*)

Scheme 118



54% yield, >99 % ee

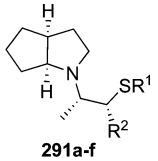
thiol-containing ligand **288** proved to be better than the corresponding alcohol-containing ligand **289**. The sulfur atom possesses a high affinity toward zinc atoms as compared to oxygen atoms, and the metal thiolate complex formed was expected to strongly block a specific prochiral face of the coordinated aldehyde. Ligand **288** was used in the synthesis of (*R*)-3-ethylphtalide **290** (Scheme 118) with up to 99% ee.

The authors calculated the activation energy and experimental yield for the expected alcohol by using the chiral ligand **288**. The energy difference between both transition states was large enough to explain the high enantiomeric excess found with benzaldehyde (97% ee) (Scheme 117).

Aurich *et al.*[200,201] prepared ligands **291a−f** and **292a−c** based on a 2-azabicyclo[3.3.0]octane skeleton. These ligands were used in the test reaction. The yield and selectivity were also higher with these thioacetate and thio ligands than with their alcohol analogues (Scheme 119).

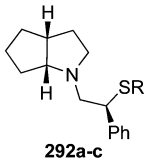
Chelucci *et al.*[202] prepared sulfur-containing pyridine ligands **293−296** (Scheme 120). The ability of these new ligands to provide asymmetric induction in the enantioselective addition of diethylzinc to benzaldehyde was examined. The results obtained with ligands **293** and **295** were very disappointing, even if the corresponding alcohols gave 91 and 28% ee, respectively. Therefore, the authors decided to synthesize ligands **294** and **296**, which can form a six-membered chelating ring with the zinc derivative and may

Scheme 119



291a-f

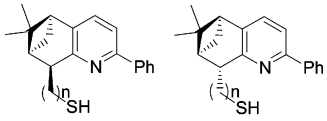
Ligand	R^1	R^2	Yield (%)	ee (%)
291 a	H	H	100	84 (*R*)
291 b	H	Ph	100	90 (*R*)
291 c	Ac	H	100	82 (*R*)
291 d	Ac	Ph	100	90 (*R*)
291 e	$S\rightarrow_2$	H	-	
291 f	$S\rightarrow_2$	Ph	92	86 (*R*)



292a-c

Ligand	R	Yield (%)	ee (%)
292 a	H	100	64 (*S*)
292 b	Ac	95	60 (*S*)
292 c	$S\rightarrow_2$	88	60 (*S*)

Scheme 120



n=0 : **293**
n=1 : **294**

n=0 : **295**
n=1 : **296**

Ligand	Yield (%)	ee (%)
293	87	12 (*S*)
294	78	5 (*S*)
295	88	51 (*R*)
296	76	51 (S)

improve the enantioselectivities. However, a moderate excess (51%) was found with both ligands.

Shi *et al*. synthesized C_2-symmetric diphenylthiophosphoramide[203] and dialkylthiophosphoramide[204] derivatives of (1*R*,2*R*)-1,2-diaminocyclohexane and diphenylthiophosphoramide derivatives of (*R*)-1,1′-binaphthl-2,2′-diamine[205] as chiral ligands for the titanium(IV) alkoxide-promoted addition of diethylzinc to aldehydes. In the addition to benzaldehyde, they obtained 40% ee with **297a**, 18% ee with **297b**, and 53% with **298** (Scheme 121). The enantioselectivity could be increased up to 64% ee in the addition of diethyzinc to 3-(benzyloxy)benzaldehyde. With ligand **297** (P═S ligand), and compared to the corresponding P═O ligand, they observed an inversion of the absolute configuration of the desired product. According to the authors, this could be explained by the different electron-withdrawing abilities of the P═S and P═O bonds. No ligand exchange could take place because of the lower acidity of the NH proton in ligand **297b**, and they suggested complex **A** as a possible intermediate. With the diphenylphosphoramide ligand, complex **B** was proposed.

2.5.4. Ligands with an S-Noncoordinating Atom

Bolm and co-workers[206,207] synthesized β-hydroxy sulfoximines **299a**−**d**, containing a chiral sulfur atom (Scheme 122). These ligands are not *S*-coordinating, but interestingly, the chirality in these structures was only due to the presence of the chiral sulfoximine moiety.

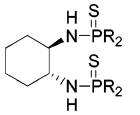
Tested in the reaction of enantioselective alkylation of aldehydes, these ligands gave high enantiomeric excesses with benzaldehyde. The asymmetric induction was dependent on the catalyst structure. The best selectivities were obtained with two alkyl groups at the hydroxyl-bearing β-carbon. The authors provided an X-ray analysis of the dimeric zinc alkoxide molecular structure derived from *rac*-**299c**. The asymmetric amplification in the catalysis observed with nonenantiomerically pure **299c** proved the nonmonomeric nature of the species formed in solution. The use of 10 mol % of **299c** of 23% ee resulted in the formation of the expected alcohol with 64% ee in 70% yield. Additional NMR spectroscopy analyses have been performed by the authors.

Carreno, Ruano, *et al*.[208] used β-hydroxysulfoxide ligands **300**−**301** (Scheme 123) in the enantioselective addition of diethylzinc to benzaldehyde. The best enantioselectivity was obtained with ligand **301c** (45% ee). When the active complex was formed by the addition of ligand **301c** and $AlMe_3$, the enantioselectivity was increased to 55% ee. The authors observed variable amounts of benzyl alcohol, resulting from the reduction of benzaldehyde, under the standard alkylation conditions; the values for the phenylpropanol/benzylic alcohol ratio ranged from 1.1 to 7.6. Chelucci *et al*.[209] prepared chiral 2-(1-*p*-tolylsulfinyl)alkylpyridines **302a**−**c** (Scheme 123). The two epimers at the carbon stereocenter of these ligands were separated by flash chromatography, and the corresponding enantiopure ligands were tested in the addition of diethylzinc to benzaldehyde. Good yields (>85%) were obtained, however with low enantioselectivities (<19% ee).

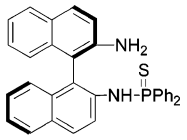
Carretero *et al*.[210,211] synthesized amino-substituted *tert*-butylsulfinylferrocenes as new ligands for the asymmetric addition of diethylzinc to aldehydes. Among the different ligands, such as substituted amines (**303a** and **303b**), amides (**304a**−**d**), and sulfonamides (**305**−**306**), the best ligands proved to be the sulfonamide ligands **305b** and **305c**, with up to 88% ee (80% yield) with benzaldehyde and up to 96% ee (78% yield) with methyl 4-formylbenzoate (*p*-CO_2Me−C_6H_4CHO) (Scheme 124). The authors synthesized the *p*-tolyl sulfoxide analogue of **305b**, which gave the addition product to benzaldehyde with lower results (32% ee versus 80% ee with **305b**). In the case of ligands **306a**−**b**, which only possess planar chirality, similar enantioselectivities were found, showing that the planar chirality of the ferrocene was more important than the stereogenic sulfur atom to perform an efficient asymmetric induction. The authors concluded that these ligands behaved as *N*-monocoordinating ligands rather than bidentate *N*,*O*- or *S*,*N*-chelating ligands.

Qin *et al*.[212] synthesized new chiral sulfinamido ligands **307a**−**g** and **308**−**312**. Depending on the ligand structure, the authors obtained very different results in terms of activity and enantioselectivity in the addition of diethylzinc to benzaldehyde (Scheme 125). The best result was obtained with ligands **307a**,**b** and **307d**. Methylation of the phenol group (ligand **307g**) or the presence of a sulfinamide (ligand **308**) had a dramatic negative effect on the activity. The α-sulfinamido alcohol ligands **310** and **312** showed lower catalytic activity and enantioselectivities compared to those of β-sulfinamido alcohol ligand **307a**. With all these results in hand, the authors suggested that both the nitrogen atom and the oxygen atom of the sulfinamido group, as well as

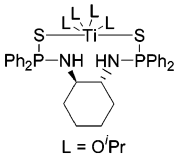
Scheme 121



Ligand	R
297a	Ph
297b	OEt

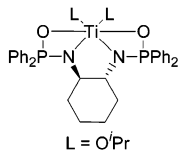


298



L = O^{i}Pr

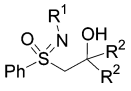
Complex A



L = O^{i}Pr

Complex B

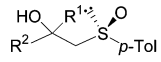
Scheme 122



299 a-d

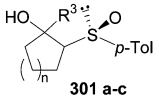
Ligand	R^1	R^2	aldehyde	Yield (%)	ee (%)
299a	Me	-$(CH_2)_3$-	benzaldehyde	55	84
299b	Me	-$(CH_2)_9$-	benzaldehyde	50	88
299c	Me	Me	benzaldehyde	73	85
299c	Me	Me	*p*-Cl-benzaldehyde	79	79
299c	Me	Me	*p*-Me-benzaldehyde	48	75
299c	Me	Me	$PhCH_2CH_2CHO$	50	61
299d	Et	Me	benzaldehyde	94	68

Scheme 123



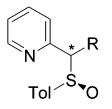
300 a-e

Ligands	R^1	R^2
(2*S*)-**300a**	^{t}Bu	H
(2*R*)-**300a**	^{t}Bu	H
(2*R*)-**300b**	^{t}Bu	CH_3
(1*S*)-**300c**	Ph	H
(1*R*)-**300c**	Ph	H
(2*R*)-**300d**	Ph	CH_3
(5*R*)-**300e**	-$(CH_2)_3$-CO_2Me	H



301 a-c

Ligands	n	R^3
(1*S*, 2*S*)-**301a**	1	H
(1*R*, 2*S*)-**301a**	1	H
(1*S*, 2*S*)-**301b**	2	H
(1*R*, 2*S*)-**301b**	2	H
(1*R*, 2*S*)-**301c**	2	CH_3



302 a-c

Ligand	R^1
302a	^{i}Pr
302b	Ph
302c	^{t}Bu

the oxygen atom of the phenol group, participated in the coordination with zinc to form a *O,N,O*-chelating transition state.

Bonini, Zwanenburg, *et al.*[101] synthesized ferrocenyloxazoline ligand **313** by ring expansion of *N*-ferrocenoylaziridine-2-carboxylic esters (Scheme 126). In the asymmetric addition of Et_2Zn to benzaldehyde, up to 46% ee was found (76% yield).

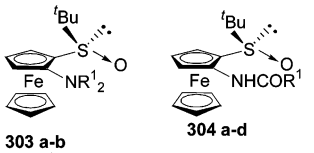
In most cases summarized here, the amino thiol ligands led to better enantioselectivities than their amino alcohol ligand counterparts, in the reaction of diethylzinc addition to aldehydes. Even if the most common building block was cysteine, we have shown in this paragraph many different ligands synthesized from phenylglycine, valine, or other amino acids. The selectivity was almost perfect in numerous cases with aromatic aldehydes. However, some improvement in the asymmetric addition of diethylzinc to aliphatic aldehydes, using sulfur-containing ligands, has to be achieved.

2.6. Asymmetric Conjugate Addition

2.6.1. Introduction

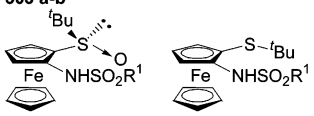
The enantioselective conjugate 1,4-addition reaction (also called Michael addition) is one of the major reactions in organic synthesis. The use of a transition metal (traditionally copper or nickel) is needed to avoid the 1,2-addition on the carbonyl group of the substrate. Despite many successes reported in the last 10 years in the area of asymmetric copper-

Scheme 124



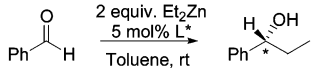
303 a-b

304 a-d



305 a-f

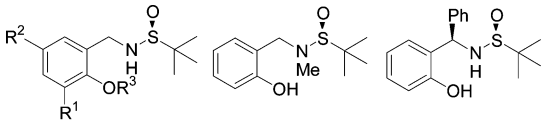
306 a-b



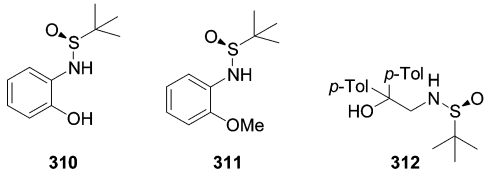
Ligand	R^1	Yield (%)	ee (%)
303a	H	93	28
303b	Me	59	6
304a	Me	76	60
304b	CF_3	67	6
304c	^{t}Bu	70	14
304d	Ph	74	8
305a	Me	90	74
305b	*p*-Tol	79	80
305b[a]	*p*-Tol	80	88
305c	*p*-MeO-C_6H_4	82	82
305c[a]	*p*-MeO-C_6H_4	76	86
305d	*p*-NO_2-C_6H_4	62	58
305e	mesityl	68	48
305f	α-naphthyl	51	42
306a	*p*-Tol	85	82
306b	*p*-MeO-C_6H_4	81	74

a. Reaction run at -20°C

Scheme 125



307 a-g **308** **309**

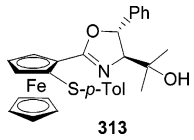


310 **311** **312**

Ligand	R^1	R^2	R^3	Yield (%)	ee (%)
307a	H	H	H	89	94
307b	Me	H	H	90	94
307c	^{t}Bu	H	H	67	79
307d	H	Me	H	87	94
307e	H	OMe	H	15	78
307f	H	NO_2	H	66	84
307g	H	H	Me	47	33
308	-	-	-	36	0
309	-	-	-	40	17
310	-	-	-	70	40
311	-	-	-	78	0
312	-	-	-	80	75

catalyzed 1,4-organometallic additions to Michael acceptors,[213−217] there is a need to improve systems in terms of yield and enantioselectivity, particularly when linear aliphatic enone substrates are involved (Scheme 127). The sulfur-

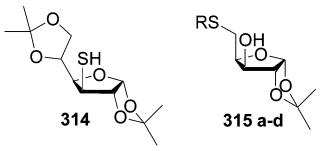
Scheme 126



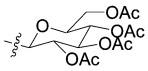
313

Scheme 127

Scheme 128



314 **315 a-d**

Ligand	R	Conv. (%)	ee (%)
315a	Me	78	49
315b	^{i}Pr	98	44
315c	Ph	80	62
315d		41	20

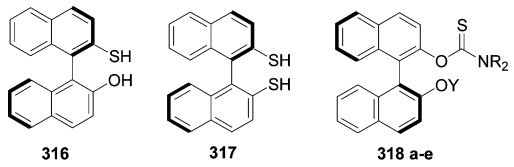
containing ligands have been less studied than their phosphorus counterparts. Furthermore, even if the enantioselectivities obtained were excellent with the phosphorus ligand, one of the major drawbacks in the copper-catalyzed Michael addition of Grignard and diorganozinc reagents to enones and α,β-unsaturated carbonyl compounds was the high substrate specificity. In this context, the design and development of new ligands, with, for example, the use of other heteroatoms than the sulfur atom, was required. In this section, (*S*,*O*)-, (*S*,*N*)-, and (*S*,*P*)-ligands and ligands with *S*-noncoordinating atoms used in the Cu-catalyzed conjugate addition reaction will be discussed, together with the ligands used in the analogous Ni-catalyzed reaction.

2.6.2. Copper-Catalyzed Asymmetric Michael Addition

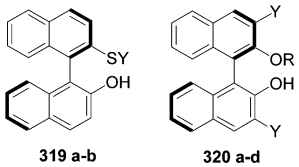
2.6.2.1. Chiral *S,O*-Ligands. In 1993, Spescha and Rihs[218] described the enantioselective copper-catalyzed 1,4-addition of Grignard reagents to 2-cyclohexenone with a thiosugar derived ligand **314**. They observed an excellent yield and regioselectivity in the 1,4-addition product, with an enantioselectivity up to 60% ee, strongly dependent on the reaction conditions. They also obtained an X-ray crystal dimeric structure of the chiral complex [Cu(**314**)$((Ph)_2$PCHCHP$(Ph)_2)$]. However, different addition tests on aliphatic α,β-unsaturated substrates failed. Pamies, Ruiz, and co-workers[219] have synthesized (*S*,*O*)-ligands derived from D-(+)-xylose. This was the first example of thioether-based catalysts for the copper-catalyzed asymmetric conjugate addition of organometallics to enones (Scheme 128).

In the $Cu(OTf)_2$-catalyzed 1,4-addition of diethyzinc to 2-cyclohexenone, the best result was obtained with ligand **315c**, which gave 80% conversion and 62% ee. In general, the regioselectivities in the 1,4-product were good for all ligands. In the same article, the authors tested the ligands

Scheme 129



316 **317** **318 a-e**



319 a-b **320 a-d**

L*	R	Y
318a	Me	H
318b	Et	H
318c	Me	Me
318d	Me	$C(O)NMe_2$
318e	Me	$P(N^iPr_2)_2$
319a	-	$C(S)NMe_2$
319b	-	^{n}Bu
320a	H	SMe
320b	$C(S)NMe_2$	Me
320c	$C(S)NMe_2$	$C(O)NEt_2$
320d	$C(S)NMe_2$	SMe

315 in the addition of trimethylaluminium to *E*-non-3-en-2-one as the substrate. Only 34% ee with 10% conversion was obtained with the ligand **315c**.

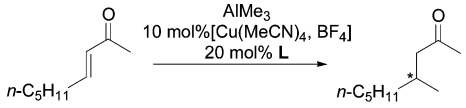
Woodward *et al*. developed a large-scale preparation of racemic and enantiopure monothiobinaphthol ligands for the Cu-catalyzed conjugate addition of organometallic reagents to both linear and cyclic enones.[220−222] The design of this class of ligands was based on the presence, in the deprotonated corresponding ligand, of both hard naphtolate (allowing strong interaction with the terminal organozinc species) and soft thionaphtolate donors (capable of coordinating organocuprates). This case was supposed to be ideal for the bimetallic Cu-catalyzed conjugate addition. However, active catalysts were formed in all cases, but only modest enantioselectivities were obtained: 36% ee and 66−84% yield in the $[Cu(MeCN)_4BF_4]$-catalyzed addition of $ZnEt_2$ to 2-cyclohexenone with ligand **316**, and 55% ee with 30% yield in the $[Cu(MeCN)_4BF_4]$-catalyzed addition of BuMgCl to cyclohexenone with ligand **317** (Scheme 129).

Later, the same group screened the different ligands for the copper(I)-catalyzed 1,4-addition of $AlMe_3$ to linear enones such as (*E*)-3-nonen-2-one. Thiocarbamate donor ligands **318a**−**e** gave promissing results, with enantioselectivities up to 50% ee with 80% yield. Ligands **318a** and **318b**, possessing a free hydroxyl function, gave the best results. Variations on the organometallic species or experimental conditions did not significantly improve the enantioselectivities. Modest results were obtained using ligand **318a** with other substrates: (*E*)-hept-3-en-2-one (51% yield, 46% ee), (*E*)-5-methylhex-3-en-2-one (43% yield, 43% ee), or cyclohexenone (26% yield, 42% ee).[223]

Other similar ligands **319a**−**b** and **320a**−**d** were synthesized and tested in the copper(I)-catalyzed 1,4-addition of $AlMe_3$ to (*E*)-3-nonen-2-one. An enantiomeric excess of 71% was obtained with **319b** (79% yield). The introduction of alternative binding sites lowered the enantioselectivity (see the results with **320a**−**d,** Scheme 130).[224]

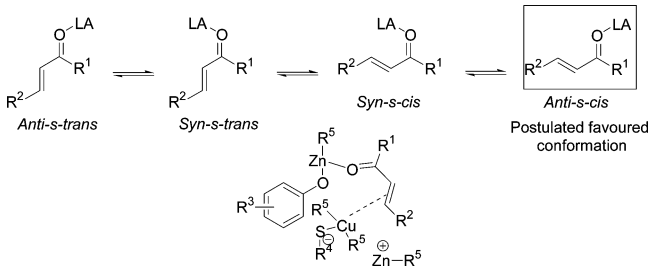
The authors proved a nonlinear effect in this reaction with the use of ligand **318a**. One explanation of this phenomenon

Scheme 130



Ligand	Yield (%)	ee (%)
318a	80	50
318b	75	40
318c	31	12
318d	23	15
318e	63	8
319a	70	42
319b	79	71
320a	80	33
320b	55	62
320c	61	17
320d	92	3

Scheme 131

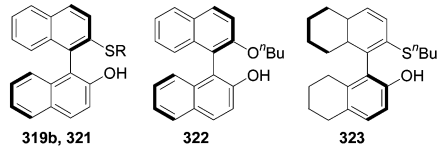


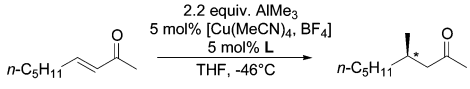
is that a mononuclear catalyst is involved and that the slight deviation observed is due to a competing dimeric catalyst. Two experiments have highlighted this mechanism. A concentration effect was observed, since the enantioselectivity with **318a** was improved to 61% ee by lowering the substrate concentration. The catalytic asymmetric course of the transformation was complicated by the presence of an achiral background reaction arising from catalyst [Cu(MeCN)$_4$BF$_4$]/AlMe$_3$, used without a chiral ligand (49% conversion, 33% yield). Changing the organometallic source with ligand **320a** had a beneficial effect: the use of ZnEt$_2$ instead of AlMe$_3$ gave 72% ee with the linear enone and 77% ee with cyclohexenone. Further mechanistic studies with this ligand were investigated, in particular with different substituted enones.[225,226]

Since the R^1 or R^2 groups affected the reactivity and/or the enantioselectivity of the reaction, the authors strongly suggested that linear enones bound the catalyst in an *anti-s-cis* arrangement prior to the 1,4-delivery of the alkyl nucleophile (Scheme 131). In the copper-catalyzed asymmetric 1,4-addition of diethylzinc compounds to different linear aliphatic enones in the presence of ligand **320a**, the enantioselectivities increase to 77% ee. With enones containing functionalities such as (CH$_2$)$_n$CH(Oalkyl)$_2$, the ZnEt$_2$ addition products undergo base-promoted cyclization.

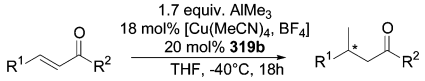
In 2003, Woodward *et al.*[227] used compounds **319b** and **321**−**322** as ligands for the enantioselective conjugate addition of AlMe$_3$ to linear aliphatic enones (Scheme 132). After careful optimizations, the authors recommended the use of highly pure AlMe$_3$. They proved that the presence of methylalumoxane (MAO), coming from the hydrolysis of AlMe$_3$, reduced the enantioselectivity of the 1,4-product. The best ligand was **319b**, and by performing the reaction under optimal conditions, *i.e.*, with 20 mol % of ligand, 18 mol % of [Cu(MeCN)$_4$]BF$_4$, and 1.7 equiv of AlMe$_3$ in THF at −40 °C for 18 h, the conjugate addition was extended to many

Scheme 132





	R	Yield (%)	ee (%)
321a	Me	34	79
321b	Et	-	-
321c	^{n}Pr	41	84
321d	^{i}Pr	24	70
319b	^{n}Bu	51	86
321e	^{n}C$_6$H$_{13}$	33	82
322	-	<5	<5
323	-	65	63



R^1	R^2	Yield (%)	ee (%)
^{n}C$_5$H$_{11}$	Me	51	86
^{n}C$_6$H$_{13}$	Me	58	86
CH$_2$^{i}Pr	Me	63	87
CH$_2$^{t}Bu	Me	46	93
^{i}Pr	Me	55	93
Cy	Me	58	92
^{n}C$_5$H$_{11}$	Et	52	83
^{n}C$_5$H$_{11}$	CH$_2$^{i}Pr	55	85
^{n}C$_5$H$_{11}$	^{i}Pr	62	76
Cy	CH$_2$^{i}Pr	64	89

other substrates with enantioselectivities of 76−93% ee and a yield higher than 46%.

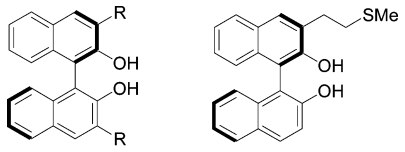
The need of having a directing group, such as a thioether, for the addition of the cuprate in the transition state was proved by the synthesis and use of the butyl ether ligand **322**. In fact, this ligand gave a poor yield and enantioselectivity. Furthermore, the use of these ligands in the addition to benzylideneacetone or to enones (bearing a conjugate vinyl function) or nitroalkenes failed. Attempted additions of AlEt$_3$ were not successful, which strongly suggested to the authors that the structure of the active catalyst incorporated an AlR$_3$-dependent substrate binding pocket. The octahydro-1,1′-binaphthyl thioether ligand **323** was synthesized and compared to the aromatic binaphthyl analogue **319b**.[228] The enantioselectivity (63% ee) using **323** was less than that with **319b**, with a comparable yield in the conjugate product.

Kang *et al.* synthesized other BINOL-based thioether ligands for the enantioselective 1,4-addition of Et$_2$Zn to enones.[229] The sulfide ligands **324b** and **324c** gave better enantioselectivities than the dithioacetals, even if the dithioacetal **324f** with a long spacer between the BINOL core and the Cu-binding site gave 56% ee (Scheme 133).

After careful optimization, ligands **324b** and **324c** were tested with different substrates to give up to 96% ee with chalcone as the substrate (Scheme 134). The addition of Et$_2$Zn on nitroolefins gave enantioselectivities of up to 79% ee. It was worth noting that the BINOL ligand itself gave 7% ee with 2-cyclohexenone as the substrate and the monosubstitued BINOL sulfide **325** gave (3*R*)-ethylcyclohexanone with 74% ee.

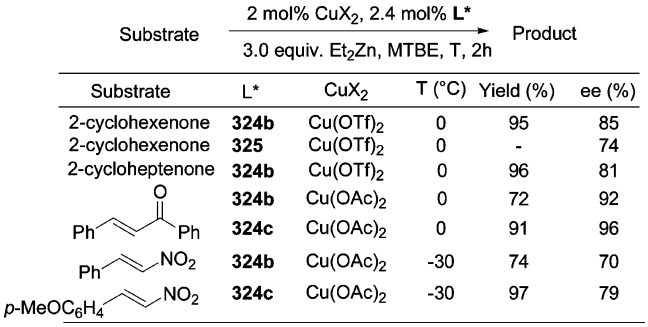
Woodward *et al.*[230] used ligand **326** for the asymmetric copper-catalyzed S$_N$2′ addition of diethylzinc to Baylis−Hillman-derived allylic electrophiles (Scheme 135). Chloride proved to be a better leaving group than bromide with respect to the enantioselectivity, though with a lower yield. For the

Scheme 133



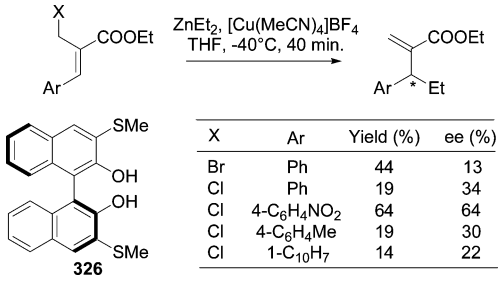
	R	Yield (%)	ee (%)
324a	CH_2SMe	86	0
324b	$(CH_2)_2SMe$	95	69
324c	$(CH_2)_2S^tBu$	91	65
324d	$CH(SMe)_2$	12	0
324e	$CH_2CH(SMe)_2$	16	11
324f	$(CH_2)_2CH(SMe)_2$	41	56

Scheme 134



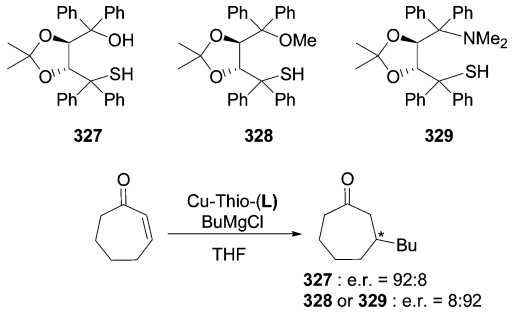
Substrate	L*	CuX_2	T (°C)	Yield (%)	ee (%)
2-cyclohexenone	**324b**	$Cu(OTf)_2$	0	95	85
2-cyclohexenone	**325**	$Cu(OTf)_2$	0	-	74
2-cycloheptenone	**324b**	$Cu(OTf)_2$	0	96	81
	324b	$Cu(OAc)_2$	0	72	92
	324c	$Cu(OAc)_2$	0	91	96
	324b	$Cu(OAc)_2$	-30	74	70
	324c	$Cu(OAc)_2$	-30	97	79

Scheme 135



X	Ar	Yield (%)	ee (%)
Br	Ph	44	13
Cl	Ph	19	34
Cl	4-$C_6H_4NO_2$	64	64
Cl	4-C_6H_4Me	19	30
Cl	1-$C_{10}H_7$	14	22

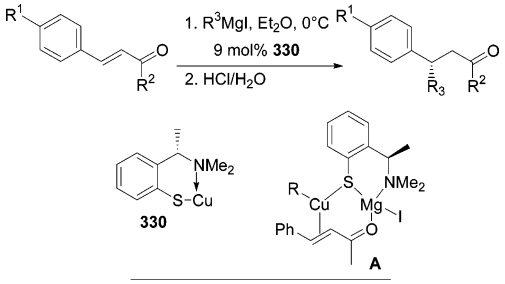
Scheme 136



authors, the stereocontrol in this reaction appeared more to be due to electronic than to steric factors (Ar = 4-C_6H_4-NO_2, ee = 64%; Ar = 4-C_6H_4-Me, ee = 30%).

As a good transition between the (*S,O*)- and (*S,N*)-ligands for this transformation, Seebach *et al*. have synthesized both alkoxy- and aminothiol derivatives from TADDOL (Scheme 136).[231,232] In the enantioselective conjugate addition of butyl Grignard reagent to cycloheptenone, they obtained the

Scheme 137



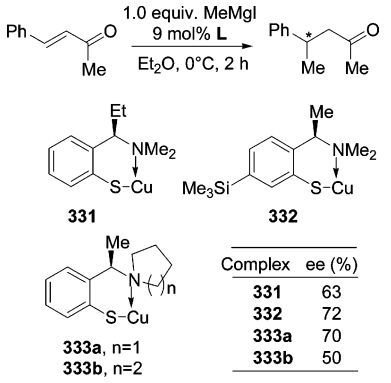
R^1	R^2	R^3	Yield (%)	ee (%)
H	Me	Me	97	76
H	Me	^{n}Bu	>95	45
H	Me	^{i}Pr	>85	10
CN	Me	Me	20	13
Cl	Me	Me	>99	69
H	Me	Me	97	76
Me	Me	Me	>99	64
OMe	Me	Me	>99	56
H	^{i}Pr	Me	98	72
H	^{t}Bu	Me	>99	45
H	Ph	Me	>99	0

expected 1,4-product with an enantiomer ratio up to 92:8 with **327** and up to 8:92 with the complexes **328** or **329**. With the same absolute configuration of the starting ligand, the stereochemical course of the conjugate addition was reversed. The solid-state structure of the copper complex of **327** was determined by X-ray analysis and proved that the Cu-catalyzed 1,4-addition with ligand **327**−**329** proceeded via a tetranuclear $[Cu_4S_4]$ species where the TADDOL-derived ligand was a nonexpected sulfur-monodentate and not a (*S,X*) bidentate ligand. Further ^{1}H NMR studies confirmed this hypothesis. Furthermore, analyses by ^{1}H NOE NMR spectroscopy suggested a different structure for the Cu complex of **327** relative to **328** (and **329**), that could explain the observed stereochemical inversion.

2.6.2.2. Chiral *S,N*-Ligands. Arenethiolatocopper (I) complexes **330** have been synthesized by van Koten *et al*.[233,234] and used in the 1,4-Michael addition of Grignard reagents to acyclic enones (Scheme 137). The experimental conditions have been carefully optimized, and the best addition method involved the controlled simultaneous addition of RMgI solutions and the substrate (at equal concentration) to catalyst **330** in Et_2O. The 1,4-addition products were obtained with excellent chemoselectivity, high yields, and good enantioselectivities (up to 76% ee). Variation of the *para* substituent on the aromatic ring lead to a small effect on the enantioselectivity, except in the case of the *p*-CN substituent. These results were explained by the formation of intermediate **A**, where the double bond was coordinated to copper and the oxygen atom to Mg. In depth NMR and crystallographic studies proved that **330** exists both in the solid state and in solution as a well-defined neutral trinuclear aggregate $[CuSAr^*]_3$.[235,236]

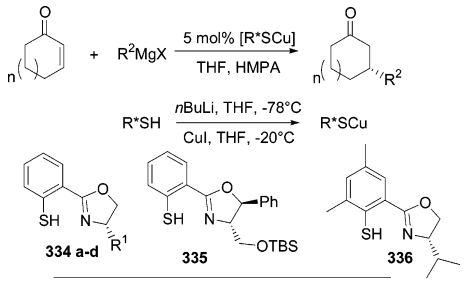
Later, van Koten, Alexakis, *et al*.[237] extended the use of chiral catalyst **330** and **331**−**333** in the conjugate addition reactions of Grignard reagents and Et_2Zn to aliphatic and cyclic enones (Scheme 138). In the addition of MeMgI to (*E*)-4-phenylbut-3-en-2-one in Et_2O, complex **330** proved to be the best catalyst. The diethylzinc addition to 2-cyclohexenone with 2 mol % of **330** gave the corresponding 2-cyclohexenone with complete conversion and 83% ee. In this reaction, a positive nonlinear effect was observed by the authors, probably a sign that the reaction mechanism involved a dimeric species. Other subtrates were tested in

Scheme 138



Complex	ee (%)
331	63
332	72
333a	70
333b	50

Scheme 139



Ligand	R^1	n	R^2	Yield (%)	ee (%)
334a	^{i}Pr	0	Bu	30	16
334a	^{i}Pr	0	^{i}Pr	43	37
334a	^{i}Pr	1	Bu	67	60
334a	^{i}Pr	1	^{i}Pr	71	72
334a	^{i}Pr	2	Bu	24	83
334a	^{i}Pr	2	^{i}Pr	55	87[a]
334b	Me	1	Bu	39	58
334c	^{t}Bu	1	Bu	46	15
334d	CH_2Ph	1	Bu	60	52
335	-	1	Bu	45	47
336	-	1	Bu	76	60

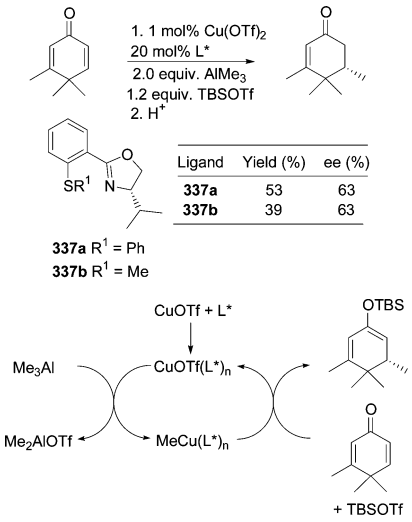
a. 10 mol% Ligand

the Et_2Zn addition with complex **330**−**333** with average results: (*E*)-4-phenylbut-3-en-2-one (**332**, 62% ee), *trans*-3-nonen-2-one (**332**, 37% ee), and *trans*-*β*-nitrostyrene (**330**, 22% ee). For cyclic enones the use of Et_2Zn was preferred, whereas Grignard reagents lead to better results in the presence of acyclic enones.

The copper-catalyzed conjugate addition of Grignard reagents to cyclic enones was also performed by Pfaltz and co-workers[238,239] They synthesized a series of mercaptoaryl-oxazoline ligands **334**. The results showed that with ligand **334a** the enantioselectivities increased with the size of the cyclic enone: from 16 to 37% ee for cyclopentenone and 83−87% ee for cycloheptenone (Scheme 139). It can be observed that the addition of ^{i}PrMgCl gave better results than BuMgCl as the reagent and the addition of HMPA was necessary to obtain good enantioselectivities. Preliminary studies with acyclic enones gave lower enantioselectivities (<20% ee). A copper(I) thiolate complex derived from ligand **334a** was isolated in analytically pure form, and the authors proposed a trimeric Cu complex containing a six-membered chairlike (Cu_3S_3) ring, as shown in the stuctural studies of van Koten and co-workers.[235] A study with ligand **334a** showed a negative nonlinear effect in the case of isopropyl-lmagnesium chloride addition to 2-cycloheptenone. No interpretation of these results is given by the authors.

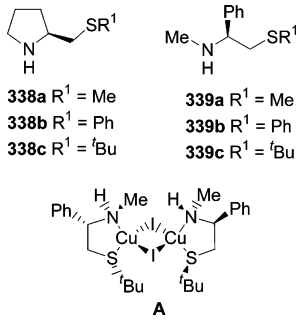
Analogous thioether ligands **337** have been used by Iwata *et al*. [240,241] in the enantioselective Cu-catalyzed addition of $AlMe_3$ to 4,4-disubstituted cyclohexa-2,5-dienone. The 1,4-adduct was obtained in 63% ee by using 20 mol % of ligand **337a** or **337b** in the presence of 1.2 equiv (with respect to the substrate) of *tert*-butyldimethylsilyltriflate (TBSOTf). This additive increased both the reaction rate and the enantioselectivity. A mechanism was proposed by the authors (Scheme 140). Replacing the thiophenyl group in ligand **337a** with a thiomethyl group (ligand **337b**) had no effect on enantioselectivity.

Scheme 140



Ligand	Yield (%)	ee (%)
337a	53	63
337b	39	63

Scheme 141

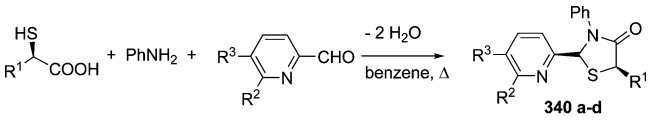


Gibson *et al*.[242] synthesized a number of chiral *β*-amino sulfide ligands derived from L-proline (**338a**−**c**) or (*S*)-phenylglycine (**339a**−**c**) for the enantioselective conjugate addition of methyllithium to 2-cyclohexenone (Scheme 141). The best ligand was **338b** with enantioselectivities up to 64% ee and 14−33% yield, but the enantioselectivities obtained proved to be strongly dependent on the methyllithium batches. The use of additives in the reaction failed to overcome this variability. Furthermore, the use of toluene as the solvent gave the opposite enantiomer to that observed with an ethereal solvent, probably due to a cuprate solvatation and aggregation, according to the authors. Complex **A**, derived from ligand **339c**, gave crystals suitable for X-ray studies. This dimeric complex with copper(I) iodide presented a C_2-symmetry, confirming the *S*,*N*-coordination.

Kellogg, Feringa, *et al*.[243] described the synthesis of pyridyl-substituted thiazolin-4-ones **340** as new ligands for the Cu(I)-catalyzed asymmetric conjugate addition of diethylzinc to enones. These ligands were obtained in quantitative yield by mixing α-mercapto acids, aniline, and 2-pyridine-carboxyaldehyde (Scheme 142). Diastereomerically pure materials were obtained by recrystallization.

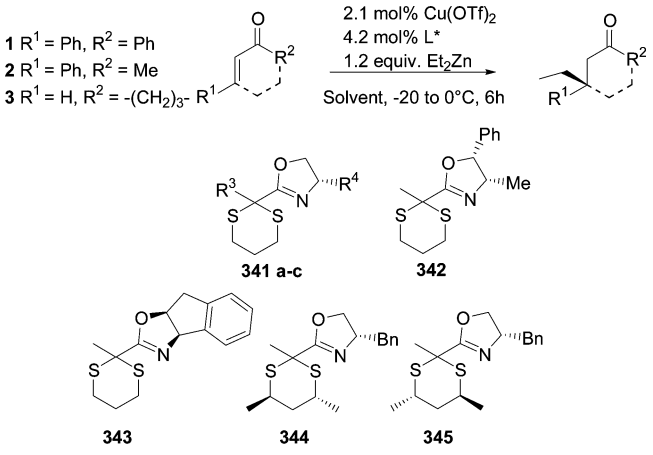
In the CuOTf-catalyzed addition of diethyzinc to cyclohexenone, the corresponding 1,4-product was obtained with

Scheme 142



L	R^1	R^2	R^3	ee
340a	Me	H	H	47
340b	Me	Me (CH=CH)	H	39
340c	Me	H	H	49
340d	^{i}Pr			62

Scheme 143

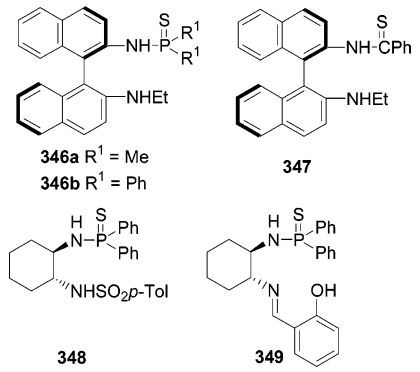


Ligand	R^3	R^4	Enone	Solvent	Yield (%)	ee (%)
341a	H	Bn	**1**	Toluene	-	-
341b	Me	Bn	**1**	Et_2O	80	62 (*S*)
341b	Me	Bn	**2**	Toluene	55	46 (*S*)
341b	Me	Bn	**3**	Toluene	>95	37 (*S*)
341c	Me	^{i}Pr	**1**	Et_2O	73	50 (*S*)
341c	Me	^{i}Pr	**2**	Toluene	49	36 (*S*)
341c	Me	^{i}Pr	**3**	Toluene	>95	24 (*S*)
342	-	-	**1**	Et_2O	60	15 (*R*)
343	-	-	**1**	Et_2O	77	69 (*R*)
343	-	-	**2**	Toluene	54	53 (*R*)
343	-	-	**3**	Toluene	>95	51 (*R*)
344	-	-	**1**	Et_2O	45	70 (*S*)
345	-	-	**1**	Et_2O	50	44 (*S*)

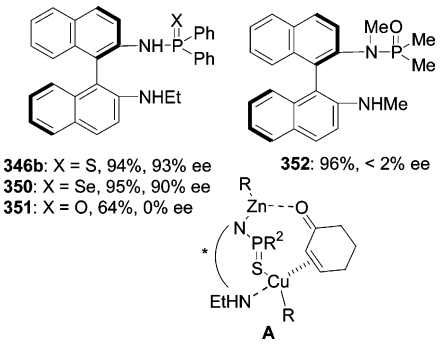
>70% isolated yields and enantioselectivities of up to 62% (Scheme 142). This is the first example of copper-catalyzed enantioselective conjugate addition of dialkylzinc reagents using sulfur-containing ligands, which gave enantioselectivities comparable to those obtained with chiral phosphorus amidites. When chalcone was used as the substrate, and even though the conversion and regioselectivity in the 1,4-product were excellent, the enantioselectivity remained low (up to 11% ee for ligand **340c**).

Ricci, Capitò, *et al*.[94] have synthesized a series of chiral oxazoline-1,3-dithianes for the enantioselective copper-catalyzed conjugate addition of diethylzinc to enones (Scheme 143). Ligand **343** gave the best enantioselectivities for all the enones tested, affording 69% ee for chalcone, 53% ee for *trans*-4-phenyl-3-buten-2-one, and 51% ee for 2-cyclohexenone. For a 1/2 ligand/metal ratio, the ESI-MASS analysis indicated that four of the eight ligand sites, most likely the nitrogen of each oxazoline and one of the thienyl sulfur atoms, were bound to the copper atom. These ligands behaved as a bidentate (*S*,*N*) ligand. The addition of substituents on the thianyl ring (ligands **344** and **345**) gave slightly better results compared to ligand **341b**. An X-ray

Scheme 144



Scheme 145



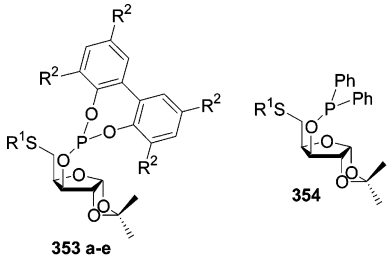
crystal analysis of ligand **343** confirmed a significant anomeric effect revealed by the axial position of the oxazoline moiety in the most stabilized ligand conformation.

Shi *et al*. developed several new stable and recoverable chiral thiophosphoramide and thioamide ligands derived from (*R*,*R*)-1,2-diaminocyclohexane, (*S*,*S*)-1,2-diphenylethylenediamine, and BINAM. The authors have recently published a review[244] on the synthesis and use of all these ligands in catalytic asymmetric C−C bond formations. We will only discuss here the best results obtained in the enantioselective organozinc addition to cyclic and acyclic enones.

The binaphthylthiophosphoramide ligand **346a** (Scheme 144) was the best ligand in the enantioselective addition of diethylzinc to five-, six-, and seven-membered cyclic enones, with 75−93% yields with 97−98% ee.[245] With acyclic aliphatic enones, using ligands **346a** and **346b**, the yields reached 82−92% with from 80 to 93% ee. The addition of dimethyl- or diphenylzinc was also investigated with good enantioselectivities. With ligand **347**, the best results were obtained in the copper-catalyzed diethylzinc addition to chalcone derivatives, with up to 73% ee.[246] When ligand **348** and LiCl as an additive were used, up to 90% ee was obtained in the diethylzinc addition to 2-cyclohexenone.[247] In the presence of iminothiophosphoramide ligand **349**, up to 75% ee was obtained in the same reaction.[248] However, this type of ligand was not efficient with 2-cyclopentenone or chalcone enones.

The authors synthesized the diphenylphosphoramide ligand **351** (Scheme 145) to verify the importance of the sulfur atom in the catalytic conjugate addition. In the same addition of diethylzinc to 2-cyclohexenone, the expected product was isolated with 64% yield but in its racemic form, whereas 93% ee was obtained with the sulfur-containing ligand **346b**. Due to the oxygen atom being a harder coordinating atom than the sulfur atom, it cannot smoothly coordinate to a softer

Scheme 146



Ligand	R^1	R^2	Conv. (%)	ee (%)
353a	Me	^{t}Bu	93	18
353b	^{i}Pr	^{t}Bu	100	9
353c	Ph	^{t}Bu	93	11
353d	^{i}Pr	H	74	27
353e	Ph	H	64	41
354a	^{i}Pr	-	100	64
354a	^{i}Pr	-	63	72[a]
354b	Me	-	100	53
354c	Ph	-	100	15

a. 0°C instead of r.t.

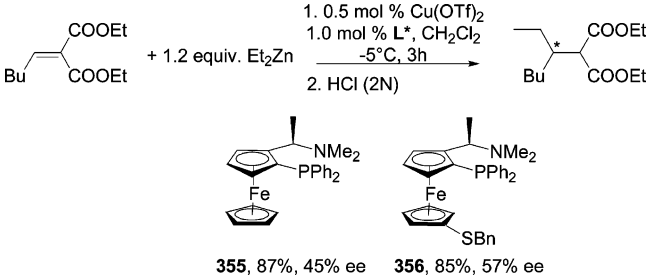
metal center, such as Cu(I), according to the hard−soft-acid−base (HSAB) theory.[249] According to this theory, a selenium-containing ligand such as **350** should have similar reactivity as the sulfur ligand **346b**, and indeed afforded 95% yield with 90% ee. Further NMR studies together with the result obtained with ligand **352** (<2% ee in the same reaction) pointed out the significant role of the acidic proton of thiophosphoramide in the catalytic reaction system. Furthemore, the authors did not observed any nonlinear effects with ligand **346b** and thus assumed that the active species was a monomeric Cu(I) complex. In conclusion, they suggested the possible structure **A** as active species in the catalytic system.

2.6.2.3. Chiral *S,P*-Ligands. Diéguez *et al.*[250] prepared thioether-phosphite D-xylose-derived ligands **353a**−**e** for the copper-catalyzed asymmetric 1,4-addition of diethylzinc to 2-cyclohexenone (Scheme 146). In all cases, the chemoselectivities in the 1,4-product were higher than 97%. The best results in terms of enantioselectivity were obtained in dichloromethane with ligand **353e** (41% ee). Changing the substituent in the thioether moiety produced an effect on both the reactivity and the selectivity. Thioether-phosphinite ligands **354** gave up to 64% ee in the same reaction.[251] Decreasing the reaction temperature to 0 °C lead to 3-ethylcyclohexanone with 72% ee. The conjugate addition of $AlMe_3$ afforded higher activities but lower enantioselectivities.

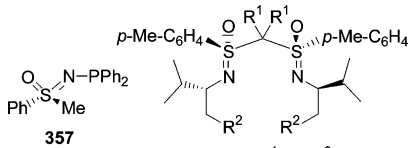
Alexakis *et al.*[252] described the asymmetric conjugate addition to alkylidene malonates with different ligands, such as (*N,P*)-PPFA **355** and a benzothioether analogue **356**. The latter gave the same product yield with a higher enantioselectivity (57% versus 45% ee) (Scheme 147).

2.6.2.4. Ligands with an *S*-Noncoordinating Atom. Tye *et al.*[253] synthesized the new sulfoximide-containing ligand **357** for the Cu-catalyzed asymmetric conjugate addition of diethylzinc to enones (Scheme 148). Up to 44% ee (60% yield) was obtained for the transformation of 2-cycloheptenone. The C_2-symmetrical bis(sulfoximines) **358** have been prepared by Reggelin *et al.*[254] and have been used in the copper complex-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone with excellent yield and up to 36% ee with ligand **358c**.

Scheme 147



Scheme 148

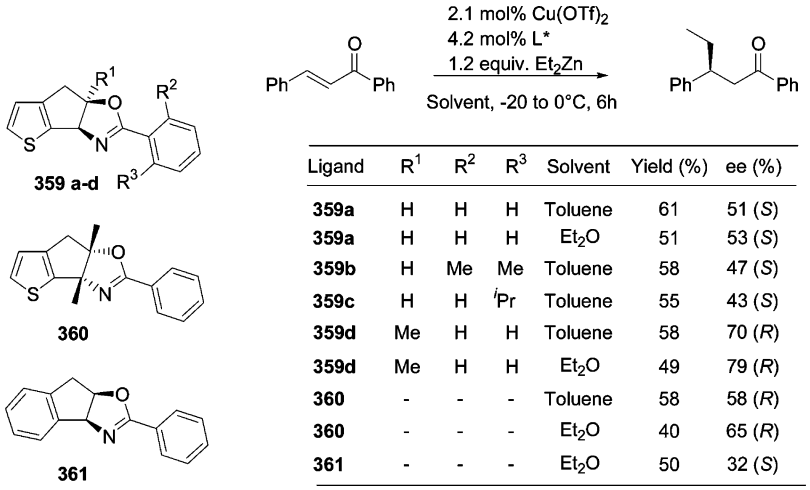


Ligand	R^1	R^2
358a	H	OH
358b	Me	OH
358c	H	Cl

Ricci *et al.*[255] synthesized several new ligands **359**−**361** based on a oxazoline-cyclopenta[*b*]thiophene backbone (Scheme 149). In the copper-catalyzed enantioselective addition of Et_2Zn to chalcone, the corresponding product was obtained with moderate yield and enantioselectivities up to 79% ee with ligand **359d**. The authors assumed that there was no relationship between the structure of the ligand and the enantioselectivity observed in the conjugate addition. It was important to prove that ligand **361**, derived from *cis*-aminoindanol, gave lower results in terms of enantioselectivity than the cyclopenta[*b*]thiophene derived ligand **359a**. DFT-computational and ESI-mass spectral investigations proved that these ligands behaved as monodentate ligands toward Cu^+. The nitrogen atom of the oxazoline coordinated the copper, and the sulfur atom in the thiophene moiety did not seem to have any close contact to the metal. The electron-rich thiophene ring gave a higher electron density to the oxazoline nitrogen, which could explain the better results obtained with **359a** compared to **361**.

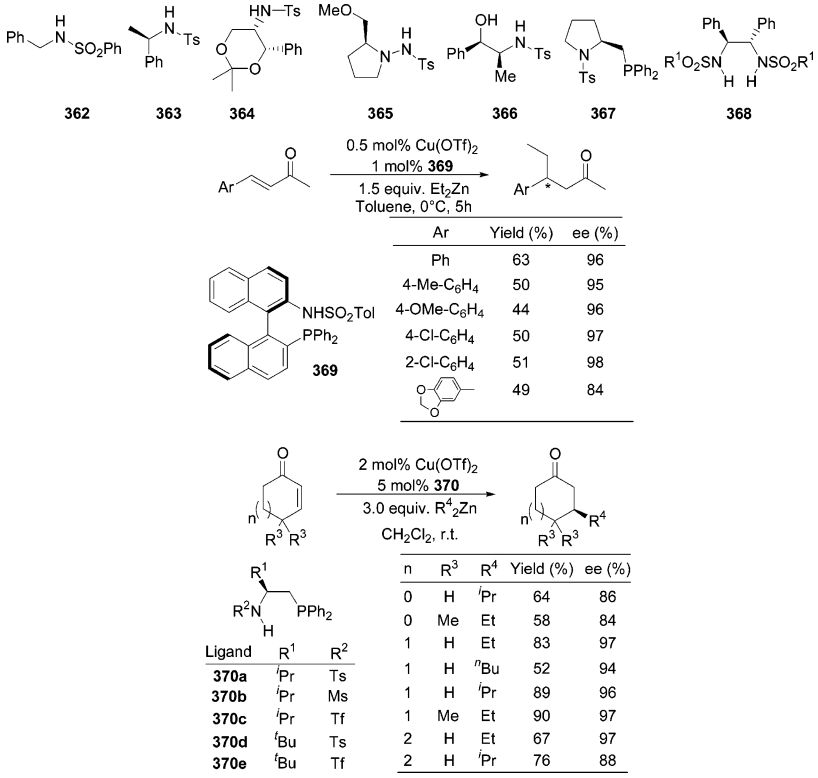
Sulfur-containing but non-coordinating ligands such as sulfonamide have been widely used in the conjugate addition reaction. In fact, since the preliminary studies by Noyori *et al.*,[256,257] who used racemic copper(I) sulfonamide ligand **362** in the conjugate addition of diorganozincs to α,β-unsaturated ketones, several chiral sulfonamide ligands were developed. Sewald *et al.*[258] used a catalytic amount of chiral sulfonamide **363**−**366** in the Cu(I)-catalyzed conjugate addition of Et_2-Zn to 2-cyclohexenone with enantioselectivities of up to 31% ee with **363**. The use of stoichiometric amounts of chiral catalyst did not lead to an increase in the ee. Tomioka *et al.*[259] obtained good yield but poor enantioselectivity (8% ee) with ligand **367** in the addition of Me_2CuLi to chalcone. Later, the use of chiral bis(sulfonamides) **368** in the addition of Et_2Zn to 2-cyclohexenone afforded the desired compound in good to moderate yield with up to 28% ee.[260] Morimoto *et al.*[261] prepared a chiral phosphine-sulfonamide ligand **369** and used it in the enantioselective copper-catalyzed conjugate addition of diethylzinc to several benzylideneacetones with moderate yields and excellent enantioselectivities. Leighton *et al.*[262] synthesized five phosphine-sulfonamide ligands derived in two steps from amino alcohols **370a**−**e** for the Cu-catalyzed enantioselective addition of dialkylzincs to cyclic enones. Up to 97% ee and 86% yield were obtained

Scheme 149



Ligand	R^1	R^2	R^3	Solvent	Yield (%)	ee (%)
359a	H	H	H	Toluene	61	51 (*S*)
359a	H	H	H	Et_2O	51	53 (*S*)
359b	H	Me	Me	Toluene	58	47 (*S*)
359c	H	H	^{i}Pr	Toluene	55	43 (*S*)
359d	Me	H	H	Toluene	58	70 (*R*)
359d	Me	H	H	Et_2O	49	79 (*R*)
360	-	-	-	Toluene	58	58 (*R*)
360	-	-	-	Et_2O	40	65 (*R*)
361	-	-	-	Et_2O	50	32 (*S*)

Scheme 150



Ar	Yield (%)	ee (%)
Ph	63	96
4-Me-C_6H_4	50	95
4-OMe-C_6H_4	44	96
4-Cl-C_6H_4	50	97
2-Cl-C_6H_4	51	98
	49	84

Ligand	R^1	R^2
370a	^{i}Pr	Ts
370b	^{i}Pr	Ms
370c	^{i}Pr	Tf
370d	^{t}Bu	Ts
370e	^{t}Bu	Tf

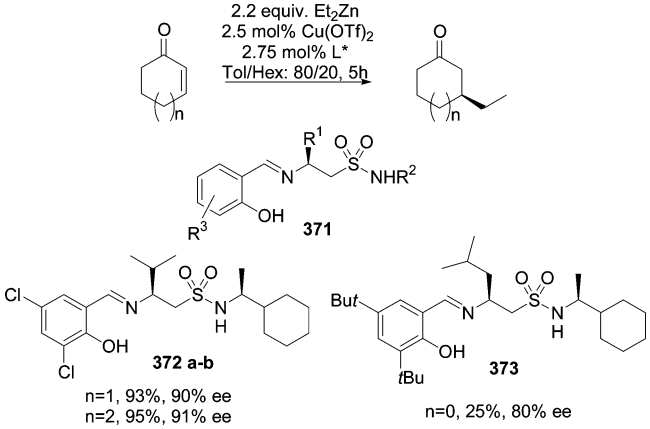
n	R^3	R^4	Yield (%)	ee (%)
0	H	^{i}Pr	64	86
0	Me	Et	58	84
1	H	Et	83	97
1	H	^{n}Bu	52	94
1	H	^{i}Pr	89	96
1	Me	Et	90	97
2	H	Et	67	97
2	H	^{i}Pr	76	88

for the addition on 2-cyclohexenone on a 10 g scale. The scope of the reaction is represented in Scheme 150.

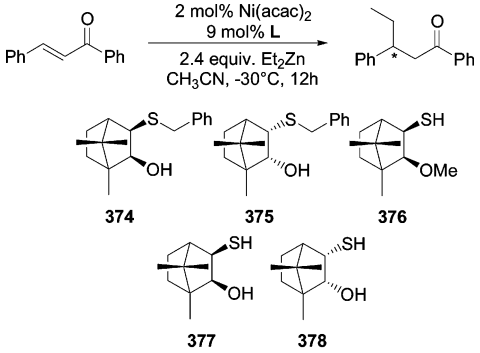
Gennari, Piarulli, *et al.*[263,264] synthesized a combinatorial library of 125 new Shiff base ligands, with the general structure *N*-alkyl-*β*-(*N*′-salicylideneamino)alkanesulfonamides **371**. A multisubstrate high-throughput screening was performed, and the best results in the 1,4-conjugate addition of Et_2Zn to cyclic enones are shown in Scheme 151. Up to 91% ee was found with ligand **372** and 2-cycloheptenone as substrate (95% yield). Moderate enantioselectivities were obtained with acyclic enones (up to 50% ee).

The same methodology has been applied for the copper-catalyzed enantioselective conjugate addition of diethylzinc to nitroolefins,[265] and enantioselectivities of up to 58% ee were obtained with (*E*)-(2-nitrovinyl)benzene as the substrate.

Scheme 151



Scheme 152



Ligand	Yield (%)	ee (%)
374	99	20 (*R*)
375	94	60 (*S*)
375[a]	68	86 (*S*)
376	48	22 (*S*)
377	86	12 (*S*)
378	40	2 (*S*)

a. 50 mol% of **375**.

Numerous ligands have proved to be highly efficient in the conjugate addition of organometallic reagents (RMgX, R_2Zn, or R_3Al) to cyclic or acyclic substrates. In all these examples, sulfur ligands gave results (with respect to the yield and enantioselectivity) comparable to those of the phosphorus ligands. Commonly, 0.5−5 mol % of $Cu(OTf)_2$ or $Cu(OAc)_2$ salt and 1−10 mol % of chiral ligand were used in toluene, dichloromethane, or diethyl ether, at low temperature for a few hours. The addition of diethylzinc became predominant, but the cost and/or the commercial availability of diorganozinc species limited its application in industry.

2.6.3. Nickel-Catalyzed Asymmetric Michael Addition

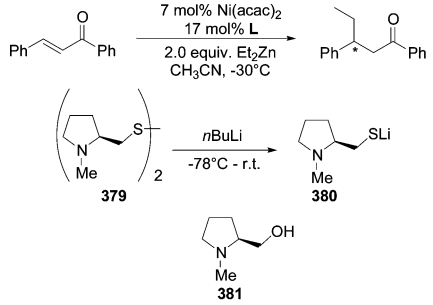
Nickel salts can be used instead of copper salts to promote the conjugate addition reaction. In some cases, developed below, the authors tested both the Cu and Ni salts and found better results with nickel salts, without further development.

2.6.3.1. Chiral *S,O*-Ligands. Ligands derived from (1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol have been reported by Yang *et al*.[266] for the asymmetric conjugate addition of diethylzinc to chalcone catalyzed by the $Ni(acac)_2$ complex. The 1,4-addition proceeded in 60% ee with 9 mol % of ligand **375**. The enantioselectivity was increased to 86% ee with a 50% molar ratio of **375**, with respect to the substrate (Scheme 152).

2.6.3.2. Chiral *S,N*-Ligands. Gibson[267] has prepared enantiopure β-amino disulfides **379** and β-amino thiolates **380** as ligands for achieving the catalytic enantioselective diethylzinc addition to chalcone with enantiomeric excesses of up to 50% (85% yield) with ligand **379**. The thiolate **380**, generated in situ by the treatment of **379** with butyllithium in THF, did not allow an increase in the ee's. In contrast, the corresponding β-amino alcohol (*N*-methyprolinol **381**) gave only 6% ee, which demonstrated the beneficial effect of the sulfur-chelation site for this reaction (Scheme 153).

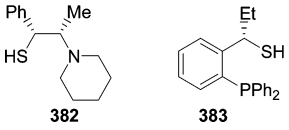
Kang *et al*.[268] screened several ligands for the asymmetric conjugate addition of diethylzinc to chalcone. Among them, ligands **382** and **383** have proved to be the best, with up to 74% ee (50% yield) and 27% ee (34% yield), respectively. The best results were obtained with 30 mol % of ligand and a 1/20 ratio of metal/ligand. The authors found that the ee

Scheme 153



Ligand	Yield (%)	ee (%)
379	85	50 (*S*)
380	87	37 (*S*)
381	90	6 (*R*)

Scheme 154



of the product was strongly dependent on the ligand concentration and on the nickel-to-ligand ratio (Scheme 154).

Christoffers *et al*. synthesized several sulfur-containing ligands for the enantioselective Michael reactions. These ligands were derived from either 2-thiophene-oxazoline-thioether or 2-pyridine-oxazoline-thioether for **384** and **385**,[269] thioether ligands were derived from chiral α-hydroxy acids **386** and **387**,[270] diamino and diimino thioethers ligands were derived from **388** and **389**,[271] and thiodiglycols ligands[272] were derived from **390** and **391**. However, all these ligands gave only up to 19% enantiomeric excess in the addition of β-oxoester to methyl vinyl ketone catalyzed by $NiCl_2 \cdot 6H_2O$ or $Ni(OAc)_2 \cdot 4H_2O$ (Scheme 155). A high number of metal salts were tested without increasing the enantioselectivity. An X-ray single-crystal structure analysis of complex [**384a** Cu] proved that the ligand **384a** was a (*S,N*)-bidentate ligand with oxazoline-*N* and thioether-*S* atom coordination to the metal center.

2.6.3.3. Ligands with an *S*-Noncoordinating Atom. Numerous β-hydroxysulfoximine ligands were synthesized by Bolm *et al*.[273] and used in the enantioselective conjugate addition of diethylzinc to chalcone derivatives. The optically active sulfoximines were prepared by the addition of the lithium salt of **A** to different ketones and aldehydes (Scheme 156). Up to 72% ee was obtained with ligand **392**. The authors assumed a nonmonomeric nature of the active species in solution, as suggested by the asymmetric amplification in the catalysis with a sulfoximine of low optical purity.

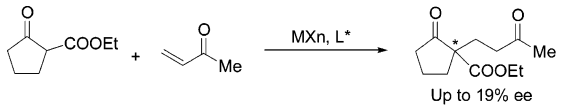
2.7. Miscellaneous

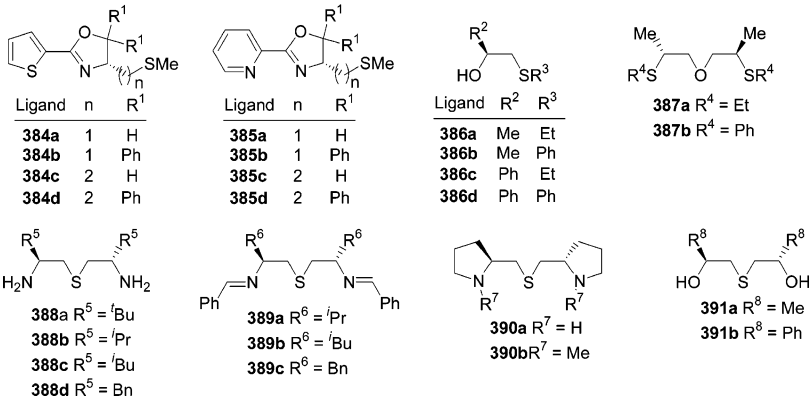
2.7.1. Asymmetric Cyclopropanation

The asymmetric cyclopropanation of alkenes with diazoesters catalyzed by ruthenium complexes coordinated with sulfur-containing ligands was also considered.[274] In this study, sulfur-containing ligands based on chiral 2,5-bis(oxazoline)-thiophene (Thiobox **393**) were synthesized, fully characterized by X-ray analysis, and efficiently used in the ruthenium-catalyzed asymmetric cyclopropanation reaction (Scheme 157).

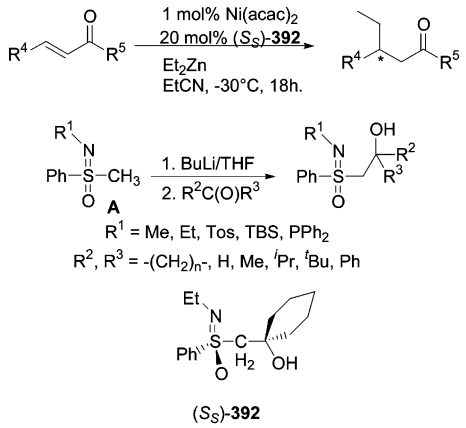
When the *N,S,N*-ligands **393** were used in the ruthenium-catalyzed asymmetric cyclopropanation of diphenylene with

Scheme 155



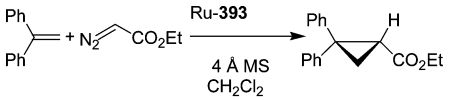


Scheme 156



R^4	R^5	Yield (%)	ee (%)
Ph	Ph	71	70
4-MeO-Ph	Ph	48	70
Ph	4-MeO-Ph	45	72
Ph	4-Cl-Ph	57	62

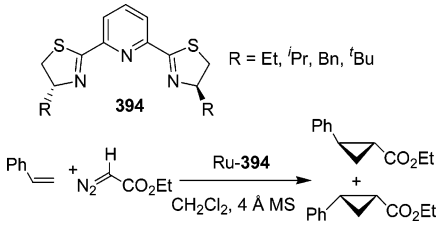
Scheme 157



393	ee (%)	Yield (%)
R = Et	99	85
R = ^{i}Pr	98	77
R = Benzyl	96	72
R = ^{t}Bu	98	63

a diazoester, high enantioselectivities were obtained, up to 99% ee at room temperature in CH_2Cl_2. Compared to results obtained with the catalyst analogue *N*,*N*,*N*-Ru-pybox in the cyclopropanation of 1,1-diphenylethene, better results are reported when *N*,*S*,*N*-Ru-thiobox was used. According to the authors, the differences may arise from different catalysts structures with, on the one hand, a N−S−N bond angle much larger than the N−N−N bond angle and, on the other hand, a stronger Ru−S coordination resulting from soft−soft interactions.

Scheme 158



Ru-catalyzed asymmetric cyclopropanation with diazoesters was also performed by Masson *et al*. using chiral 2,6-bis(thiazolinyl)pyridines.[275] These homochiral ligands were synthesized from dithioesters and commercially available enantiopure 2-aminoalcohols. When the cyclopropanation of styrene with diazoethylacetate was carried out with these ligands and $[Ru(p\text{-cymene})Cl_2]_2$ as *in situ* catalysts, enantioselectivities of up to 84% were obtained (Scheme 158).

However, the comparative evaluation of enantioselective control of chiral Ru-Pybox and Ru-thia-Pybox showed many similarities. The modification of the five-membered ring did not greatly influence the enantioselectivity.

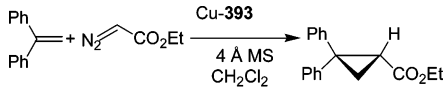
The chiral C_2-symmetric sulfur-containing ligands based on bis(oxazoline) **393**, synthesized and well characterized by Gao *et al*., were also tested in the copper(I)-catalyzed cyclopropanation of diphenylethene.[276]

The optimization of the conditions was carried out using ligand **393**. The best reaction conditions revealed that the reaction should be performed in dichloromethane with 4 Å molecular sieves and did not reveal any temperature influence on the reaction course. When the substituents were ethyl, phenyl, or *tert*-butyl, the results demonstrated that the enantioselectivity increased with the steric bulk of the substituent (see Scheme 159). The best result was obtained when the substituent was a *tert*-butyl group with an enantioselectivity of 97%.

Aggarwal *et al*. described the use of catalytic amounts of chiral sulfide in the cyclopropanation of phenyldiazomethane and enones.[277] This reaction between electron deficient alkenes and phenyldiazomethane is catalyzed by transition metals such as $Rh_2(OAc)_4$ (Scheme 160) or $Cu(acac)_2$.

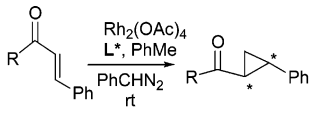
The chiral sulfide **395** used was the 1,3-oxathiane derived from camphorsulfonyl chloride. This sulfur-containing ligand

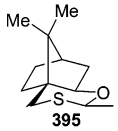
Scheme 159



R	Yield (%)	ee (%)
R = Et (*R*)	84	91
R = ^{i}Pr (*S*)	76	89
R = Ph (*R*)	56	86
R = ^{t}Bu (*S*)	71	97

Scheme 160





395

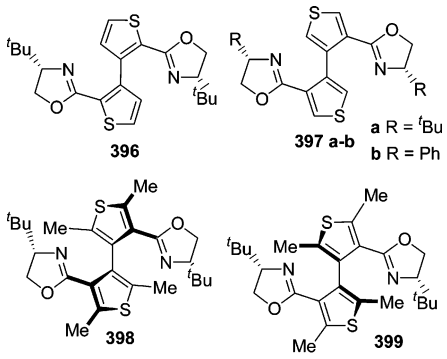
R	Yield (%)	Sulfide equiv.	ee (%)
Ph	38	1.0	97
Ph	38	0.2	97
Me	55	1.0	98
Me	14	0.2	98
p-BrC_6H_4	35	1.0	98

was tested with various enones in stoichiometric and catalytic amounts. Corresponding chiral cyclopropane derivatives were obtained in moderate to good yields and with excellent levels of enantioselectivity (up to 98% ee). The yields were always lower when substoichiometric amounts of sulfide were employed, but the enantioselectivities were identical. The *p*-bromo derivative of (*E*)-chalcone was also treated with phenyldiazomethane, yielding the corresponding cyclopropanes. The absolute stereochemistry of this cyclopropane was determined by X-ray analysis. These analyses lead the authors to propose that the sulfur ylide preferentially adopted a conformation in which the filled orbital on carbon is orthogonal to the lone pair on sulfur. This prefered conformation could explain the origin of chiral induction. This work was extended to include diazoesters; however, the use of chiral 1,3-oxathiane **395** was not successful with these more stable diazo compounds.

New bis(oxazolines) with atropisomeric 3,3′-bithiophene backbones were synthesized and structurally and electronically characterized by Sannicolò and co-workers.[278] They investigated the electronic and steric effect of bis(oxazoline) ligands on the Cu(I)-catalyzed cyclopropanation of styrene (Scheme 161). In this context, electrochemical experiments with the determination of the oxidative potential were used as a reliable index of the electronic density on the nitrogen atom of the chelating groups of new and, for comparative purposes, of already known bis(oxazolines).

The corresponding Cu(I) complexes were synthesized and tested in the enantioselective catalytic cyclopropanation of styrene with ethyl diazoacetate. All these chiral ligands were active in the cyclopropanation, but the desired cyclopropane was generally isolated in modest yield. They also led to low enantioselectivities, since only ligand **399** afforded the targeted cyclopropane in up to 67% ee. Similar results were obtained with ligand **399** and the biphenyl-based bis(oxazoline) analogue, indicating that the difference in the electronic effect did not influence the styrene cyclopropanation. The steric properties of the chiral ligands seemed to be much more important. This was confirmed by the fact that the axially free chiral bithiophene **396**, **397a**, and **397b** led to nearly racemic products.

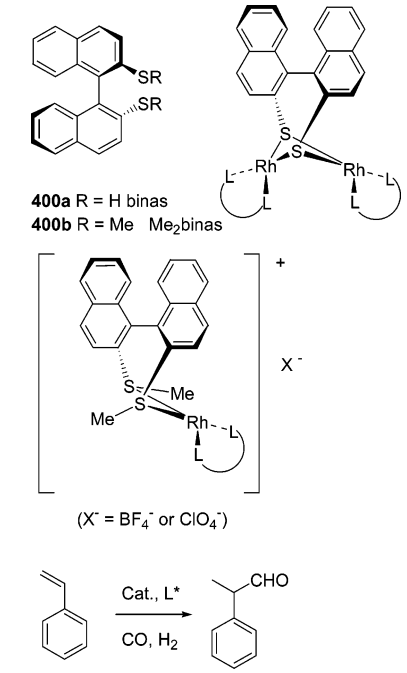
Scheme 161



Ligand	yield(%)	trans/cis	ee(%)
396	30	57/43	2
397a	29	75/25	6
397b	32	70/30	11
398	12	73/27	16
399	30	74/26	67

substrate/catalyst = 100

Scheme 162

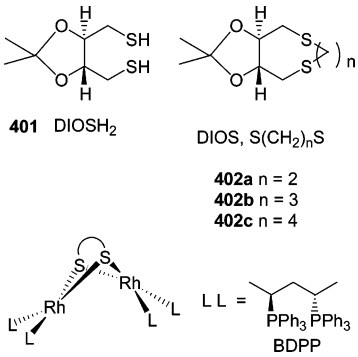


2.7.2. Asymmetric Hydroformylation

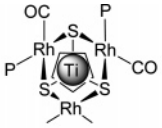
Asymmetric hydroformylation of styrene by rhodium(I) catalysts with chiral ligands containing sulfur donor atoms was described by Claver and co-workers.[279] The authors demonstrated the potential of binas **400a** and of its dimethyl thioether (Me_2binas **400b**) in the enantioselective hydroformylation of styrene (Scheme 162).

Dinuclear neutral and cationic complexes (see Scheme 162) were synthesized by the reaction of ligands **400a** and **400b** with $[Rh(\mu\text{-OMe})(cod)]_2$ and $[Rh(cod)_2]^+ X^-$, respectively (cod = cycloocta-1,5-diene). The use of these *S*,*S*-ligands in the catalytic hydroformylation led to a very good activity but a low enantioselectivity, since the enantiomeric excesses never exceeded 15%.

Scheme 163



Scheme 164



403

Ligand	% conv	%ee
1,2-bis(diphenylphosphine)ethane (dppe)	25	-
1,3-bis(diphenylphosphine)propane (dppp)	36	-
(2S,3S)-bis(diphenylphosphine)butane ((-)CHP)	32	<1
(2S,4S)-(-)-2,4-bis(diphenylphosphine)pentane ((-)BDPP)	95	5
(S)-(-)2,2'-bis(diphenylphosphine)-1,1'-binaphtyl ((+) BINAP)	18	15

Two years later, the same team performed the asymmetric hydroformylation of styrene using dinuclear thiolato-bridged rhodium complexes with diphenyl phosphine chiral auxiliary ligands (Scheme 163).[280]

In order to study the influence of the dinuclear framework of the thiolate precursor, different thiolate and dithiolate bridged rhodium complexes were combined with chiral diphosphines to be used as a catalytic precursor system. The addition of BDPP produced an increase in the enantioselectivity of up to 43% ee when the Rh−DIOS−**402b** complex was used. The combination of chiral (+)- or (−)-DIOS and (+)- or (−)-BDPP afforded no improvement in the enantioselectivity.

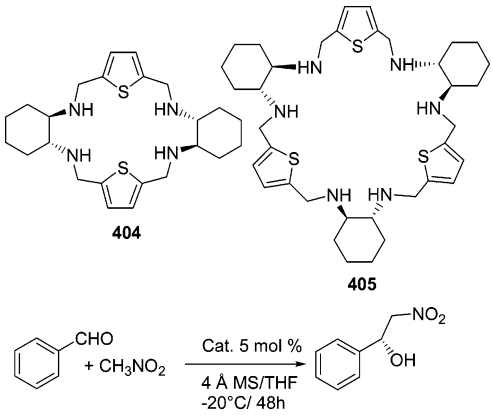
Early−late heterotetranuclear complexes ($TiRh_3$) **403** with bridging sulfido ligands combined with *P*-donor ligands were also used in asymmetric hydroformylation of styrene by Casado *et al*. (Scheme 164).[281]

In this reaction, the complex $[CpTi(\mu_3\text{-}S)_3\{Rh(tfbb)\}_3]$ was efficiently active under mild conditions (10 bar $CO/H_2 = 1$ at 353 K). To explore the effect of the added phosphorus ligand and the possibilities of this system for the asymmetric hydroformylation of styrene, achiral diphosphines such as dppe and dppp have been used without chiral inductions. Once more, chiral diphosphines were studied, but only BINAP chiral diphosphines show a modest enantiomeric excess of 15%.

2.7.3. Henry Reaction

The nitroaldol reaction or Henry reaction is a powerful method for carbon−carbon bond formation in organic synthesis. The asymmetric catalytic version of this reaction has attracted particular attention in the past decade, and more recently, sulfur-containing ligands were evaluated by several groups as potential efficient ligands. In this context, some chiral N_4S_2- and N_6S_3-donor macrocycles (see Scheme 165) were used as ligands in the enantioselective Henry reaction mediated by Zn(II) as Lewis acid.[282] These *S*,*N*-ligands were synthesized by condensation of 2,5-thiophene carboxaldehyde with (1*R*,2*R*)-diaminocyclohexane and subsequent reduction with $NaBH_4$.

Scheme 165



Catalyst	Yield (%)	ee (%)
404 (Zn II)	45	39
405 (Zn II)	54	51
404 (2 Zn II)	63	57
405 (3 Zn II)	68	75

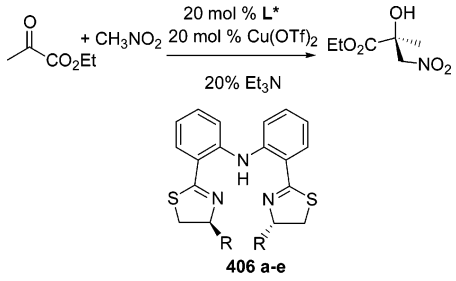
The catalysts were prepared by treatment with 1, 2, or 3 equiv of diethylzinc. The results showed that the use of these *S*,*N*-macrocylic ligands was efficient in the enantioselective approach, since the reaction afforded the nitroaldol in good yield and with an enantioselectivity reaching 75% ee when the trinuclear **405** (3 Zn(II)) complex was used (Scheme 165).

Another approach was the use of bis(thiazolines) as tridentate ligands in the Henry reaction for comparison with the well-known analogous bis(oxazolines). In this context, Xu *et al*. have synthesized a series of C_2-symmetric bis(thiazolines) with a diphenylamine backbone as linkage between both thiazoline rings.[283] Their application as ligands for Cu(II) in the catalytic asymmetric nitroaldol reaction of an α-ketoester proved their real efficiency compared to the bis(oxazoline) analogues.

Comparative studies demonstated that bis(oxazoline)−Cu(II) complexes furnished in neat reaction conditions moderate enantioselectivities (up to 60% ee) while bis(thiazolines) gave slightly better enantioselectivities (up to 70% ee for the *tert*-leucinol derivative; see Scheme 166). This last value improved to 82% ee when the catalyst was used in dichloromethane at −20 °C, though with a significant loss in yield (29%).

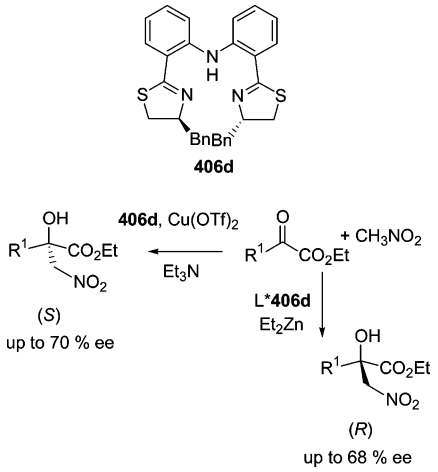
More recently, the same group published the influence of the metal nature on the enantioselectivity in the asymmetric reaction catalyzed by C_2-symmetric tridentate bis(oxazoline) and bis(thiazoline) complexes.[284] They found that the absolute configuration of the desired nitroaldol depends on the nature of the Lewis acid used. When the Lewis acid used to prepare the catalytic complex was $Cu(OTf)_2$, the major product was the (*S*)-enantiomer, and when it was Et_2Zn, the reaction afforded the (*R*)-enantiomer.

Scheme 166



L*	R	Yield (%)	ee (%)
406a	^{i}Pr	76	47
406b	^{i}Bu	40	8
406c	Ph	30	63
406d	Bn	75	9
406e	^{i}Bu	55	70

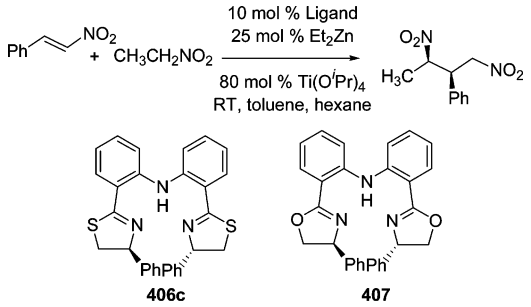
Scheme 167



This reversal of the absolute configuration of the product suggested that the potential ability of a tridentate coordination and hydrogen donation of the NH group in the C_2-symmetric tridentate chiral ligands **406d** and in the bis(oxazoline) analogue (see Scheme 167) played a crucial role in the enantioselective catalytic Henry reaction, since the replacement of the NH group by a CH_2 group resulted in the (*R*) enantiomer with $Cu(OTf)_2$ while with Et_2Zn the reaction afforded poor enantioselectivity. It is noteworthy to mention here that a new asymmetric reaction was very recently developed by these authors. They found efficient conditions to perform Zn(II)-catalyzed stereoselective addition of nitroalkanes to nitroalkenes.[285] As their investigations concerning the Henry reaction led them to propose a dinuclear zinc catalyst for both the activation of α-keto esters and orientation of nitromethane, they were interested to test its activity for the formation of 1,3-dinitro compounds by Michael addition (see Scheme 168).

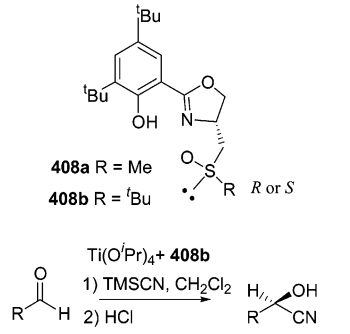
Tridentate C_2-symmetric bis(oxazolines) (see, for example, **407**, in Scheme 168) were at first used for the optimization of the conditions. In the presence of $Ti(O^iPr)_4$ to activate diethylzinc, the reaction proceeded smoothly at room temperature in nonpolar solvents, mainly resulting in the *syn* Michael adduct. The ligand fine-tuning showed that the bis(oxazoline) derived from phenylglycinol **407** in Scheme 168 afforded the product with a high conversion and enantioselectivity. Interestingly, the corresponding thiazoline **406c** led to a slight enhancement in the reaction selectivity, unfortunately accompanied by a decrease in the product yield. The proposed mechanism implies the formation of a dinuclear Zn(II) complex, with one zinc atom coordinated to the nitro group of the nitroalkene and the other one to that of nitronate. This new catalytic asymmetric procedure is an elegant way to form 1,3-dinitroalkanes as valuable synthons toward the preparation of enantioenriched 1,3-diamines and cyclic thioureas.

Scheme 168



L*	conv (%)	dr (*syn*:*anti*)	ee (%) *syn*
407	96	6.1 : 1	91
406c	74	11.7 : 1	95

Scheme 169



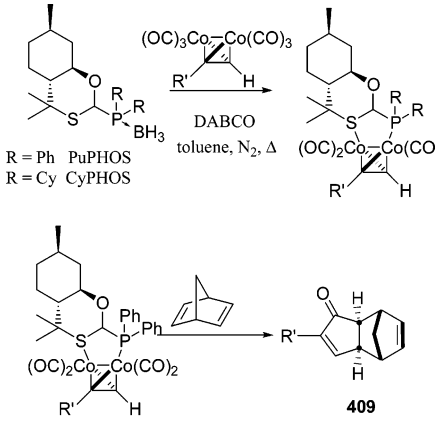
Aldehyde	yield (%)	ee (%)
benzaldehyde	85	57
4-methoxybenzaldehyde	80	57
4-nitrobenzaldehyde	51	0
2-nitrobenzaldehyde	48	10
3,4-dimethoxybenzaldehyde	72	61

2.7.4. Silylcyanation

Chiral sulfoxide-containing ligands for the catalytic addition of trimethylsilylcyanide to aldehydes were synthesized by Rowlands.[286] The ligand structure was based on the phenolic oxazoline scaffold **408** with introduction of the sulfur substituent via cysteine derivatives (*S*-methyl cysteine; see Scheme 169).

The chiral titanium complex was synthesized in situ from $Ti(O^iPr)_4$ and a diatereoisomeric mixture of sulfoxides **408** in dichloromethane. It proved impossible to isolate both compounds in diastereomerically pure form; only the first eluted sulfoxides could be purified. The reaction of benzaldehyde with trimethylsilylcyanide was then performed and optimized. Dichloromethane was found to be the best solvent for both a good reaction yield and enantiomeric excess compared with toluene and THF. The temperature influence was also examined, showing that a higher temperature

Scheme 170



R'	Conditions	yield (%)	ee (%)
Ph	Tol / 50°C	99	99
TMS	Tol / 50°C	92	57
TMS	CH_2Cl_2/ NMO/ r.t.	93	97
TMS	CH_2Cl_2/ NMO/ r.t.	94	95
TMS	CH_2Cl_2/ NMO/ 45°C	52	27*
CMe_2OH	CH_2Cl_2/ NMO/ r.t.	98	70

* R = Cy

resulted in an increased reactivity together with a lower selectivity. In order to investigate the influence of the steric bulk on the sulfoxide moiety, the *tert*-butyl derivatives were synthesized. In this case, the pure (*S*)-sulfoxide was isolated by chromatography, characterized by X-ray crystallography, and used as an enantiopur ligand. An interesting increase in the enantioselectivity of up to 57% at −84 °C was observed. The effect of the sulfoxide configuration was then investigated in this context, and the use of the opposite configuration on the sulfoxide moiety resulted in a reversed enantioselectivity. The test of the analogous ligand without the sulfoxide moiety derived from leucinol and phenylalaninol showed an important reduction in both the activity and selectivity of the catalyst. These results clearly indicated the major role played by the sulfoxide moiety in the silylcyanation reaction.

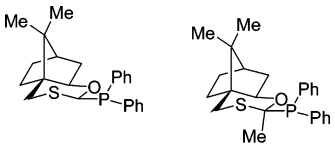
The variation of the aldehydes as substrates showed that the catalyst was sensitive to both steric and electronic effects. The aromatic ring had a great effect on the selectivity, and the electron-donating substituents gave the best enantiomeric excess of up to 61% ee (Scheme 169).

2.7.5. Intermolecular Pauson–Khand Reaction

The Pauson−Khand reaction (PKR) is an interesting way to synthesize cyclopentane-based compounds from alkenes or alkynes by using stoichiometric amounts of the prochiral dicobalt hexacarbonyl complex ($Co_2(CO)_8$). This reaction attracted much interest this past decade,[287] but even if great progress has been achieved in the catalytic intramolecular version of this reaction, the challenge probably lies in the development of a general catalytic asymmetric reaction.

The synthesis and use of bidentate *S*,*P*-ligands, such as PuPHOS and CyPuPHOS derived from Pulegone, in the enantioselective intermolecular Pauson−Khand reaction was described by Verdaguer *et al*. (see Scheme 170).[288] Bidentate ligands were considered in order to increase both the reactivity of the chiral complex and the diastereoselectivity of its formation.[289] These chiral bidentate ligands were designed to drive the coordination of the sulfur in the

Scheme 171



410 CamPHOS **411** Me-CamPHOS

R'	time	yield (%)	ee(%)
Ph	0.5h	93	97
^{t}Bu	3h	75	6
^{t}Bu	18	80	40
$SiH_2(CH_3)_3$	3h	68	56
CH_2Me_2OH	4d	90	50

dicobalt−alkyne cluster to the cobalt atom not bound to the phosphorus atom. In this context, the distance between the phosphorus and the sulfur atoms in the ligand design was crucial.

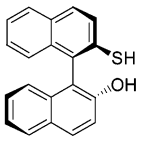
The chiral cobalt complexes were obtained by a ligand exchange reaction with hexacarbonyldicobalt−alkyne in toluene. However, this approach yielded a diasteromeric mixture, and the major isomers were isolated by isomerization−crystallization sequences. Chiral complexes were tested in the intermolecular Pauson−Khand reaction of various alkynes with norbornadiene, leading to the corresponding enone **409** in up to 93% yield and 97% ee.

The intermolecular PKR of the resulting *S*,*P*-cobalt complexes with norbornadiene was examined under thermal and *N*-oxide activation conditions. Heating the diastereomerically pure complex (R′ = Ph) with 10 equiv of norbornadiene at 50 °C in toluene afforded the corresponding *exo*-cyclopentenone in quantitative yield and 99% ee. Under the same conditions, the PKR of the analogous trimethysilyl complex provided the expected product in high yield but with a lower enantioselectivity (ee = 57% ee). The reaction conditions were modified in order to upgrade the enantioselectivity, and the results were positive when the reaction was performed in dichloromethane in the presence of NMO. The authors assumed that the thermal activation promoted the isomerization of the *S*,*P*-ligand, leading to a nonstereoselective process (Scheme 170).

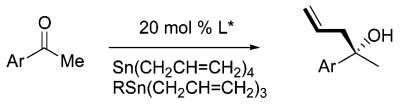
The syntheses of *S*,*P*-ligands derived from camphor were also developed by Verdaguer *et al*. for the diastereoselective coordination to alkyne−hexacarbonyldicobalt complexes.[290] Two chiral ligands CamPHOS **410** and MeCamPHOS **411** were obtained in good yield in their borane-protected form. The influence of the alkyne group (R′ in Schemes 170 and 171) on their coordination to dicobalt−hexacarbonyl−alkyne complexes was evaluated. MeCamPHOS **411** provided a high diastereoselectivity (up to 90% de). This result is probably due to a thermodynamic equilibration yielding the more stable isomer. The resulting chiral complexes were then tested in the intermolecular Pauson−Khand reaction with norbornadiene. The results showed that CamPHOS and MeCamPHOS provided the expected products in good yield but with opposite absolute configurations.

This behavior was explained on the basis that ligands **410** and **411** led to pseudoenantiomeric tetracarbonyl complexes, as confirmed by circular dichroism analysis. Introduction of a methyl group on the carbon bridge between phosphorus and sulfur atoms increased the CamPHOS selectivity dramatically from 33% to 90% de of the opposite sign. The absolute configuration of the new bridged complexes was

Scheme 172



(R_a)-**412**



Ar	Dry Method yield (%)	Dry Method ee (%)	Wet Method yield (%)	Wet Method ee (%)
Ph	43	92	>98	89
4-BrPh	51	92	97	86
3-BrPh	53	85	>99	88
4-MePh	32	90	78	82
2-$C_{10}H_7$	53	87	>98	84

established by chemical correlation from their intermolecular Pauson−Khand products. Along these lines, the authors also demonstrated the usefulness of circular dichroism to assign the absolute configuration of dicobalt clusters that bear bridged *S*,*P*-ligands.

2.7.6. Allylstannation of Ketones

Monothiobinaphthol was used as a chiral promoter in the enantioselective catalytic allylation of aryl ketones with organotin reagents such as $Sn(CH_2CH{=}CH_2)_4$/$RSn(CH_2CH{=}CH_2)_3$.[291,292] The allylation of acetophenone by this mixture was very efficient, since the homoallylic alcohol was obtained with up to 92% ee in good yield.

However, the enantioselectivity decreased when the conversion increased, probably due to achiral background reactions in anhydrous media ("dry method"). Fortunately, the authors noticed that the presence of a small amount of water inhibited these background reactions and increased drastically the catalyst activity (see Scheme 172). In this enantioselective approach, the presence of both $RSn(CH_2CH{=}CH_2)_3$ and water was essential but the results are not very reproducible.

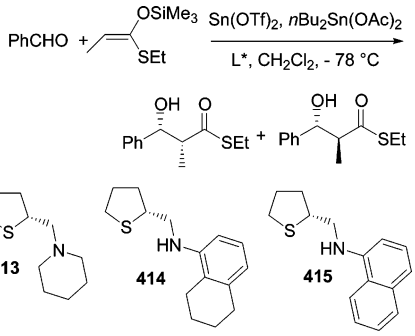
2.7.7. Aldol Reaction

At the beginning of the nineties, Kobayashi *et al*. prepared *S*,*N*-chelates for the tin-mediated aldol reaction of silyl enol ethers with aldehydes (Scheme 173). Compared to analogous diamines, these ligands were expected to form more acidic complexes.[293]

They indeed led to the expected *syn* aldol as major product with good yield and enantiomeric excess up to 92%, whereas the corresponding diamines provided less active complexes. Other aldehydes were further transformed, leading for most of them (substituted benzaldehydes, aliphatic unsaturated aldeydes) to the aldol adducts with more than 90% ee. To the best of our knowledge, this reaction, albeit conducted successfully under those conditions, was no more studied with sulfur-containing ligands.

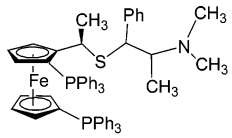
Togni and Häusel synthesized sulfur-containing ferrocenylphophine ligands for the asymmetric gold(I)-catalyzed aldol reaction (see Scheme 174).[294] This reaction consists in

Scheme 173

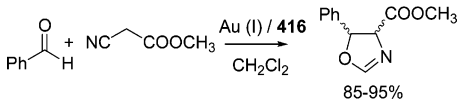


L*	yield (%)	syn/anti	ee (%)
413	72	90/10	72
414	85	84/16	60
415	85	96/4	92

Scheme 174



416



85-95%

416	% trans (%ee)	% cis (%ee)
(3*R*,4*S*)	72 (13)	28 (22)
(3*S*,4*R*)	83 (84)	17 (71)
(3*S*,4*S*)	88 (89)	12 (16)
(3*R*,4*R*)	74 (17)	26 (18)

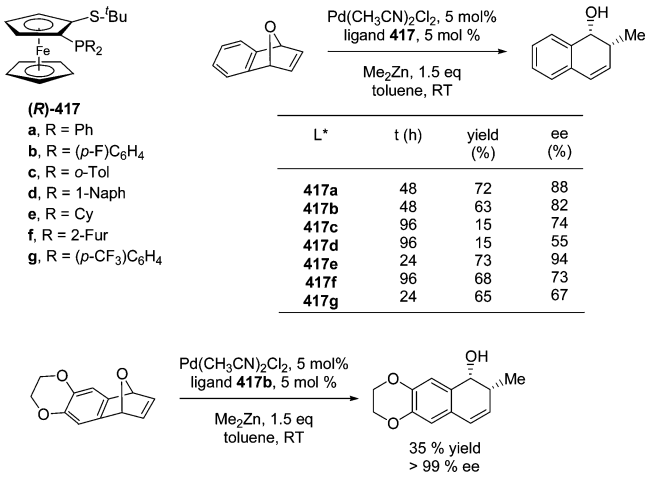
coupling benzaldehyde and methyl isocyanoacetate and results in the formation of asymmetric oxazolines. The ligands were all synthesized from chiral 2-aminoalcohols derived from *N*-methyl-ephedrine. Their use in the gold(I)-catalyzed synthesis of oxazolines showed different stereoselectivity and clearly indicated that the introduction of the sulfur atom in the side chain had a positive influence upon activity.

The best ligand (3*S*,4*S*)-**416** afforded the *trans*-oxazoline in high enantioselectivity, with up to 89% ee. The authors presumed that this ligand exists in a preferred conformation and that the methyl and phenyl substituents do not have a major steric influence in the stereoselective transition state.

2.7.8. Asymmetric Ring Opening of Mesoheterobicyclic Alkenes

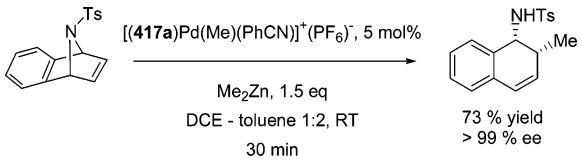
The Fesulfos ligands successfully developed by Carretero *et al*. as palladium chelates for the Tsuji−Trost reaction[55,56] or as copper chelates for Diels−Alder transformations[128,129] were also proven efficient for the palladium-catalyzed enantioselective ring opening of mesoheterobicyclic alkenes.[295] This reaction is generally efficiently performed in the presence of chiral bis(phosphines) or phosphino-oxazolines,[296] and the authors evaluated the ability of planar chiral Fesulphos to promote this reaction as precursors to isolable and air-stable palladium catalysts. A very wide variety of ligands were prepared bearing either bulky alkyl or aryl substituents on the sulfur atom.

Scheme 175



L*	t (h)	yield (%)	ee (%)
417a	48	72	88
417b	48	63	82
417c	96	15	74
417d	96	15	55
417e	24	73	94
417f	96	68	73
417g	24	65	67

Scheme 176



Associated with a palladium precatalyst, these *S,P*-coordinating ligands were first tested as catalysts for the ring-opening addition of Me_2Zn to 7-oxabenzonorbornadiene (see Scheme 175). The reaction proceeded smoothly in toluene for each case, and the best yields of isolated product were obtained using ligands **417a**, **417b**, or **417e**. The dicyclohexylphosphine **417e** provided the highest enantiomeric excess, and similar trends were observed in the analogous addition of diethylzinc. The authors also performed the asymmetric ring opening of substituted substrates (either with electron-donating or electron-withdrawing groups), and ligand **417b** promoted the addition of Me_2Zn with up to >99% ee (Scheme 174). Cationic methyl−palladium Fesulphos complexes could be isolated after the transmetallation reaction of (**417a**)$PdCl_2$ with Me_2Zn in dichloromethane, and their structures were determined by NMR and X-ray studies showing a cis stereochemistry between the methyl group and the phospholane moiety. These complexes showed similar activity and selectivity to the *in situ* prepared catalysts. A very considerable optimization of the reaction conditions was achieved by adding $NaB(ArF)_4$ as a chloride scavenger in the reaction mixture. A dramatic enhancement of the reaction rate (complete conversion within 10 min for ligand **417a**) was observed, indicating the influence of the anionic counterion (here bulky and noncoordinating) on the key cationic palladium catalyst. Under those optimized conditions, 0.5 mol % of catalyst was sufficient to promote several transformations very rapidly and efficiently. The alkylative ring opening of less reactive substrates was investigated, and complex (**417a**)$PdMe^+$ with the hexafluorophosphate anion was the more efficient for the desymmetrization of azabenzonorbornadiene derivatives (see Scheme 176).

Thanks to computational studies and X-ray analyses, the authors proposed that the high asymmetric induction obtained using Fesulpos **417a** as ligands arose from specific steric and electronic features such as a strong trans effect of the phosphine moiety, together with a major steric hindrance imposed by the stereogenic sulfur atom.

3. Asymmetric C–H Bond Formation

3.1. Introduction

Stereoselective hydrogenation and hydrosilylation reactions have been extensively studied in their asymmetric catalytic version. For these reactions, phosphine ligands have been the most efficiently developed and used. However, since the steric and electronic properties of an efficient metal complex are closely related to the targeted transformations, a large development of new chiral ligands occurred for the preparation of structurally very different chiral complexes. In this field, the most active catalysts generally tested were based on ruthenium, iridium, or rhodium complexes. Furthermore, ligands also possessing nitrogen chelating atoms were often used, inducing high enantiomeric excesses in combination with high catalytic activities. Continuing the search for other chiral ligands that combined high selectivity and high reactivity with low cost and less toxicity, the development of chiral sulfur ligands containing heterodonor *S,N*- and *S,P*- or homodonor *S,S*-chelates appeared more recently. The following section will deal with asymmetric C−H bond formation catalyzed by complexes coordinated with different sulfur-containing ligands.

In this third part of the review, we will see that sulfur-containing ligands can be employed for the formation of asymmetric C−H bonds, considering all the synthetic processes that are transfer hydrogen reductions, hydrogenations by molecular hydrogen, and reductions by borohydrides or by hydrosilylations. We will first summarize the reports concerning the reduction of carbonyl derivatives, and then we will consider those dealing with C−C double bonds.

3.2. Asymmetric Reduction of Carbonyl Groups

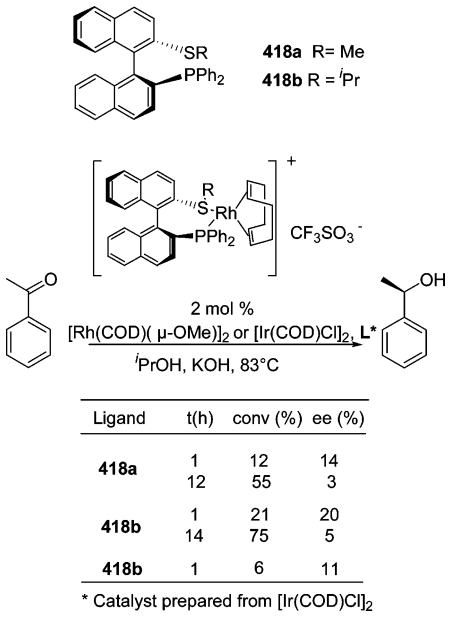
3.2.1. Asymmetric Hydrogen Transfer Reductions

The most attractive method for synthesizing chiral alcohols is the asymmetric transfer hydrogenation of prochiral ketones. The reaction generally gives the desired alcohol in high yields and good enantiomeric excesses. The reaction occurs under relatively mild conditions, avoiding the use of molecular hydrogen, because the organic solvent, generally 2-propanol, serves as the hydrogen donor. Further improvement of the catalytic activity and enantioselectivity of this reaction is a continuing challenge. We will see in this first approach to creating asymmetric C−H bonds that all sulfur-containing ligands were investigated as potential chiral ligands except the *S,S*-chelate.

3.2.1.1. Chiral *S,P*-Ligands. The use of heterodonor *S,P*-ligands in the hydrogen transfer reduction of ketones has been considered. Gladiali *et al*. described the stereocontrolled synthesis of heterobidentate *S,P*-derivatives from enantiopure (*R*)-binaphthol **418** as potential chelating ligands.[297] This approach was inspired by their work on the synthesis of rhodium complexes containing atropoisomeric sulfur ligands[298] in which the sulfur atom became stereogenic upon coordination to the metal.

Rhodium complexes were synthesized, characterized by ^1H, ^{13}C, and ^{31}P NMR and by elemental analysis (Scheme 177), and then tested as new complexes for hydrogen transfer reduction of acetophenone by 2-propanol. Hence, the use of *in situ* prepared complexes by addition of 1 equiv of chiral ligand in which the sulfur atom is substituted by a methyl group **418a** or by an isopropyl group **418b** to $[Rh(COD)(\mu\text{-OMe})]_2$ afforded at best only 20% ee, and this value

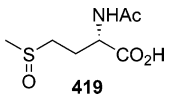
Scheme 177



Ligand	t(h)	conv (%)	ee (%)
418a	1	12	14
	12	55	3
418b	1	21	20
	14	75	5
418b	1	6	11

* Catalyst prepared from $[Ir(COD)Cl]_2$

Scheme 178



decreased as the reaction proceeded. The conversion did not exceed 55−75%, and the enantiomeric excesses were lower than 5% ee, as racemization occurred when the reaction time increased. Despite this low enantioselectivity, these results clearly indicated the potential use of chiral *S*,*P*-chelate ligands for asymmetric hydrogenation.

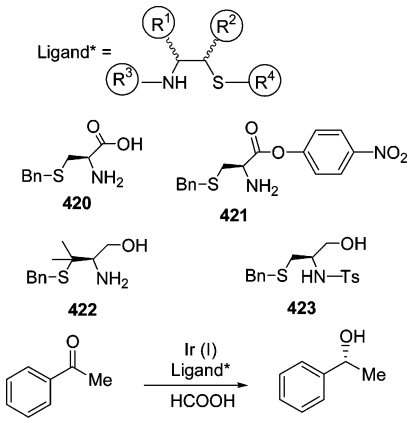
More recently, the same group reported similar results about the stereocontrolled synthesis of *S*,*P*-heterodonor ligands derived from (*S*)-BINOL through a multistep reaction.[299] The chiral ligand BINAPS **418a** was used in the Rh(I)- but also Ir(I)-catalyzed asymmetric hydrogen transfer reduction of acetophenone. However, the chiral complexes afforded only moderate enantiomeric excesses for the desired alcohol (Scheme 177).

3.2.1.2. Chiral *S*,*N*-Ligands. An enantioselective catalytic version of the hydrogen tranfer reduction using sulfur-containing ligands was developed very early by James *et al*.[300] The authors studied the ability of chiral sulfoxide-containing rhodium complexes to promote the enantioselective transfer hydrogenation of ketones. A Rh complex catalyst was prepared *in situ* by mixing $[RhCl(hexa\text{-}1,5\text{-}diene)]_2$ and a diastereoisomeric mixture of *N*-acetyl-(*S*)-methionine (*R*,*S*)-sulfoxide **419** (Scheme 178). Propanol-2-ol was used as hydrogen source, and the best results in terms of activity and enantioselectivities were obtained for a sulfoxide/Rh/^{i}PrOH ratio of 2:1:4 or 5.

Under these conditions, various aromatic ketones were reduced, albeit with low conversions but enantioselectivities up to 75% ee for 1-*p*-tolylethanol.

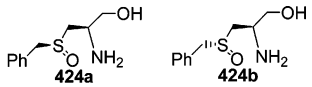
Later, Petra and co-workers[301] reported catalytic systems based on iridium(I) complexes with aminosulfides or aminosulfoxides as ligands. The general structure of these *S*,*N*-ligands is depicted in Scheme 179. The authors studied the iridium(I)-catalyzed asymmetric transfer hydrogenation of prochiral ketones in the presence of those ligands in formic acid as a hydrogen donor. In this study, the authors assumed

Scheme 179



ligand	t (h)	conv.(%)	ee (%)
420	1	26	12
421	1	58	18
422	20	97	7
423	40	20	18

Scheme 180



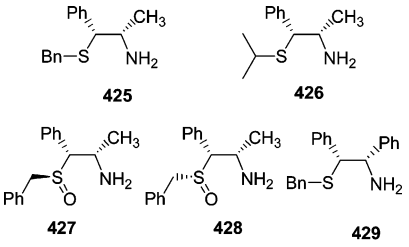
ligand	t(h)	conv.(%)	ee (%)
424a+424b	1	56	35 (*S*)
424a	1	56	27 (*R*)
424b	0.5	99	65 (*S*)

a bidentate *S*,*N*-coordination, supported by the fact that ethanolamine, representative for *N*,*O*-coordination, did not catalyze the reduction of acetophenone under these reaction conditions. In order to evaluate these systems, two series of chiral *S*,*N*-chelates were synthesized, based on (*R*)-cysteine or derived from (Nor)ephedrine and 2-aminodiphenylethanol. Optimization in terms of activity and selectivity toward the transfer hydrogenation of acetophenone was then carried out. In this context, different parameters were studied such as the influence of the catalyst precursor, ligand stoichiometry, reaction temperature, hydrogen source, and substrate variation. The first results showed that the use of *S*,*N*-chelates based on (*R*)-cysteine led to low enantioselectivities (see **420**−**423** in Scheme 179) in the asymmetric reduction of acetophenone in the presence of formic acid even though the authors prepared numerous ligands with different sterically hindered or electronically modified R^1, R^2, R^3, and R^4 groups.

The corresponding sulfoxides were prepared from commercially available (*S*)-benzyl (*R*)-cysteino to create both a more sterically hindered bulk around the sulfur-chelating atom and a new chiral center in the ligand (Scheme 180).

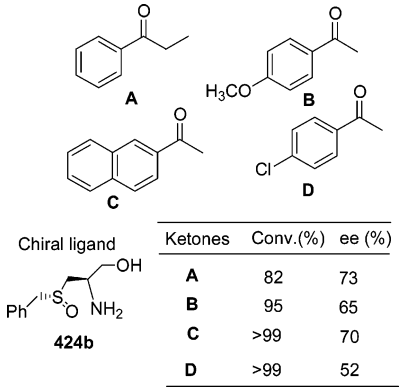
The diastereoisomeric mixture **424a** + **424b** allowed the formation of phenylethanol with 35% ee, albeit with a lower yield than that obtained with the corresponding sulfide ligand. Interestingly, the pure diastereoisomer **424a** yielded the opposite configuration product whereas diastereoisomer **424b** allowed the fast and complete formation of the (*S*) product with up to 65% ee. These results suggested an important effect of chiral cooperativity between the sulfoxide functionality and the α position of the amino alcohol.

Scheme 181



ligand	t(h)	conv.(%)	ee (%)
425	3	>99	65
426	3	>99	41
427	6	32	32
428	6	9	2
429	18	2	58

Scheme 182



Ketones	Conv.(%)	ee (%)
A	82	73
B	95	65
C	>99	70
D	>99	52

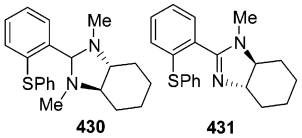
The *S*,*N*-chelates based on the (Nor)ephedrine and 2-aminodiphenylethanol skeletons allowed testing a new series of ligands possessing two chiral centers in the carbon backbone. Their use as ligands for iridium-catalyzed hydrogen transfer reduction of acetophenone generally gave better yields, but the enantiomeric excesses never exceeded 65%. Some examples are reported in Scheme 181.

Depending on the cysteine derivatives, the sulfide functionality in **425** was oxidized for the formation of the corresponding diastereoisomers; however, no optimization for the reaction was provided in terms of activity or selectivity (**427** and **428** in Scheme 181). A further catalyst optimization included the study of the catalyst precursor (with $[IrCl(COD)]_2$ as the more efficient), the metal/ligand ratio (2:5), the reaction temperature (a decrease resulting in an increase in the enantioselection), and the hydrogen source (the system being less stable when 2-propanol is used as a hydrogen donor). Other ketones were also reduced under those optimized conditions to study the scope of this new catalytic system (Scheme 182), and they showed that the reaction course was influenced by the steric and electronic properties of the substrates.

The transformation of more sterically hindered ketones (**A** and **B**) led to enhanced enantioselectivities. The highest ee (97%) reported by the authors arose from the reduction of 1-acetophenone in the presence of the aminosulfide **429** derived from 2-aminodiphenyl ethanol (see Scheme 181) using 2-propanol as the hydrogen source.

The use of chiral thioimidazolidines as ligands for the Ru-catalyzed asymmetric hydrogen transfer of aryl ketones was performed by Kim and co-workers. The synthesis of these

Scheme 183



Ligand	Substrate	Conv. (%)	ee (%)
430	Propiophenone	>99	77
430	Tetralone	>99	74
431	Propiophenone	91	71
431	Tetralone	87	73

Catalyst prepared from $RuCl_2(PPh)_3$

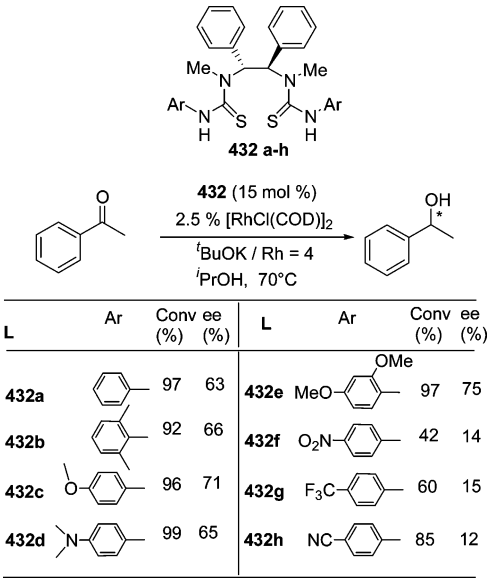
ligands was carried out from optically active (1*R*,2*R*)-(+)-*N*,*N*′-dialkylcyclohexane-1,2-diamines.[302] Brominated intermediates were treated with *tert*-butyllitium and further reacted with diphenyl disulfide to give the chiral thioimidazolidines that were used as *S*,*N*-ligands (**430** and **431**) with $RuCl_2(PPh)_3$ as catalyst precursor. Several ketones were reduced to the corresponding secondary alcohols with high conversions and enantiomeric excesses (up to 77% ee); see Scheme 183.

In order to improve the operating conditions, the influence of the ruthenium source on the asymmetric reduction of propiophenone was examined. The results showed that the system combining $RuCl_2(PPh)_3$ and ligand **430** gave a slightly higher enantioselectivity compared to the use of $[RuCl_2(p\text{-cymene})]_2$ as the ruthenium source (67% ee at 85% conversion). Finally, these results confirmed that thioimidazolidines used as ruthenium bidentate ligands could efficiently catalyze the asymmetric transfer hydrogenation of alkyl aryl ketones.

Various dithioureas bearing an aromatic ring on their terminal nitrogen atoms have been synthesized by Lemaire and co-workers.[303] These *S*,*N*-chiral ligands **432a**−**h** have been tested in the asymmetric hydrogen transfer reduction of ketones catalyzed by a rhodium complex. The dithioureas were synthesized by the addition of two isothiocyanate moieties to (*R*,*R*)-*N*,*N*-dimethyl-1,2-diphenylethylenediamine. Various electron-withdrawing and electron-donating substituents on the aromatic rings were evaluated for the reactivity and the enantioselectivity of the corresponding complexes (Scheme 184).

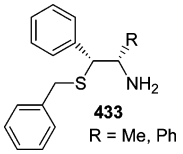
These results indicated that the steric hindrance around the nitrogen atoms bound to the aromatic rings had only a minor influence. Dithioureas bearing electron withdrawing or donating groups have been synthesized and tested. The selectivity of the hydrogen tranfer reduction dramatically decreased with the introduction of an electron-withdrawing group (see **432f**, **432g**, and **432h**; Scheme 184). The *ee* values obtained in those cases were very low (around 15%). The introduction of a CN group led to a higher conversion than the introduction of a CF_3 group. With electron-donating groups, the reverse effect was observed (see **432b**, **432c**, and **432e**), but the activity remained more or less constant compared to that of the nonsubstituted ligand **432a**. Nevertheless, almost no difference was noted using dithiourea **432d** compared to **432a**; it is possible that the NMe_2 group attached to the aromatic ring competed with the other nitrogen atoms or with the sulfur atoms of the ligand with the subsequent modification of the selectivity. The effect of ketone substitution was also evaluated; in these cases, the reactivity was dramatically influenced by the electronic effect of the substituent. This variation on both the activity and the

Scheme 184



L	Ar	Conv (%)	ee (%)	L	Ar	Conv (%)	ee (%)
432a		97	63	432e	MeO, OMe	97	75
432b		92	66	432f	O_2N	42	14
432c	O	96	71	432g	F_3C	60	15
432d	N	99	65	432h	NC	85	12

Scheme 185



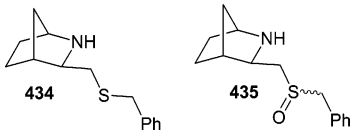
selectivity was probably due to the modification of the electron density around the binding site of the ligand. The coordination of model thioureas has been studied by density functional theory (DFT) calculations. The electronic effects have also been analyzed, and an interpretation of the variation in the enantiomeric excess, based on a supposed change in the coordination mode, is given. These experimental and theoretical studies point out that the coordination of the thioureas takes place through the sulfur atom.

Prochiral ketones were enantioselectively reduced to the corresponding alcohols by a biocatalytic reduction system that was compared to the use of ruthenium(II)−amino alcohol and iridium(I)−amino sulfide complexes as organometallic catalysts.[304]

Catalytic systems for transfer hydrogenation in which sulfur-containing ligand **433** was employed were obtained by combining with IrCl(COD)]$_2$ as the catalyst precursor (Scheme 185). These chiral iridium complexes were then tested for the enantioselective reduction of various aryl-functionalized, dialkyl-functionalized, α,β-unsaturated, and chloro-substituted ketones and compared to other reported systems. Transfer hydrogenation experiments were carried out using propan-2-ol as a hydrogen donor. The results in asymmetric transfer hydrogenation showed that the corresponding chiral alcohols could be obtained with moderate to high enantiomeric excess (up to 97% with complete conversion of acetonaphtone). Unfortunately, the substituent on the chiral ligand **433** used for these catalytic tests was not specified. Both the biocatalytic and the metal-catalyzed systems were able to selectively reduce various prochiral ketones but only the biocatalyst system was efficient for the chloro-substituted ones.

The synthesis and evaluation of two new classes of *S*,*N*-ligands for catalytic transfer hydrogenation were reported by Andersson and co-workers.[305] In order to prepare more

Scheme 186



active ligands, they developed a class of sulfur-containing ligands based on cyclohexyl amino sulfides (Scheme 186). The bicyclic ligands were easily prepared as racemic mixtures and then separated by chiral preparative HPLC. The influence of different backbones and substituents on the amino sulfides was investigated in the acetophenone transfer hydrogenation conditions using [Ir(COD)Cl]$_2$ as the metal precursor and different hydrogen sources.

When formic acid was used as the hydrogen donor, ligand **434** led to a complete conversion after 6 h at 60 °C and the (*R*)-compound was produced with 15% ee. At room temperature, the reaction was very slow (30% conversion after 96 h), but interestingly, the (*S*)-product was isolated as the major isomer with 28% ee. No explanations were given for a rationalization of these results. When ^{i}PrOH was the hydrogen donor, the enantiomeric excesses increased to 63% (*R* isomers). The use of the sulfoxide analogue **435** led to no reaction in formic acid, whereas in 2-propanol it afforded the best enantioselectivity for the reduction of acetophenone (up to 80% ee).

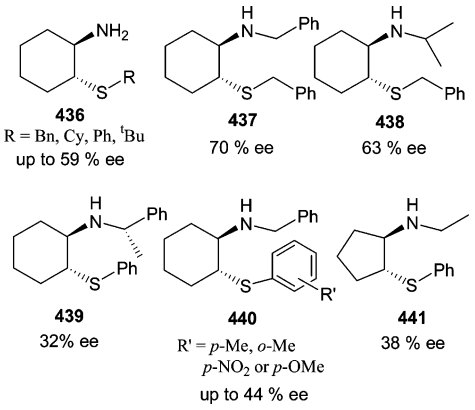
In order to obtain ligands easily functionalizable on both the nitrogen and the sulfur atoms, a new class of cyclohexyl-amino sulfides derived from cyclohexene oxide was then synthesized.

All the chiral sulfur-containing ligands were evaluated in the transfer hydrogenation reaction of acetophenone in ^{i}PrOH as the hydrogen donor. The results obtained with primary amines **436** gave rise to more efficient catalysts than the previously described bicyclic ligands. However, the best value for the ee only reached 59%. When bulky substituents were placed on the sulfur atom, a decrease in both activity and selectivity was observed for **439**, **440**, and **441** (32, 44, and 38% ee). Amino sulfides, with a secondary amine (**437**, **438**), gave a higher enantiomeric excess than the corresponding primary amine: respectively, 63 and 70% ee (compared to less than 59% for **436** type). The results obtained with the aryl-substituted sulfur analogues showed that electron-donating aryl substituents induced a slight increase in the enantiomeric excess whereas electron-withdrawing groups gave lower enantiomeric excess.

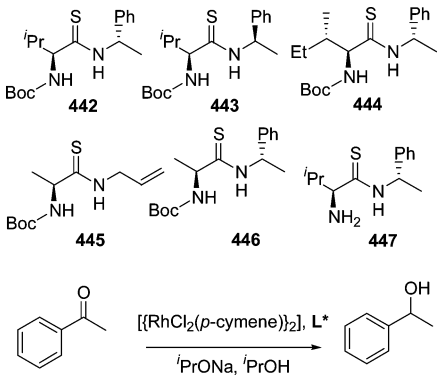
More recently, Zaitsev and Adolfsson described the preparation and application of novel chiral sulfur-containing ligands for rhodium- and ruthenium-catalyzed reduction of aryl, alkyl ketones under transfer hydrogenation conditions.[306]

In order to increase the stability of the active catalytic metal complexes, they replaced the amide oxygen in Boc-protected amino acid amides with a sulfur atom (see Scheme 187). This substitution resulted in a dramatic improvement in both the activity and the selectivity of the Rh or Ru complexes in the asymmetric hydrogen transfer reduction of several ketones (Scheme 188). In addition, the modification of the catalytic system with the lithium salt led to a novel and more efficient class of Ru and Rh catalysts in 2-propanol. Under optimized conditions, the authors obtained the secondary alcohol from various aromatic ketones in generally high yields and excellent enantioselectivities (up to 97% ee) using only 0.25 mol % catalyst and 0.6 mol % ligand **442** loading. A notable aspect of these sulfur-

Scheme 187



Scheme 188



Ligand	conv(%)	ee(%)
442	49	81
443	64	78
444	47	81
445	46	42
446	45	59
447	74	59

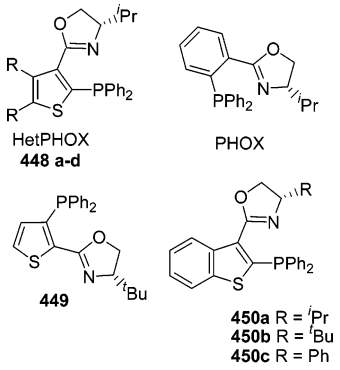
containing ligands was that generally the analogous amide led to racemic products and when a chiral induction was observed, it was associated with a switch in absolute configuration of the products. According to the authors, this inversion may occur from a different coordination mode and suggests another hydrogen transfer pathway.

Once again, the positive influence of sulfur ligands in asymmetric catalysis is demonstrated by these results. A small change in the ligand structure (sulfur atom instead of an oxygen atom) had a dramatic influence on the activity and selectivity of the catalysts, and as a result, highly selective enantioswitchable catalysts were obtained starting from the same ligand backbone.

3.2.1.3. Ligands with an *S*-Noncoordinating Atom. The synthesis of chiral phosphino-oxazoline ligands containing thiophene or benzothiophene backbones was recently described by End and co-workers.[307] This new family, called HetPHOX ligands, was tested in transfer hydrogenation reactions catalyzed by ruthenium complexes.

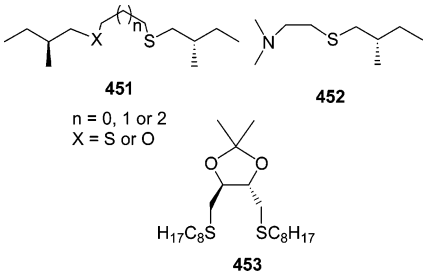
In order to compare both the activity and the enantioselectivity of the different chiral ligands, the authors chose the hydrogen transfer reduction of acetophenone catalyzed by ruthenium complexes. All reactions were carried out under the same conditions and stopped after 30 min. All the Ru complexes based on HetPHOX-derived ligands showed lower catalytic activity in this reaction when compared to the chiral phosphino-oxazoline analogue (PHOX; see Scheme 189), but

Scheme 189



Ligand	yields (%)	ee (%)
449	22	99
450a	47	89
450b	27	81
450c	24	70

Scheme 190



the expected alcohols were isolated with good enantioselectivity (ee up to 99%). Even if *S*,*N*-ligands proved their good efficiency for promoting metal-catalyzed asymmetric transfer hydrogenation, up to now they do not compete with the *N*,*N*-ligands, at least in terms of enantioselectivity.[308]

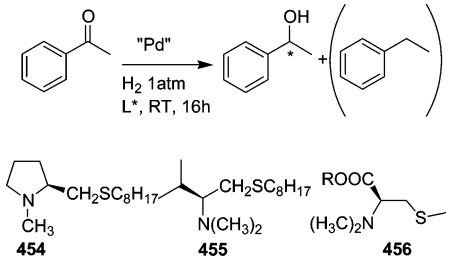
3.2.2. Asymmetric Reduction with Molecular Hydrogen

Another way to synthesize chiral alcohols by reduction of prochiral carbonyl compounds is the use of molecular hydrogen associated to a catalytic process based on transition metal complexes, generally of Pd, Ru, Rh, or Ir.

3.2.2.1 Chiral *S*,*S*-Ligands. Lemaire and co-workers described the synthesis and use of chiral sulfur-containing ligands (see Scheme 190) in the asymmetric hydrogenation of acetophenone catalyzed by palladium complexes under atmospheric hydrogen pressure.[309] In this context, thiapodand *S*,*S*-ligands **451** afforded very low conversion and no asymmetric induction. The absence of chiral induction was explained by the structure of the ligand itself as a conformationally unconstrained compound, and an alternative proposed was the use of *S*,*S*-ligand **453** derived from the known DIOP. The influence of the number of methylene groups between both sulfur atoms was studied, but it did not improve the reactivity or the enantioselectivity of the corresponding catalysts. It was then confirmed that thiapodands **451** poisoned the palladium atom, since, in the absence of ligand, acetophenone was totally converted into ethylbenzene and when these ligands were used the transformation into ethylbenzene did not take place. In this case, the reduction of acetophenone into 1-phenylethanol was chemoselective giving exclusively the alcohol.

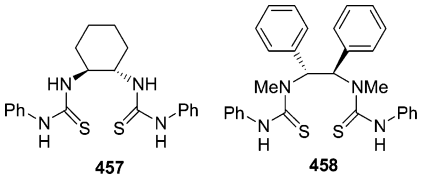
The conversion increased in all solvents used (up to 60% in heptane), but the enantioselectivity remained modest.

Scheme 191

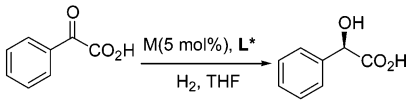


454 **455** **456**

Scheme 192



457 **458**



M	L*	Yield (%)	ee(%)
$[Rh(NBD)_2]BF_4$	**457**	19	47
$[Rh(NBD)_2]BF_4$	**458**	28	54
$[Ir(COD)_2]BF_4$	**457**	1	-
$[Ir(COD)_2]BF_4$	**458**	16	6

These results were probably due to the major rigidity of the ligand structure. The influence of the nature of the heteroatom was then evaluated by changing one sulfur atom by an oxygen or a nitrogen atom (see **452** in Scheme 190). In some cases, only the conversion was improved up to 91%, but the asymmetric induction never exceeded 3%.

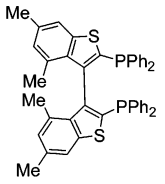
3.2.2.2. Chiral *S,N*-Ligands. Lemaire and co-workers also described in the same article[309] the synthesis of chiral dithio and azathio ether ligands as potential palladium *S,N*-ligands for the asymmetric catalytic reduction of acetophenone under atmospheric pressure hydrogen. They systematically studied the chemoselectivity, since this reaction can afford ethylbenzene, and the enantioselectivity of this reaction.

The *S,N*-ligands synthesized from various amino acids (proline, valine, and cysteine, respectively, gave **454**, **455**, and **456**) were tested in the asymmetric hydrogenation of acetophenone catalyzed by 5 mol % $Pd(OAc)_2$ in the presence of the different *S,N*-ligands (ligands/palladium = 1), but no significant induction was observed (Scheme 191).

Sulfur-containing ligands, with a dithiourea backbone, were also tested by Lemaire *et al.* in the asymmetric hydrogenation of carbonyl compounds. The authors reported the exclusive reduction of phenylglyoxylate methyl ester under molecular hydrogen pressure catalyzed by cationic chiral dithiourea complexes of rhodium or iridium (see Scheme 192).[310]

The activity and enantioselectivity slightly increased when dithiourea **458** was used instead of **457**, in which the isothiocyanate moieties were the same for both dithioureas and only the structure of the chiral diamine part differed. This difference suggested that the coordination did not occur exclusively via the sulfur atom. Moreover, a dramatic loss of activity and enantioselectivity was observed when these dithioureas were used with the iridium catalyst instead of the corresponding diamines. Therefore, the sulfur atom probably also contributed to form the metallic complexes. As for diamines, the nature of the solvent was very important. Finally, it is important to note the influence of the solvent on both the activity and the enantioselectivity of the catalytic systems. Dioxane, methanol, and dichloromethane were successively tested, leading to a loss of activity and values of 58%, 19%, and 17% ee for the enantioselectivity, respectively.

Scheme 193



(+) or (-) 459

substrate	ligand	T°C	t(h)	Yield (%)	e.e. (%)
ethyl acetoacetate	**(+) 459**	70	2	95	>99
methyl benzoylacetate	**(-) 459**	25	100	92	90
methyl phenylglyoxylate	**(-) 459**	25	100	90	78
methyl pyruvate	**(-) 459**	25	100	100	88

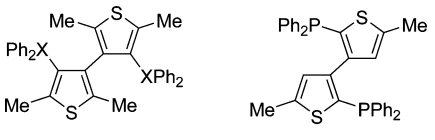
3.2.2.3. Ligands with an *S*-Noncoordinating Atom. Another approach in the use of sulfur-containing ligands in catalytic hydrogenation was developed by Sannicolò and coworkers. They prepared bis(diphenylphosphine) bidentate ligands in which heteroaromatic rings were introduced in the backbone, generally as a thiophene ring.[311] It is important to note that in this approach the ligands are sulfur-containing but not *S*-coordinating ligands. The aim of their work was to control the electronic effects at the phosphorus atoms by using an electron-rich heterocycle. They first reported the synthesis of optically pure diphenylphosphino-biheteroaryls and their use as chiral atropoisomeric chelating diphosphine ligands in the stereoselective hydrogenation of β-oxoester catalyzed by Ru(II) complexes.

The chiral ruthenium(II) complexes were prepared *in situ* from $[Ru(C_6H_6)Cl_2]$ and ligand **459** in DMF. They were then tested in the hydrogenation of α- and β-ketoester under the same experimental conditions described for BINAP−Ru(II) dichloride.[312] The results obtained (Scheme 193) showed that these new ligands induced enantioselectivities of up to >99% ee.

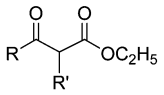
They later described the efficient synthesis of enantiopure (+)- and (−)-2,2′,5,5′-tetramethyl-4,4′-bis(diphenylphosphino)-3,3′-bithiophene **460** (tetraMe-BITIOP), in six steps with approximately 30% overall yield,[313] and its use as a C_2-symmetric chelating ligand of Ru(II) or Rh(I) complexes in some catalytic hydrogenation reactions.

The aim of their project was to prepare chiral biheteroaromatic ligands combining high electronic density at phosphorus and low bite-angle value for an efficient use in catalytic hydrogenation reactions. The electronic avaibility at phosphorus was evaluated by cyclic voltammetry, and the comparison of the redox potential values of **460** and **462** clearly demonstrated that the phosphine group in the β-position of the thiophene moiety was more electron-rich. The use of these ligands in asymmetric hydrogenation of functionalized carbonyl and olefinic substrates (see section 3.3.1.3) generally afforded the desired products with good enantioselectivities. The enantiomeric excesses were excellent

Scheme 194



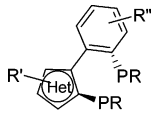
460 : X = P tetraMe-BITIOP **462**
461 : X = PO tetraMe-BITIOPO



a R = CH_3 R' = H
b R = C_6H_5 R' = H
c R-R'= $(CH_2)_3$

substrate	T(°C)	t(h)	ee (de) (%)
a	40	3	94
a	70	1	98
b	45	2	93
c	80	-	50 (77)
c	80	-	99 (84)

Scheme 195



463

(up to 99% ee at 95% conversion) for the asymmetric hydrogenation of α- and *β*-ketoesters (Scheme 194).

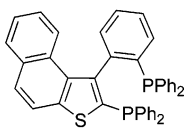
In this approach, tetraMe-BITIOP **460** was a very efficient chiral ligand in enantioselective homogeneous hydrogenation. The authors showed that the variation of electronic properties in the phosphorus could change gradually from an electron-poor to an electron-rich situation depending on the nature of the heterocycle (thiophene) and the position of the diphenylphosphino groups.

Another approach proposed by Sannicolò *et al*. for the hydrogenation of functionalized ketones and olefins was to prepare a new asymmetric ligand based on aryl groups substituted with five-membered heterocycles[314] (Scheme 195).

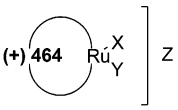
This design was based on the possible electronic modulation on diphenylphosphino groups by the combination of five-membered heteroaromatic systems with a carbocyclic moiety, giving C_1-symmetric diphosphines **463** (Scheme 195). The evaluation of the electronic availability of the phosphine group was again performed by cyclic voltammetry. The analysis of the oxidation potentials of diphenylphosphino groups confirmed that both phosphorus atoms in **464** had very different electronic properties.

In order to evaluate these ligands, preliminary catalytic experiments were performed in hydrogenation reactions. The results obtained in these experiments demonstrated that diphosphine **464** afforded quite good stereoselectivities (Scheme 196). Even if this ligand gave a lower enantiomeric excess for the hydrogenation of 2-acetamidoacrylates, the enantioselectivities found in the hydrogenation of *β*-ketoesters and methyl phenylglyoxylate were fully comparable to those produced by the most efficient DuPHOS and BINAP ligands. The stereoselectivities obtained with **464** were often similar to those obtained with C_2-symmetric analogues. Ligand **464** was considered by the authors as a model for a new class of chiral ligands in which the electronic properties can be modulated.[315] The synthesis was improved in order to increase the variety of these novel C_1-symmetric chelating

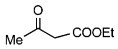
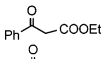
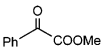
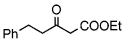
Scheme 196



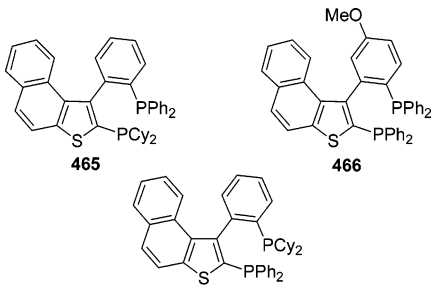
464



464a X = Y = Cl
464b X = C_6H_6 Y = Z = Cl
464c X = Y = COD Z = Cl

Cat.	Substrate	S/C	T(°C)	t(h)	ee(%)
464a		1000	40	3.5	96
464a		240	55	6	73
464a		1000	40	8	97
464b		243	50	24	85
464b		445	50	30	93

Scheme 197



465 **466**

467

diphosphines with stereogenic axes displaying a mixed aryl-heteroaryl atropisomeric backbone (Scheme 197).

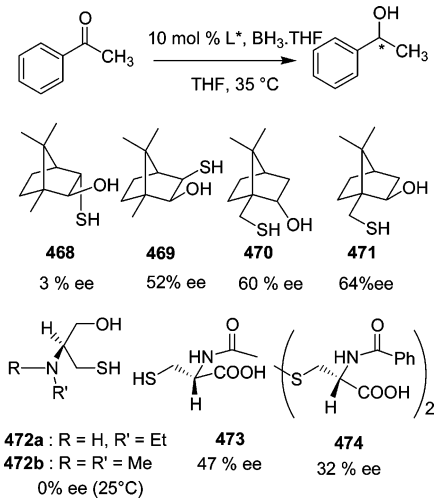
A simple synthesis in four steps was described starting from commercially available *β*-thionaphthol and *ω*,2-dibromoacetophenone. The electronic availability of the ligand at phosphorus was evaluated once more by cyclic voltammetry experiments. The values of the electrochemical oxidation potential of the ligands seemed to be influenced by the nature of the heterocyclic scaffold and its position. The presence of the methoxy group on the phenyl moiety in **466** did not modify the oxidative potential value obtained for **464**. A possible interpretation of this result suggests the existence of conformational effects in solution, and the configurational stability of the ligand was evaluated by ^{31}P NMR experiments. The analyses demonstrated that naphthothiophene-based diphosphanes were found to be configurationally stable and do not racemize under 130 °C. Preliminary catalytic experiments with Ru(II) complexes of enantiopure diphosphane (+)-**466** were then carried out, which showed that the catalytic hydrogenation of *β*-ketoesters gave the desired hydroxyesters in good yields and very good enantioselectivities of up to 99.9% ee.

3.2.3. Borohydride Derivatives as Chiral Reducing Agents

3.2.3.1. Chiral *S,O*-Ligands. Several chiral 1,2- and 1,3-hydroxythiols derived from (*R*)-camphor, (1*S*)-(+)-10-camphorsulfonyl chloride, cysteine, and cystine derivatives were prepared and evaluated as catalysts in borane reduction of prochiral ketones by Fiaud and co-workers.[316]

The evaluation of the nature of the reducing agent, BH_3·THF or catecholborane, in the reduction of acetophenone with the different *S,O*-ligands depicted in Scheme 198

Scheme 198

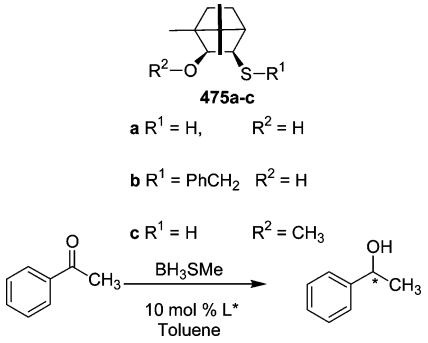


showed that both the activities and selectivities displayed by catecholborane were lower than those obtained with BH_3·THF. The best enantioselectivities were obtained using ligand **471** in the reduction of acetophenone in 1-phenylethanol (up to 64% ee). After these preliminary results, ligand **471** was selected for further investigation in order to optimize reduction parameters such as temperature, solvent, or catalyst-to-substrate ratio. The enantioselectivity of the reaction proved to be very temperature dependent, with the best value obtained around 50 °C. Whereas the nature of the solvent did not affect the enantioselectivity, the catalyst-to-substrate ratio slightly improved the enantioselectivity up to 75% ee when the reaction was performed under stoichiometric conditions. Under the best experimental conditions (10 mol % catalyst in THF), various ketones were successfully reduced with an enantioselectivity that depended on the substrate structure (variation between 5 and 64% ee). The variation of the chiral auxiliary was also investigated in order to evaluate the influence of the nitrogen substitution on the selectivity. In this context, *S*,*N*-ligands **472b**, **473**, and **474** were compared as catalysts in the borane reduction of acetophenone. The results proved that the substitution on the nitrogen atom was very important, since the *N*,*N*-dimethylcysteinol ligand **472b** displayed no enantioselectivity (see Scheme 198).

Yang and Lee reported the use of (1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol (MerCO) and its derivatives as chiral *S*,*O*-ligands in asymmetric borane reduction of ketones.[317]

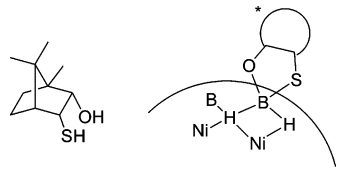
All chiral ligands **475a**−**c** were synthesized easily from camphor. In order to optimize the reaction conditions for using these ligands in catalytic asymmetric reductions, the influence of the solvent, temperature, and stoichiometry in the borane reduction was examined. The best enantioselectivities were obtained in a nonpolar solvent such as toluene. The temperature studies indicated that high enantiomeric excesses were generally obtained when the reaction temperature was kept at 50 °C. The authors proposed that under this temperature the effective chiral reducing agent was not completely formed. Consequently, at lower temperature, a major part of the ketone was directly reduced to its racemic form by free borane, thus lowering the enantioselectivity. When the reaction temperature markedly exceeded the optimal temperature, the reaction between free borane and ketone may be fast, also resulting in a decrease in the enantioselctivity. The alkylation of either the 2-hydroxyl or

Scheme 199



Ligand	T(°C)	Yield (%)	%ee	Config.
475a	25	92	73	*S*
475a	50	96	87	*S*
475a	110	93	6	*S*
475b	25	87	4	*S*
475c	25	84	22	*R*

Scheme 200



(1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol

the 3-mercapto group also led to a decrease in the enantioselectivity, confirming the weak coordination with boron (Scheme 199).

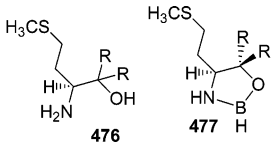
Another approach involved a heterogeneous version for the reduction of acetophenone by elemental boron.[318] After preliminary studies dealing with Ni-supported oxazoborolidines prepared by reaction of an amino alcohol with elemental boron in amorphous nickel boride (NiB_2), Molvinger and Court prepared a nickel-supported oxathiaborolidine by reaction of (1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol (Scheme 200) with amorphous NiB_2, applying the same procedure.

With the resulting heterogeneous catalyst, poor enantioselectivities were observed in the reduction of acetophenone by borane. However, when the nickel surface was at first passivated by poisoning with 3-methylthiophene, the reaction of (1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol with nickel boride afforded oxathiaborolidine anchored to the nickel nanoparticles, and moderate but better enantioselectivities were observed (31.5% ee and 24% ee when the catalyst was reused). These results clearly indicated a competitive interaction between the sulfur atoms on both the chiral ligand and methylthiophene with a nearly complete recovery of the surface by methylthiophene. The *S*,*O*-ligand is thus preferentially coordinated to the anchored boronic reducing species, leading to a more selective catalyst.

3.2.3.2. Chiral *S*,*N*-Ligands. Other sulfur-containing ligands were investigated in the enantioselective catalytic reduction of ketones by borane. In this context, Mehler and Martens have reported the synthesis of sulfur-containing ligands based on the L-methionine skeleton[319] (Scheme 201) and their application as new enantioselective catalysts for the borane reduction of ketones.

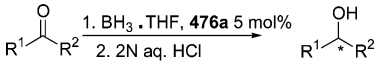
The *in situ* formed chiral oxazaborolidine **477** catalysts have been used in homogeneous catalytic reduction of

Scheme 201



476 **477**

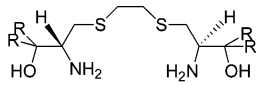
476a R = Ph
476b R = *p*-C_6H_4-Me
476c R = *p*-C_6H_4-OMe



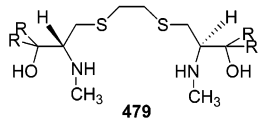
ketone	ee %
acetophenone	79
ω-chloroacetophenone	95
ω-bromoacetophenone	>99
methyl-2-naphtylketone	77

Results for R = Ph

Scheme 202



478



479

Ligand	ee (%)
478a: R = -CH_2CH_3	82
478b: R = -$(CH_2)_4$ -	64
478c: R = -C_6H_5	68
479a: R = -CH_2CH_3	69
479b: R = -$(CH_2)_4$ -	14
479c: R = -C_6H_5	8

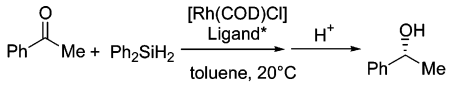
Chemical yields 85-92 %, catalyst* 5 mol %

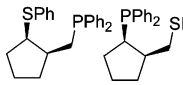
aromatic ketones. The corresponding chiral secondary alcohols were obtained in nearly quantitative yields (80−95%) and in high enantiomeric excesses, up to >99% (Scheme 201). It is important to note that the *S,N*-ligands **476** could be recovered from the aqueous layer or the distillation residue and recycled in another enantioselective reduction. However, the recycling efficiency was not discussed.

New sulfur-containing C_2-symmetrical bis-*β*-*primary*- and *sec*-amino-*tert*-alcohols have been synthesized from (*R*)-cysteine and successfully used as chiral ligands in the enantioselective borane reduction of acetophenone.[320]

The results of the homogeneous catalytic reduction of acetophenone with the catalysts based on the various ligands depicted in Scheme 202 generally showed both good activities and good enantioselectivities, but one can notice that an important decrease in the enantiomeric excess was observed when the analogous *β*-*sec*-amino alcohols were used (ligands **479b** and **479c**). In this approach, the secondary amino group with low sterical substitution (**479a**) seemed to be the best combination, affording the desired alcohol with 69% ee. The best result in terms of enantioselectivity was obtained with the primary amino alcohol **478a**, affording 1-phenyl-1-ethanol in up to 82% ee.

Scheme 203

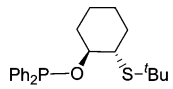




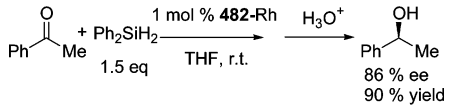
480 **481**

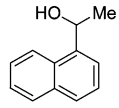
Ligand	conv (%)	ee (%)
480	99	57
481	56	12

Scheme 204



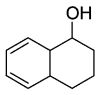
482



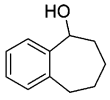


98 % ee
99 % yield

94 % ee
95 % yield



92 % ee
91 % yield



98 % ee
90 % yield

3.2.4. Hydrosilylation

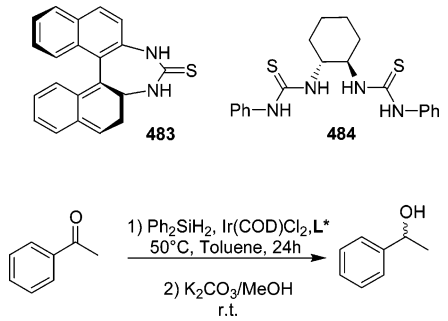
3.2.4.1. Chiral *S,P*-Ligands. The preparation and the application of *S,P*-ligands in the rhodium-catalyzed asymmetric hydrosilylation of ketones were described by Achiwa and co-workers.[321] The new ligands were based on a chiral cyclopentane sulfide−phosphine backbone (**480** and **481**, Scheme 203).

The corresponding *P,S*-Rh complexes proved to be enantioselective, but only 57% ee was obtained under the best conditions for ligand **481**. The effects of the temperature and solvent were examined, but the enantioselectivity of the reaction could not really be improved.

Another approach in the use of *S,P*-ligands for the hydrosilylation reaction was proposed more recently by Evans and co-workers.[322] In fact, considering the success of this class of ligands for the hydrogenation of carbon−carbon double bonds, as we will see in section 3.3.1.2., the authors chose to test the efficiency of the corresponding rhodium complexes in other transformations and especially in the enantioselective hydrosilylation of ketones. They first evaluated ligand **482**, as the more efficient chelate, to perform the rhodium-catalyzed reduction of acetophenone with diphenylsilane. Then they used the rhodium−**482** combination in the hydrosilylation of various aromatic ketones, and catalysis by this complex led to the desired alcohols in good yields and enantioselectivities up to 99% (see Scheme 204).

The optimization of the reaction conditions led to the use of a Rh complex bearing a norbornadiene ligand and a triflate counterion in the presence of phenyl(1-naphthyl)silane as a more efficient reducing agent. This optimized catalyst was used for the reduction of a large variety of ketones with a

Scheme 205



very high efficiency, since complete conversion and up to 98% ee were obtained in some cases (Scheme 204).

Aryl methyl ketones were reduced very rapidly, allowing the reaction to be run at low temperatures, resulting in higher selectivities. A variety of phenyl alkylketones were also reduced with high enantioselectivies as well as cyclic aromatic ketones such as benzosuberone and thiochromanone. The wide scope of this catalytic system was further proved by the hydrosilylation of various dialkylketones and substituted β-ketoesters.

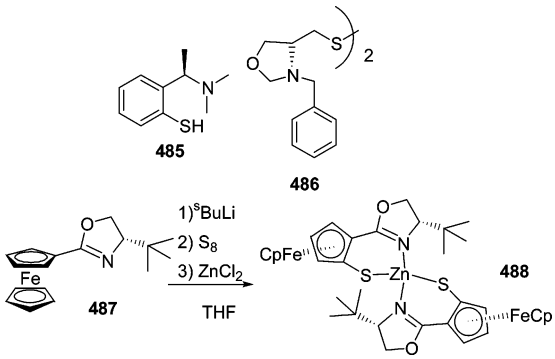
3.2.4.2. Chiral *S,N*-Ligands. Lemaire and co-workers described the synthesis of several thioureas (mono- and dithioureas) and their use as chiral inductors for the iridium-catalyzed hydrosilylation of acetophenone.[323] These *S,N*-ligands were synthesized in good yield. The use of enantiomerically pure C_2-symmetric monothioureas as ligands for iridium afforded catalysts yielding only moderate efficiencies. The influence of the ligand/metal ratio was very important for the selectivity of the transformation, and up to 25% ee was reached when the ligand was present in a 6-fold excess in toluene at 50 °C.

Dithioureas were also used in the hydrosilylation of acetophenone in the presence of $[Ir(COD)Cl]_2$. In this case, no chiral induction was observed despite good conversions. Only the use of ligand **484** (Scheme 205) as an iridium chelate in the presence of Ph_2SiH_2 improved the enantioselectivity, but the best enantiomeric excess value only afforded 52%, after an optimization of the reaction conditions. The use of $[Rh(COD)_2]BF_4$ as catalyst also led to disappointing results under similar conditions. The influence of the ratio ligand/iridium/dithiourea **484** was also investigated for the hydrosilylation of acetophenone. An increase of the enantiomeric excess was observed associated to a significant decrease of the catalytic activity with a 10-fold excess of ligand (74% ee for only 30% conversion), probably due to the presence of various complexes in the reaction mixture.

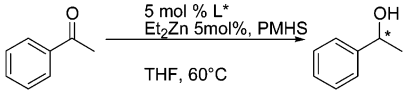
More recently, Riant *et al*. described the application of *S,N*-chelating chiral ligands in the catalytic asymmetric hydrosilylation of ketones in the presence of polymethylhydroxysilane (PMHS).[324] A new *S,N*-chelating zinc catalyst **488** was evaluated in the asymmetric hydrosilylation of ketones using the cheap and safe PMHS and compared to the chiral complexes derived from ligands **485** and **486.** The *S,N*-zinc complex **485** was obtained directly by a one-pot procedure starting from ferrocene oxazoline **487** (see Scheme 206). After formation of highly diastereoselective ortholithiated ferrocene, the reaction with electrophilic sulfur gave the corresponding lithium thiolate, which reacted with anhydrous zinc chloride, yielding the desired complex **488**.

A preliminary optimization was carried out by studying the effect of the solvent and the temperature on both the conversion and the enantioselectivity. THF was the best

Scheme 206

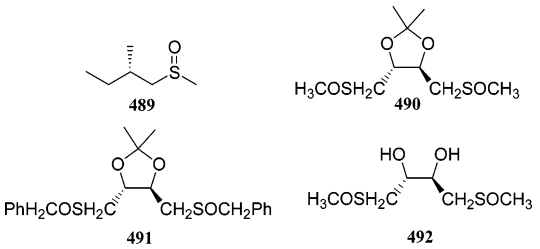


Scheme 207



Ligand	Time(h)	Conv(%)	ee(%)
485	6	23	3
486	6	69	8
487	2	100	51
488	24(R.T.)	100	61

Scheme 208



solvant regarding both activity and enantioselectivity. Under the same conditions, ligands **485** and **486** afforded low activities and almost no enantiomeric induction compared to complex **488** (Scheme 207).

Various ketones were also tested and generally a complete reduction was observed, the arylketones were more reactive than the nonaromatic ones. Even if the enantioselectivities still remained low for the reduction of various ketones (between 9 and 55% ee), this study showed that new families of *in situ* prepared chiral sulfur-containing ligands can be successfully used for the enantioselective hydrosilylation of prochiral ketones.

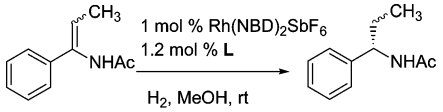
3.3. Asymmetric Reduction of C–C Double Bonds

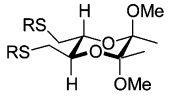
3.3.1. Asymmetric Reduction with Molecular Hydrogen

3.3.1.1. Chiral *S,S*-Ligands. A ruthenium complex containing the chiral sulfoxide ligand **489** was used by James *et al*. as a catalyst for the hydrogenation of prochiral olefins.[9] The chiral ligand was synthesized from (*S*)-(−)-2-methylbutanol in four steps and allowed to obtain an enantiomeric excess of 12% for the hydrogenation of itaconic acid. Other chiral sulfoxide ligands derived from (2*R*,3*R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(alkylsulfinyl)butane monohydrate (**490** and **491**) were synthesized by the same group. The corresponding acetal-cleaved derivative **492** was also prepared (Scheme 208).[325]

These ligands were tested as a mixture of the diastereoisomers for the preparation of the corresponding ruthenium-

Scheme 209

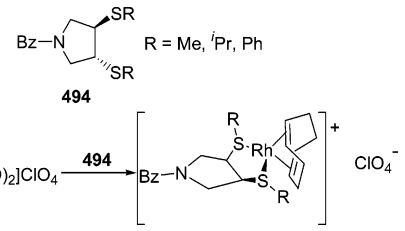




493a R=Ph
493b R=^{t}butyl

Ligand	Conv. (%)	ee (%)
493a	95	21
493b	37	18

Scheme 210



(II) neutral complexes. These catalysts were used in the catalytic hydrogenation of various prochiral olefinic acid substrates. They were active catalysts, leading to the chiral products with enantiomeric excesses of up to 25% for the hydrogenation of itaconic acid. Infrared and NMR analyses indicated that the sulfoxide moieties were all *S*-bonded.

Chiral thioether ligands derived from tartrates were synthesized and employed as *S*,*S*-bidentate ligands of Rh(I) complexes.[326] Their use for the asymmetric hydrogenation of *N*-acetyl-1-phenylethylenenamine gave complexes (see **493** in Scheme 209) that showed good activity but low enantioselectivity.

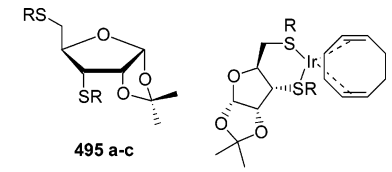
When the phenyl group on the sulfur atom was replaced by a *tert*-butyl atom, only 37% conversion and 18% ee were obtained. Compared to their diphenylphosphine analogues, these *S*,*S*-ligands did not show similar enantioselectivity. Generally, the enantiomeric excesses in the same reaction were over 70% for the analogous *P*,*P*-ligands.

Rhodium complexes of (*R*,*R*)-1-benzyl-3,4-dithioether pyrrolidines **494** (degus R) were synthesized and characterized by Ruiz *et al*. (Scheme 210).[327] These complexes were tested as catalysts in the hydrogenation of acrylic acids (*Z*-α-acetamidocinnamic acid and itaconic acid); unfortunately, they remained inactive under different reaction conditions (temperature, solvent, and H_2 pressure).

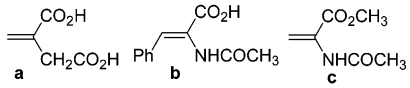
Sugar dithioether derivatives were synthesized from 1,2-*O*-isopropylidene-3,5-di-*O*-trifluoromethanesulfonyl-D-xylofuranose.[328] These new chiral C_1-symmetrical dithioether ligands with $[Ir(cod)_2]BF_4$ in dichloromethane yielded the corresponding chiral cationic iridium complexes, which were tested further in the catalytic hydrogenation of prochiral olefins.

The catalytic system was generated *in situ* from $[Ir(cod)_2]$-BF_4 and the corresponding dithioether *S*,*S*-ligand in dichloromethane. The chiral complexes were then used in the iridium asymmetric hydrogenation of itaconic acid **a**, (*Z*)-α-(acetamido)cinnamic acid **b**, and methy α-(acetamido)-acrylate **c** at room temperature under atmospheric pressure of H_2. Moderate conversions and enantioselectivities were obtained depending on the substituent on the dithioethers. Thus, the conversions and asymmetric inductions were better for the precursor containing the bulky and electron-rich

Scheme 211

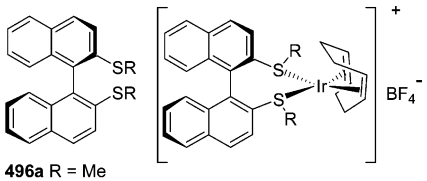


495 a-c



L*	R	a	b	c
495a	Me	14 % ee	nd	4 % ee
495b	^{i}Pr	62 % ee	37 % ee	13 % ee
495c	Ph	17 % ee	12 % ee	7 % ee

Scheme 212



496a R = Me
496b R = ^{i}Pr
496c R = ^{t}Bu

ligand, since the ligand **495b** (Scheme 211) substituted by ^{i}Pr promoted the complete hydrogenation of itaconic acid in 12 h with an enantiomeric excess of 62%.

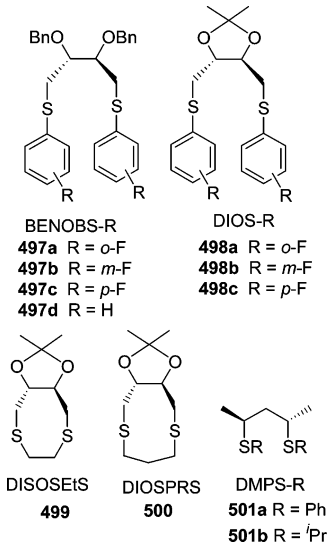
Ligands with two equivalent sulfur donors possessing a C_2-symmetry have been synthesized from the corresponding binaphthyl or biphenanthryl diols in order to investigate the potential of these chiral *S*,*S*-ligands in asymmetric catalytic processes.[329] In this context, different (*R*)-binaphthyl dithiols substituted by alkyl groups on the sulfur atom in order to increase the steric bulk were synthesized, and the corresponding mononuclear cationic Ir(I)−cyclooctadiene complexes have been prepared and characterized (Scheme 212).

NMR studies provided evidence that, in all cases, the coordination of the ligands proceeded with complete stereoselectivity at the newly generated *S*-stereocenters, affording only one stereoisomer, whatever the bulk of the alkyl substituent on the sulfur atom. Moreover, their reaction with molecular hydrogen gave in each case *cis*-dihydride complexes only.

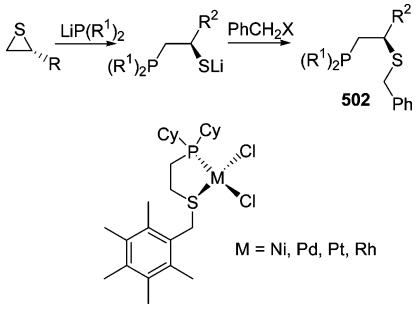
The cationic complexes derived from these chiral ligands were then tested in the hydrogenation of α,β-unsaturated acid derivatives. In all cases, the catalysts were active but poorly enantioselective, since the enantiomeric excesses never exceeded 5%. More recently, a series of cationic Ir(I) complexes containing chiral dithioether ligands derived from L-(+)-diethyltartrate and (2*R*,4*R*)-2,4-pentanediol were synthesized by Masdeu-Bultó *et al*. in order to study the influence of the sulfur substituents and the metallacycle size on the hydrogenation reaction.[330]

The combination of these ligands with $[Ir(cod)_2]BF_4$ afforded the corresponding chiral cationic iridium(I) complexes. Catalytic experiments of the iridium complexes showed that a mixture of diastereoisomers was obtained when the complexes were formed with ligands **497**, **498**, or **501**, probably due to the sulfur inversion process with decomposi-

Scheme 213



Scheme 214

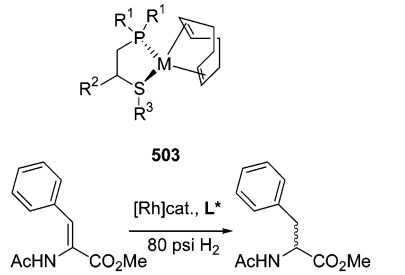


tion of the complexes. This behavior was not observed with the bicyclic ligands **499** and **500**; in these cases, the complexes were stable. Iridium complexes containing seven- and six-membered metallacycles (**497** and **498**) reacted with acrylic acid derivatives through *S*-ligand substitution, and the rate of this substitution was related to the position of the fluorine atom on the aromatic ring (fluorine atoms at the *ortho*-, *meta*-, or *para*-positions; see Scheme 213). Chelating ligands (**497**, **498**) were displaced in all cases by the substrate to form an [Ir(substrate)(cod)]$^+$complex, which is the catalytic species in the hydrogenation. This behavior was not observed with complexes containing a bis(metallacycle) (ligands **499** and **500**). However, these catalytic systems showed poor activities and enantioselectivities (up to 15% ee for **499**).

3.3.1.2. Chiral *S,P*-Ligands. The synthesis of chiral episulfides that could be ring-opened using lithium salts of phosphine such as $LiPR_2$ (R = Cy, Ph) was described by Hauptman *et al*. as a new access to chiral *S,P*-ligands.[331] This reaction is regiospecific; the ring opening occurring exclusively at the less hindered carbon. The lithium salts obtained reacted then with benzyl halide derivatives to give a large variety of heterodonor *S,P*-ligands in good yield (50−93%).

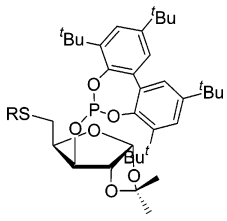
Their bidentate nature was established by preparing various nickel, palladium, platinium, or rhodium square-planar metal complexes (Scheme 214). Some of them were structurally characterized by NMR spectroscopic data and X-ray analyses, particularly the Pd and Rh complexes. The corresponding rhodium complexes were used as catalysts for the asymmetric hydrogenation of α-enamide esters (Scheme 215).

Scheme 215



L	R^1	R^2	R^3	conv(%)	ee(%)
503a	Cy	CH_3	CH_3	100	26.6(S)
503b	Cy	CH_3	CH_2Ph	100	50.1(S)
503c	Cy	CH_3	$CH_2(C_6(CH_3)_5)$	100	18.3(S)
503d	Cy	Cy	$CH_2(C_6(CH_3)_5)$	100	38.8(R)
503e	Ph	CH_3	$CH_2(C_6(CH_3)_5)$	74	24.7(S)

Scheme 216



All the Rh complexes were active catalysts for this enantioselective hydrogenation reaction; some examples are given in Scheme 215, but the enantiomeric excesses never exceeded 50%. Finally, no correlation could be established between the enantioselectivity and the *S,P*-ligand structure or its electronic properties.

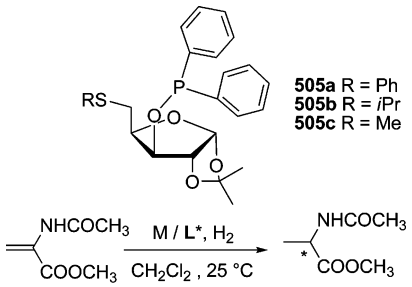
Claver *et al*. developed a series of chiral thioether−phosphite ligands derived from 1,2-*O*-isopropylidenexylofuranose (Scheme 216).[332]

The chiral ligands were also used for Ir(I) and Rh(I) catalytic hydrogenation of functionalized olefins. The catalytic system was generated *in situ* from $[Ir-(cod)_2]BF_4$ and the corresponding ligand. In this context, only iridium complexes were active in the catalytic hydrogenation of itaconic acid and produced enantioselectivities of up to 51%. Enantiomeric excesses were moderate, but under milder conditions, they were similar to the best ones obtained for other mixed *S,P*-donor ligand systems reported in the literature.

More recently, Claver *et al*. described the asymmetric hydrogenation of prochiral olefins catalyzed by furanoside thioether−phosphinite Rh(I) and Ir(I) complexes.[333] The thioether−phosphinite ligands were substituted in this case by different aryl or alkyl groups on the sulfur atom. They were tested in the asymmetric hydrogenation of trisubstitued olefins catalyzed by rhodium and iridium complexes.

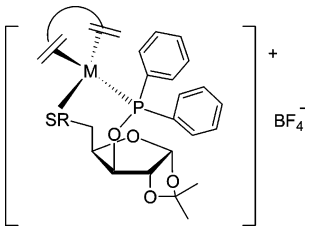
High enantiomeric excesses (up to 96% for Rh/**505b**, PH_2 = 30 at 0 °C) and good activities were obtained for α-acylaminoacrylate derivatives, with generally more than 75% conversion in dichloromethane (Scheme 217). The enantiomeric excesses depended on the steric bulk of the substituent on the sulfur atom. A bulky group on the thioether

Scheme 217



M / L*	PH_2(bar)	% Conv	% ee
Rh / **505a**	30	86	68
Ir / **505a**	1	100	50
Rh / **505b**	30	83	93
Ir / **505b**	1	95	63
Rh / **505c**	30	75	54
Ir / **505c**	1	60	30

Scheme 218



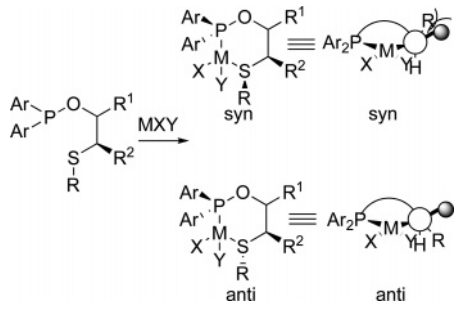
moiety, such as ^{i}Pr, combined with the rhodium metal had a positive effect on the enantioselectivity, since up to 93% ee could be oberved. The complexes were fully characterized by NMR analyses.

These studies revealed that the reaction of these chiral *S*,*P*-ligands with $[M(cod)_2]BF_4$ yielded complexes $[M(cod)(P-SR)]BF_4$ (Scheme 218), which were present in only one diastereomeric form, having the sulfur substituent in a pseudoaxial disposition. Reaction with molecular hydrogen led to iridium complexes $[IrH_2(cod)(P-SR)]BF_4$, showing the *cis* addition of H_2 on the metal. For complexes $[IrH_2(cod)(P-SPh)]BF_4$ and $[IrH_2(cod)(P-SMe)]$, only one isomer was present in solution. However, for the complex $[IrH_2(cod)(P-S^iPr)]BF_4$, which contained the more hindered substituent on sulfur, two isomers were detected. In all cases, there was a pseudoaxial disposition of the sulfur substituents.

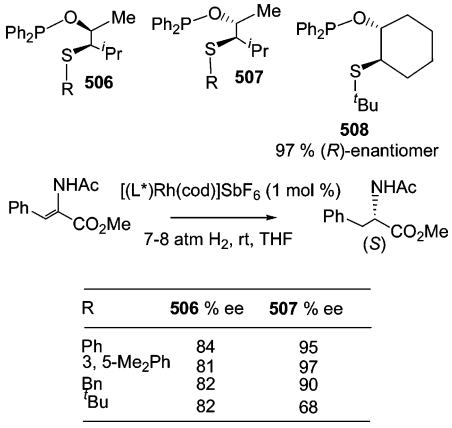
Chiral mixed phosphorus/sulfur ligands, already described by Evans *et al.*[322] as efficient Pd chelates for performing enantioselective Pd-catalyzed allylic alkylation and amination, were tested as Rh ligands to perform asymmetric carbon double bond hydrogenation. For controlling the configuration at sulfur and avoiding the easy inversion of the newly formed metal-coordinated thioether, the authors optimized the structure of the ligand backbone. They proved that the introduction of bulky substituents adjacent to the sulfur donor forced the sulfur substituent into an *anti* orientation (see Scheme 219) to minimize the steric hindrance.

A large variety of ligands bearing numerous substituents at phosphorus (Ar), at sulfur (R), and on the backbone (R^1, R^2) were prepared and tested in the hydrogenation of (Z)-methyl acetamidocinamate. Acyclic *S*,*P*-chelates (see **506** and **507** in Scheme 220) associated to rhodium were efficient catalysts under 7−8 atm of hydrogen. Some noticeable results are reported in Scheme 220, in which type **507** ligands proved generally better in terms of enantioselectivity, with the optimal ligand in this series bearing a 3,5-dimethylphenyl

Scheme 219



Scheme 220



R	**506** % ee	**507** % ee
Ph	84	95
3, 5-Me_2Ph	81	97
Bn	82	90
^{t}Bu	82	68

substituent at sulfur. However, the cyclic ligand **508** induced the highest enantiomeric excess (97%) when the reaction was performed at atmospheric hydrogen pressure. Due to the inversion of the stereocenter α to the sulfur donor, the opposite product enantiomer was obtained by using this catalyst.

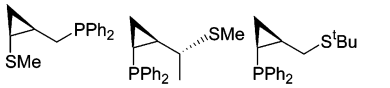
These new rhodium complexes were successfully used for the hydrogenation of various substituted acetamidoacrylates, delivering the expected products with up to 98% ee. These catalysts were also interestingly described as tolerant to a wide range of *N*-protecting groups. Since the nature of this group had little effect on the selectivity of the reaction, these catalysts allowed the challenging hydrogenation of tetrasubstituted enamides in an enantioselective way.

The authors proposed a mechanistic approach for this catalytic hydrogenation based on NMR analyses and X-ray crystallographic determination of a catalyst−substrate complex. The model involved regioselective binding of the substrate due to the different *trans* influences between the phosphorus and sulfur atoms and the enantiofacial discrimination induced by the new sulfur stereocenter. The authors proved that the ligand induces a very high level of selectivity along the reaction to select only one out of four possible diastereoisomers.

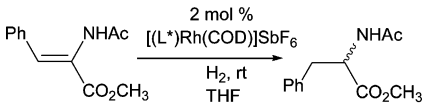
More recently, a series of chiral *S*,*P*-ligands based on a cyclopropane backbone have been synthesized and evaluated in the rhodium-catalyzed hydrogenation of a dehydroamino acid by Molander and co-workers.[42]

These new *S*,*P*-ligands were first used in the palladium-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate with dimethyl malonate and in the Tsuji−Trost reaction (see sections 2.4 and 2.2.3). After this evaluation, the authors selected some of them and, in particular, ligand **511**, which gave the best results in the Tsuji−Trost reaction. These ligands were used in other catalytic reactions, such as the rhodium-catalyzed hydrogenation of a dehydroamino acid

Scheme 221

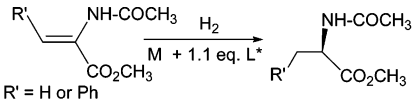


509 510 511

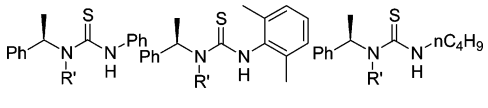


Ligand	Pressure(psi)	time(h)	conv(%)	ee(%)
509	100	42	27	5
510	100	42	93	46
511	14,7	48	99	41
511	120	19	41	47

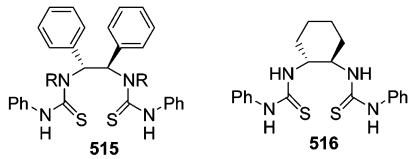
Scheme 222



monothioureas : enantioselectivity < 6 % ee



512 513 514



R = H up to 37 % ee
R = Me < 6 % ee

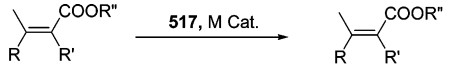
up to 70 % ee

(Scheme 221). However, even though the selected ligands were generally active, only moderate enantioselectivities were obtained (up to 47% ee under 120 psi of H_2).

3.3.1.3. Chiral *S,N*-Ligands. The study and comparison of monothiourea and dithiourea as chiral ligands for Rh-, Ir-, or Ru-catalyzed hydrogenation of enamides was reported by Lemaire and co-workers.[334] In this context, optically pure monothioureas (**512**−**514**) were easily obtained from the corresponding chiral amines and isothiocyanates and the dithioureas analogues (**515** and **516**) from optically pure diamines by reaction with 2 equiv of phenylisothiocyanate (Scheme 222).

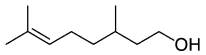
The hydrogenation of methyl-2-acetamido acrylate and α-acetamidocinnamic methyl ester was carried out under hydrogen catalyzed by Rh, Ir, or Ru complexes using the different *S,N*-ligands combined in various ligand to metal molar ratios. The author did not report the results when the metal was iridium because the enantiomeric excess was very low (ee < 15%). In order to compare the influence of their structures, all the chiral ligands were tested in the asymmetric enamide hydrogenation. These *S,N*-ligands were active, but no significant enantioselectivities were observed for monothioureas (ee under 6%). The C_2-symmetry structure of the dithioureas seemed essential for the enantioselectivity, since in these cases ee values of up to 70% were obtained for the Rh and Ru catalysts.

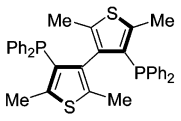
Scheme 223



a : R, R' = H R" = Ph
b : R, R' = CH_3 R" =H
c : R = Ph, R' = NH-CO-CH_3, R" = H
d : R = α–Naphth, R' = NH-CO-CH_3, R" = CH_3

e :





517 tetraMe-BITIOP

substrate	M catalyst	solvent	P (kg/cm2)	S/C	T(°C)	ee (%)
a	$RuCl_2$	MeOH	50	160	20	94
b	Rup-cymene	MeOH	10	3000	25	94
c	$Ru(Ph)Cl_2$	EtOH	3	90	25	87
d	$Ru(allyl)_2$	THF/MeOH	20	80	10	94
e	$Rh(COD)_2BF_4$	MeOH	100	160	25	92

3.3.1.4. Ligands with an *S*-Noncoordinating Atom. Sannicolò *et al.* described the efficient synthesis of enantiopure (tetraMe-BITIOP) **517** as a C_2-symmetric chelating ligand of Ru(II) or Rh(I) complexes (see section 3.2.2.3), in order to prepare chiral biheteroaromatic ligands combining high electronic density at phosphorus and low bite-angle value for an efficient use in catalytic hydrogenation reactions.

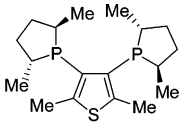
The use of these ligands in the asymmetric hydrogenation of carbon−carbon double bonds of *N*-acetyl-α-enamino acids or esters (Scheme 223) generally afforded the desired products with good enantioselectivities. The enantiomeric excesses were generally around 90%, and up to 94% ee was reached. TetraMe-BITIOP **517** was also a very efficient chiral ligand in this enantioselective homogeneous hydrogenation and was efficiently used for the selective hydrogenation of the allylic double bond of geraniol **e**.

More recently, Sannicolò *et al.*[335] described the synthesis of a new thiophene-based analogue of (*R,R*)-Me-DuPHOS called UlluPHOS. This new C_2-symmetric diphospholane ligand was characterized and used in some classic asymmetric hydrogenation reactions of olefins and ketones catalyzed by Rh or Ru complexes. The activity and the selectivity of the UlluPHOS ligand were evaluated and compared to those of the Me-DuPHOS one.

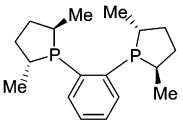
The analytical studies of the new structure showed very similar geometries while the electronic density was higher in the thiophene derivative **518** (Scheme 224). The use of UlluPHOS as a ligand for Ru and Rh complexes in different asymmetric hydrogenation reactions showed that this new ligand induced analogous results in terms of enantioselectivities compared to the Me-DUPHOS ligand (Scheme 224). The most important difference between both ligands was found by comparing the reaction rates. The authors observed that the use of UlluPHOS considerably increased the activity of the complexes.

The application of *P,N*-sulfinyl imine ligands to iridium-catalyzed asymmetric hydrogenation of olefins was described by Schenkel and Ellman.[336] The asymmetry induced by this new class of ligands is only due to the chirality of the sulfur center, coming from the sulfoxide group as a non-sulfur-coordinating moiety.

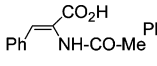
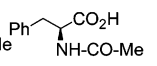
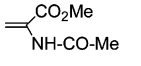
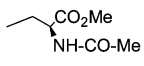
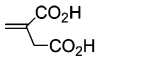
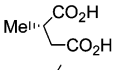
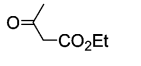
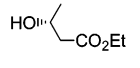
Scheme 224



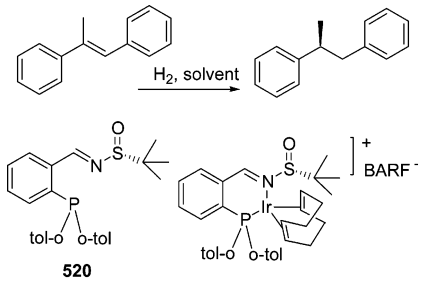
518 (*R,R*)-UlluPHOS



519 (*R,R*)-Me-DuPHOS

Substat	Product	P_{H2} (psi)	Time (h)	Conv. % 518 (519)	ee % 518 (519)
		30	60	100(100)	98.9(95)
		40	60	100(100)	>99.5(>99.5)
		30	340	77(69.4)	48(54)
		1470	1440	33.6(36)	58(60)

Scheme 225



520

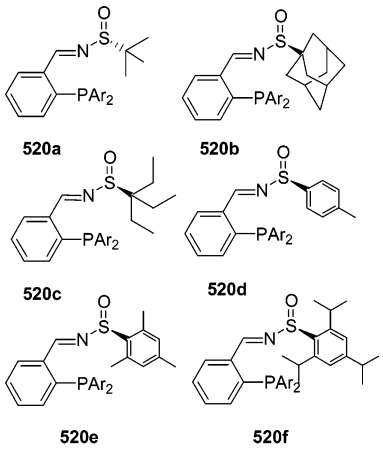
BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

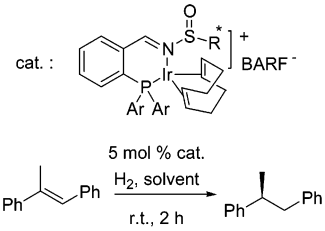
These sulfur-containing ligands were prepared from commercially available *tert*-butanesulfinamide by condensation with aldehydes and ketones. The asymmetric hydrogenation conditions were first optimized by using ligand **520** in the hydrogenation of α-methylstilbene (Scheme 225). The optimization of the experimental conditions revealed an important effect on both the rate of reaction and the enantioselectivity when solvent, pressure, and counterion were varied. Under the best reaction conditions (CH_2Cl_2, 50 bar H_2, and tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($BARF^-$) as counterion), the influence of the sulfinamide structure modification was then evaluated. In this context, different ligands were synthesized from a collection of sulfinamides with a wide range of steric and electronic properties. The increase of the steric bulk of the sulfinamide by the introduction of a 1-adamantane or 3-ethylheptane group did not improve the enantioselectivity. These results were attributed to an unfavorable geometry around the metallic center. The use of arylsulfinyl imines clearly showed a negative impact on the enantioselectivity (Scheme 226).

Functionalized olefins were then examined as substrates. In this context, α,*β*-unsaturated esters and allylic alcohols were tested in the asymmetric hydrogenation reaction using different complexes. The best results were obtained with the Ir complex derived from **520a** (Ar = *o*-tol) for the hydrogenation of both types of substrates, with up to 65 and 70% enantiomeric excess, respectively.

Other sulfur-containing but noncoordinating ligands based on thiophene **521** and on benzothiophene **522** derivatives, respectively, were used in the iridium-catalyzed asymmetric hydrogenation of olefins.[337] For all catalytic reactions, the

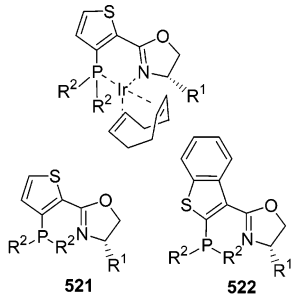
Scheme 226



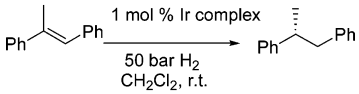


L*	Ar	conv (%)	ee (%)
520a	*o*-tol	>99	94
520b	*o*-tol	58	84
520c	*o*-tol	75	84
520d	*o*-tol	>99	5
520e	*o*-tol	52	7
520a	3,5-dimethyl -phenyl	53	57
520a	Ph	20	55

Scheme 227



521 **522**

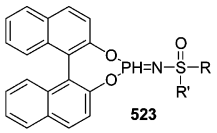


R^1	R^2	conv (%)	ee (%)
^{i}Pr	Ph	>99	77
^{t}Bu	Ph	>99	95
^{t}Bu	*o*-Tol	>99	97
^{t}Bu	Cy	>99	99

complexes proved to be highly active (total conversion after 2−4 h) and the enantioselectivity was generally excellent, up to 99% ee (Scheme 227).

The same evolution in the enantiomeric excess was observed with the benzothiophene ligand **522**, but the enantiomeric excess values were generally higher with the thiophene core. Finally, hydrogenation of allylic alcohols was

Scheme 228



523

		CO_2CH_3 / CO_2CH_3	CO_2CH_3 / NHAc	CO_2CH_3 / Ph / NHAc	Ph / NHAc
***R*-Binol**	**523a** R = Ph, R' = Me	99 (*R*)	98.8 (*S*)	97.0 (*S*)	87.5 (*S*)
	523b R = R' = Me	99 (*S*)	98 (*R*)	94.0 (*R*)	76.0 (*R*)
	523c R = R' = Ph	98 (*R*)	98.2 (*S*)	95.2 (*S*)	84.5 (*S*)
***S*-Binol**	**523a** R = Ph, R' = Me	99 (*R*)	98.2 (*S*)	94.0 (*S*)	64.0 (*S*)

also investigated using all these complexes. The results showed high conversion and enantioselectivity (up to 94% ee).

More recently, *N*-phosphino sulfoximines derived from (*R*)- or (*S*)-BINOL (Scheme 228) have been synthesized for the first time by Reetz[338] *et al*. Their use in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins afforded excellent enantioselectivities of up to 99% ee.

The different ligands are very stable under dry conditions, and they can react with $[Rh(cod)_2]BF_4$, yielding the corresponding chiral complexes $[Rh(cod)(L^*)_2]BF_4$, which were used as precatalysts in the hydrogenation of several functionalized olefins (Scheme 228). In the main cases, the configuration at the sulfur atom only had a small influence on the enantioselectivities. It was important only in the hydrogenation of *N*-(1-phenylvinyl) acetamide. (*R*)-BINOL/(*S*)-sulfoximine (**523a**) constitute the matched case (87.5% ee) in contrast to the mismatched combination (*S*)-BINOL/(*S*)-sulfoximine (64% ee). Ligands (**523b, 523c**) possessing an achiral sulfoximine moiety are less efficient in the hydrogenation of the same substrate.

Chiral bidentate phosphine thiazoles have been prepared and successfully applied as ligands in the homogeneous iridium-catalyzed asymmetric hydrogenation of trisubstitued aryl olefins by Hedberg and co-workers. All the chiral ligands were designed to be highly modular (Scheme 229). In order to systematically vary the ligand structure, the authors started by the evaluation of the cyclic backbone. In this context, the authors synthesized ligands with five-, six-, and seven-membered cyclic backbones and the corresponding iridium complexes were evaluated in the hydrogenation of olefins.[339]

All these ligands gave excellent conversions and enantioselectivities. After these preliminary results, a six-membered cyclic backbone was preferred. Therefore, different enantiomerically pure cyclic six-membered ligands were synthesized principally by varying the steric bulk on the phosphine or on the heteroaromatic ring (see **527a**, **527b**, and **527c** in Scheme 229).

The complexes **525** and **527** proved to be highly efficient in the asymmetric hydrogenation of a wide variety of trisubstituted olefins. Unsurprisingly, the steric bulk of the heteroaromatic substituent and the size of the phosphine substituents were important for achieving high enantioselectivity. For substrate **c**, the 2-*H*-thiazole complexes **527b** and **527c** proved to be superior, giving high conversions and excellent enantioselectivities (up to 95% ee) compared to ligands **524**, **525**, and **526**. These results led the authors to propose a selectivity model to match different substrates against different catalysts. In this way, good to excellent enantioselectivities were obtained for typically difficult substrates. Geometrically different derivatives of α- and β-methyl cinnamic acid ethyl esters were hydrogenated, to demonstrate the validity of the selectivity model and to verify the importance of steric and electronic matching of the catalyst and the substrate.

3.3.2. Borohydride Derivatives as Chiral Reducing Agent

Rhodium complexes derived from *S*,*S*-ligands based on degus R were also tested as catalysts in the hydroboration of styrene with catecholborane[327] (Scheme 230). In this case, a moderate activity was observed, and both regioselectivity and enantioselectivity were very poor (ee < 6%). As for the hydrogenation of acrylic acids and hydroformylation of styrene dithioethers, chiral *S*,*S*-ligands did not provide any advantages *P*,*P*- or *P*,*N*-ligands.

3.3.3. Hydrosilylation

The chelating *S*,*P*-heterodonor ligand 2-diphenylphosphanyl-1,1′-binaphthalene-2′-thiol (BINAPS) was also used in the hydrosilylation of styrene.[299]

These phosphanyl sulfide ligands gave better results in the hydrogen transfer reduction in terms of enantioselectivity, but the conversion and the regioselectivity in this reaction were more dependent on the substituent group of the sulfur atom (Scheme 231).

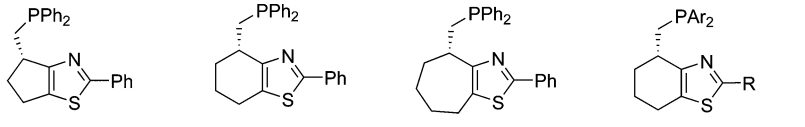
3.4. Conclusion

In this third part dedicated to the asymmetric carbon−hydrogen bond formation, we have seen that sulfur-containing ligands can be engaged in all the synthetic processes that are transfer hydrogen reductions, hydrogenations by molecular hydrogen, or reductions by borohydrides or by hydrosilylation. Concerning the reduction of carbonyl derivatives, *S*,*P*-, *S*,*N*-, and non-coordinating sulfur ligands were generally tested. In all cases, the best chelates were the containing but noncoordinating ligands such as the C_2-chiral biphosphines based on thiophene and developed by Sannicolò. The sulfur atoms in the carbon skeleton showed very positive effects in reduction processes. The same positive influence of the sulfur atom was observed in the asymmetric reduction of carbon−carbon double bonds, however, but in this case, *S*,*P*-ligands are the most promising chelates, allowing the formation of a C−H bond, with competitive results in terms of enantioselectivities, and in some cases up to 98% ee can be observed. Also *S*,*S* and *S*,*O* chelates were investigated in the enantioselective reduction of carbonyl groups and C−C double bonds but with much less success. Finally, this section confirms, one more time, the large potential use of sulfur-containing chiral ligands in enantioselective catalytic systems.

4. Asymmetric C–N Bond Formation

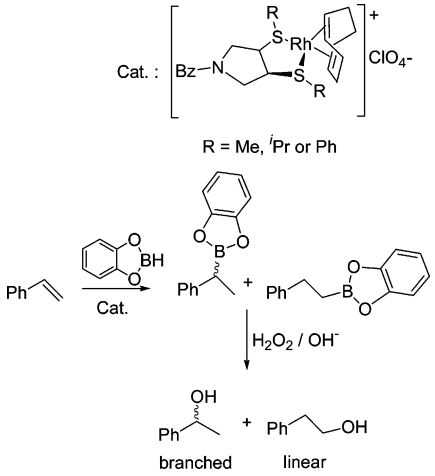
The intramolecular hydroamination reaction of alkenes is an atom economic process leading to the formation of nitrogen heterocycles which are found in numerous biologically active compounds. The pioneering work of Marks and co-workers has shown the ability of lanthanocenes to perform hydroamination/cyclization reactions.[340] More recently, non-cyclopentadienyl rare earth complexes,[341] as well as transition metal complexes and others, have been reported to catalyze intramolecular hydroamination of alkenes. Yet, enantioselective hydroamination reactions have been less studied and only a few chiral asymmetric catalysts have been reported

Scheme 229

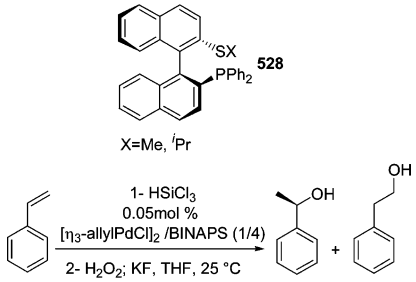


Substrate	524 (conv% ee%)	525 (conv% ee%)	526 (conv% ee%)	527a (conv% ee%)	527b (conv% ee%)	527c (conv% ee%)
Me, Ph; Ph **a**	>99 94	>99 >99	>99 98	>99 >99	>99 77	>99 48
Me, CO_2Et; Ph **b**	99 86	>99 98	99 95	>99 98	91 87	99 69
Me; Ph, CO_2Et **c**	99 3	85 rac	97 3	99 72	99 95	99 95

Scheme 230



Scheme 231

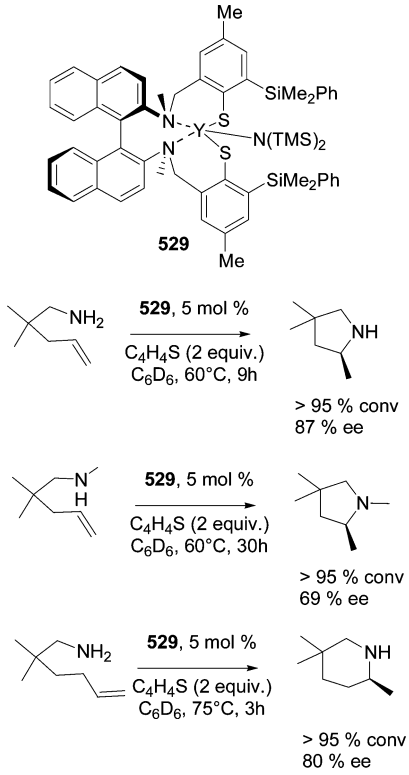


R (ligand)	t(h)	conv (%)	ee (%)
Me	39	41	4 (S)
iPr	41	72	51 (R)

up to now.[342] For most of them, efficient catalysts for the asymmetric cyclization of aminoalkenes are prepared from lanthanides with different types of ligands, *i.e.*, derived from binaphthol,[343] binaphthylamine,[344] or bis(oxazolines)[345] and are either isolated or used *in situ*.

Sulfur-coordinating ligands also recently proved efficient associated with yttrium to perform the asymmetric hydroamination/cyclization of aminoalkenes. Livinghouse *et al*.

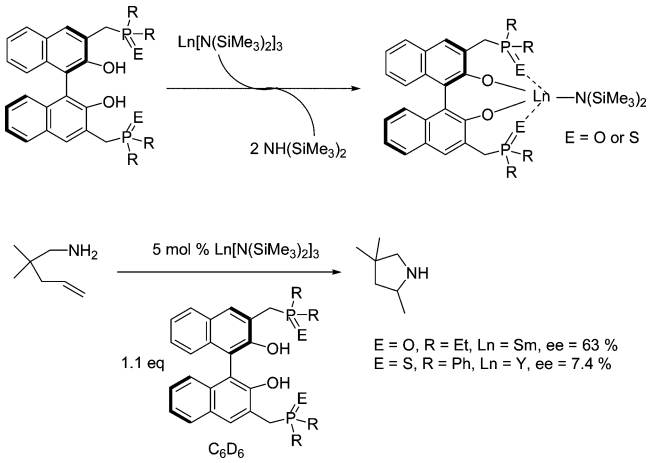
Scheme 232



synthesized axially chiral dithiol ligands, with the chirality being introduced via a binaphthylamine unit (see Scheme 232).[346] The corresponding yttrium derivatives were obtained by reaction with $[Y\{N(TMS)_2\}_3]$ by amine elimination in the presence of auxiliary ligands (and especially thiophene) for accelerating the reaction. The test reaction usually performed for a better classification of the new catalysts is the cyclization of 2,2-dimethylpent-4-enylamine into the corresponding pyrrolidine as depicted in Scheme 232.

Complex **529** catalyzed very efficiently the cyclization of this aminoalkene at 60 °C, and the dimethylpyrrolidine could be isolated with 87% ee. Interestingly, this catalytic system allowed the cyclization of a secondary aminopentene derivative with up to 69% ee. The even more challenging preparation of a piperidine occurred at 75 °C and yielded

Scheme 233



2,5,5-trimethylpiperidine in high enantiomeric excess (80% ee). The results obtained by this chiral bis(thiolate) yttrium complex are among the best values reported until now in the literature, at least concerning the enantiomeric excess for this reaction.

Livinghouse *et al*. have also described that chelating bis(thiophosphinic amidate) complexes of yttrium and neodymium catalyzed the intramolecular alkene hydroamination.[347] The corresponding neutral Zr(IV) complexes also proved active at high temperature.[348] Very recently, Marks described the synthesis of a series of chiral organophosphine oxide/sulfide-substituted binaphtholate ligands.[349] The lanthanide complexes generated *in situ* from $Ln[N(SiMe_3)_2]_3$ catalyzed the hydroamination of amino alkenes, albeit with low enantioselectivity for the sulfide-substituted complex (up to 7.4% ee for the yttrium derivative, Scheme 233).

5. Conclusion

We have covered in this review around 350 references dealing with the use of chiral sulfur ligands for asymmetric catalysis over the last 20 years. This important number of reports is a clear indication for the efficient use of such ligands to promote numerous catalytic transformations, and they are now fairly renowned competitors to more usual phosphorus- or nitrogen-containing ligands. As already mentioned, their preparation probably arose from the search for synthetically easily available compounds that were furthermore relatively easy to handle and to store. The high affinity of the sulfur atom to various transition metals also promoted a lot of research in this area. Sulfur ligands act in a bidentate manner. In such a context, homodonor *S*,*S*-ligands have been described but also heterodonor ligands such as *S*,*P*-, *S*,*O*-, or *S*,*N*-chelates. Homodonor chelates were the first sulfur-coordinating ligands described for asymmetric catalysis and, particularly, for Grignard cross-coupling transformations. Although the results remained moderate in terms of enantioselectivity, the papers reported by Kellogg and co-workers in the mid-1980s were an essential proof of concept for the start of this chemistry. Later, these *S*,*S*-coordinating ligands were essentially associated to palladium precatalysts and used in the asymmetric allylic substitution reaction. We want here to emphasize that this Tsuji−Trost transformation is by far the most explored catalytic test with chiral sulfur ligands.

Under optimized conditions, *S*,*S*-coordinating ligands led to interesting results, particularly in terms of enantioselectivity, but they remained generally less well performing than their nitrogen- or phosphorus-containing counterparts. These homodonor ligands were also interestingly involved in asymmetric hydroformylation and in the enantioselective reduction of carbonyl groups by molecular hydrogen but with much less success. Much more work was performed for the synthesis and subsequent use in asymmetric catalysis of heterodonor ligands.

Due to the huge success of chiral diphosphines as chelates, analogous *S*,*P*-ligands have been prepared. Structurally different chelates were synthesized more generally as thioether/phosphines (phosphinites) ligands, with the chirality being introduced in the carbon backbone, as a planar or even as an axial chirality. These ligands proved more versatile than the *S*,*S*-ones and promoted efficiently various transformations: the nucleophilic allylic substitution, but also the Diels−Alder reaction (as the only sulfur-coordinating ligands efficient for this copper-catalyzed reaction) and, with less success, the asymmetric intermolecular Heck reaction and the copper-catalyzed asymmetric 1,4-addition to enones. In the presence of *S*,*P*-ligands, palladium precatalysts ring opened mesoheterobicyclic alkenes with high enantioselectivities. Not only carbon−carbon bond formations could be catalyzed by such *S*,*P*-ligands, they also allowed the formation of C−H bonds. However, they proved actually less enantioselective in the reduction of carbonyl groups by hydrogen transfer. Better results were obtained in the asymmetric reduction of carbon−carbon double bonds or in hydrosilylation reactions.

S,*O*-Chelates have been developed to a lesser extent, but their efficient use as chiral ligands was proven in the enantioselective addition of diethylzinc to aldehydes and also in the copper-catalyzed asymmetric Michael addition.

S,*N*-Ligands are by far the most developed and have been successfully used in almost all the reactions cited in this review. A large variety of structures are available, such as aminothioethers, iminothioethers, pyridine-thioethers, or oxazoline/thioethers (or thiophene derivatives), which proved very efficient (and competitive) for performing the Tsuji−Trost reaction under excellent conditions. As aminoalcohol analogues, aminothiols have been mainly prepared (or are commercially available) for their use in the enantioselective addition of organometallic compounds to aldehydes. In our mind, this reaction is one of the transformation in which sulfur-containing ligands give rise to better results in terms of both enantioselectivity and activity than other heteroatom-containing ligands. Asymmetric conjugate addition has been efficiently conducted with *S*,*N*-ligands, and they were also tested in several other C−C bond formations, such as the cyclopropanation and the Henry reaction. For the formation of C−H bonds, under different reducing conditions, several *S*,*N*- compounds were tested, with encouraging results in terms of enantioselectivity.

Very interestingly, some sulfur-containing ligands have been furthermore prepared, in which other heteroatoms take part in the coordination. The sulfur atom is present as a sulfoxide (sulfoximine) group, for introducing the chirality, or is part of an aromatic group, for a modification of the electronic properties of an other chelating heteroatom. These ligands were very efficient in numerous transformations, especially for the cycloadditions and Heck-type reactions, showing some interesting specificities (activity, regioselectivity, and, of course, enantioselectivity) compared to their

non-sulfur-containing analogues Those ligands, and especially axially chiral biphosphines with sulfur atoms in their aromatic carbon skeleton, were very efficient in hydrogenation reactions.

The study of sulfur ligands is more recent compared to that of *P*- or *N*-ligands, and their efficiency for promoting asymmetric catalysis is generally less impressive. By looking precisely at some transformations, however, they overtake other ligands in terms of both activity and enatioselectivity. Moreover, due to their great versatility, *S*,*N*-ligands probably have a promising future for promoting, especially, C−C bond formations. To the best of our knowledge, very few examples have been found in which sulfur-containing complexes have been recovered and reused. Due to their great stability, we assume that asymmetric heterogeneous catalysis is a good way to develop these ligands in an even more economic and environmentally friendly manner.

6. Acknowledgments

The CNRS and the MENESR are kindly acknowledged for financial support.

7. References

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CR068440H