

Account / Revue

Thioether containing ligands for asymmetric allylic substitution reactions

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Abstract

This review covers reports in the literature on the use of thioether ligands in Pd-catalysed asymmetric allylic substitution reactions from 1996 to June 2006. In the first section, we will cover the results using (S,S)-homo and (S,S)-heterodonor ligands. In the next section, we will present the results using heterodonor (S,X)-ligands, emphasizing the results obtained with (S,N)- and (S,P)-donor ligands. We also discuss any reported mechanistic aspects according to the allylic substitution results. **To cite this article:** E. Martin, M. Diéguez, C. R. Chimie 10 (2007).

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Keywords: Chiral thioether; S-ligands; Asymmetric catalysis; Palladium; Allylic substitution reactions

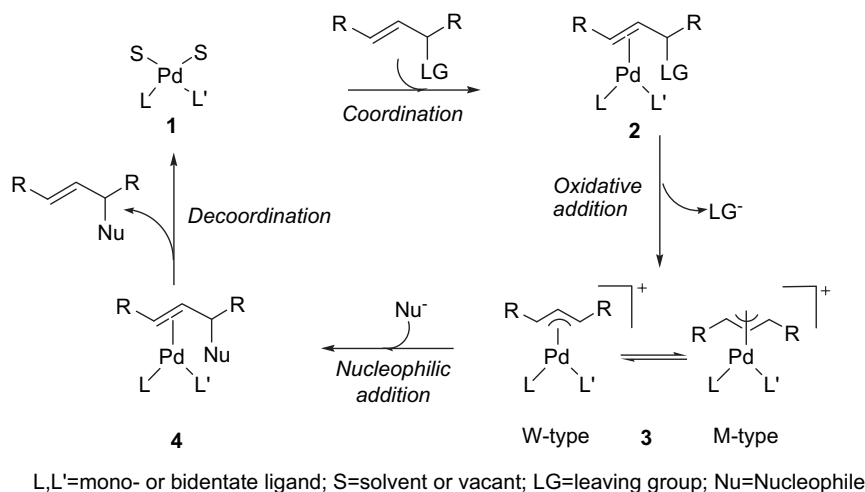
1. Introduction

The Pd-catalysed asymmetric allylic substitution (AAS) is one of the most versatile routes for preparing optically active compounds through carbon–carbon or carbon–heteroatom bond formation [1–3]. The catalytic cycle for AAS is well established and involves olefin coordination to form a η^2 -olefin complex **2**, subsequent intramolecular oxidative addition with the loss of the leaving group to produce η^3 -allyl complex **3**, nucleophilic addition to allylic moiety to generate **4** and finally, the substituted olefin decoordination to give the initial catalytic species **1** (Scheme 1).

Except for the last step (olefin decoordination), the rest of the cycle reactions offers possibilities for enantiodiscrimination [2]. In particular, when the allylic substrate generates a *meso* π -allyl intermediate (**3**, Scheme 1), the enantioselectivity is controlled by the external nucleophilic attack on the more electrophilic terminal allylic carbon of **3**. However, two diastereomeric complexes can be formed (W-type/M-type or *endo/exo* isomers, depending on the relative disposition of the allyl fragment with respect to the chiral ligand L/L'), and it can suffer an interchange through π – σ – π mechanism. Thus, the enantioselection is determined for both the regiochemistry of the nucleophilic addition and the diastereomeric composition of π -allyl intermediates. Two typical models of Pd-catalysed allylic substitutions are shown in Scheme 2, *rac*-3-acetoxy-1,3-diphenyl-1-propene (**5**) is widely used as substrate

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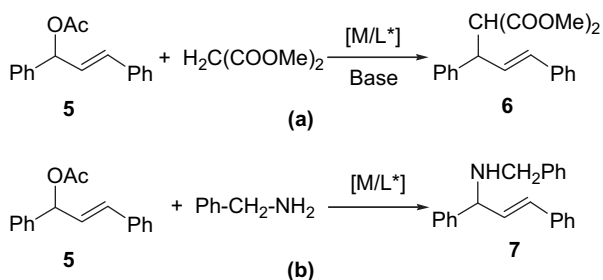
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Scheme 1. Accepted mechanism for Pd-catalysed allylic substitutions.

for alkylation reactions with dimethyl malonate (Scheme 2a) or for amination reactions with benzylamine (Scheme 2b).

Since the first enantioselective catalytic process described by Trost in 1977, many catalytic systems have been tested, affording excellent enantiomeric excesses [3]. Whereas several chiral ligands bearing nitrogen and phosphorus donors (either homo or heterodonors) are widely used in AAS [3,4], other donor atoms, such as sulphur, have been much less studied [5]. In relation to thioether containing ligands, structural data of the allylic palladium intermediates, both in solution and solid state, have been reported for several types of ligands, mainly for heterodonors, but also for sulphur homodonors. Because a mixture of diastereomers may exist in solution due to the configuration inversion at sulphur atom [6], a decrease of stereoselection may occur if the relative rates of the intermediates are similar. In spite of this feature, excellent enantiomeric excesses have been achieved in asymmetric allylic substitutions as well as in other metal-catalysed asymmetric reactions [7].

Scheme 2. Model allylic substitution reactions of **5** with soft nucleophiles: (a) dimethyl malonate (alkylation) and (b) benzylamine (amination).

Thus, this review will cover reports in the literature on the use of thioether ligands in Pd-catalysed asymmetric allylic substitution reactions in the most emerging period for this research area (1996–June 2006). In Section 2, we will cover the results using (S,S)-homo and (S,S)-heterodonor ligands. In Section 3, we will present the results using heterodonor (S,X)-ligands, emphasizing the results obtained with (S,N)- and (S,P)-donor ligands. We also discuss any reported mechanistic aspects according to the allylic substitution results.

2. (S,S)-donor ligands

2.1. (S,S)-homodonor

The first successful result using chiral dithioethers in palladium-catalysed allylic alkylation of **5** (Scheme 2a) was obtained with DEGUS-type ligands (up to 81% e.e.) (Fig. 1) [8]. Other chiral dithioether ligands, such as **9–11**, have been developed and applied in the same reaction, yielding modest-to-good asymmetric inductions [9], yielding modest-to-good asymmetric inductions [9]. Recently, the efficiency of the cyclic DIOS-S type ligands in AAS was improved by introduction of two new stereogenic centres in the propyl chain (DIOS-DMPS, **12**) [10].

The structural study of the reaction intermediates of dithioethers **8–12** showed that the coordination modes to palladium occur through both sulphur donor atoms. NMR spectra of Pd allylic complexes $[\text{Pd}(\eta^3\text{-1,3-PhC}_3\text{H}_3\text{Ph})(\text{L})]\text{PF}_6$ (**L** = **8**, **9**, **11**, **12**) show different diastereomeric species in solution. In several cases, the diastereomeric excesses are in good agreement with the enantiomeric excesses obtained in the catalytic reactions [8–10].

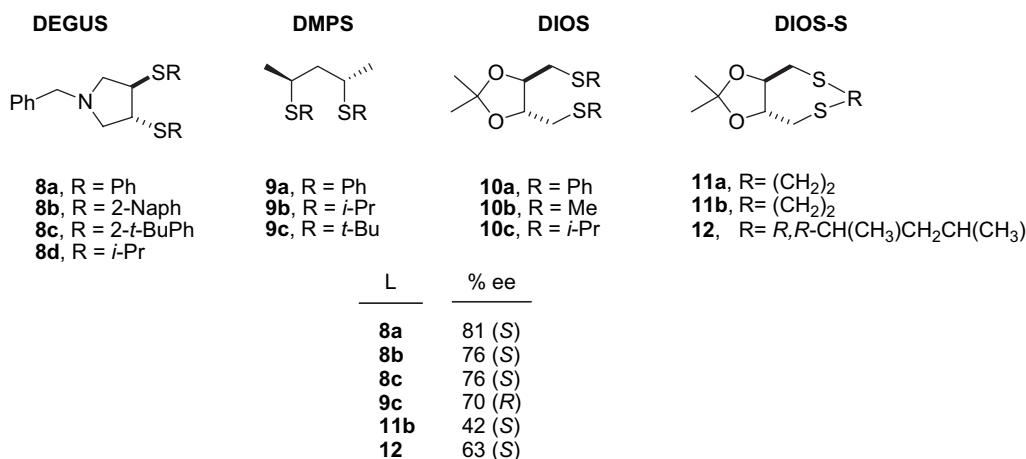


Fig. 1. Chiral dithioether ligands **8**–**12**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

The ligands **8**, **9** and **11** were also evaluated in palladium-catalysed allylic alkylation of *rac*-3-acetoxy-1-cyclohexene, obtaining 20–34% of e.e. The Pd/**9** systems were more active than Pd/**8** systems and the *butterfly*-type palladium complexes (with cyclic ligands **11**) gave the best enantioselectivities. The cyclohexenylallyl palladium complex [Pd(η^3 -cyclohexenyl)(**11b**)]PF₆ has also been prepared and studied in solution and in solid state [9].

The allylic alkylation of (*E*)-3-acetoxy-1-phenyl-1-propene (**13**) and (*E/Z*)-1-acetoxy-2-butene (**15**) catalysed by palladium complexes was studied using **8**, **9** and **11** chiral dithioether ligands (Fig. 2). Pd/**11** systems were very active and the most selective to linear isomers in the reaction with substrate **13**, whereas Pd/**9** systems gave the best enantioselectivities for the branched product. In the case of the later systems, a strong dependence on activity and selectivity of the nature of the S-substituent was observed. Using substrate **15**, excellent enantioselectivity was achieved with Pd/DMPS-*t*Bu (**9c**) [9].

The complexes [Pd(η^3 -1-PhC₃H₄)(**9b**)]PF₆, [Pd(η^3 -1-MeC₃H₄)(**9a**)]PF₆, and [Pd(η^3 -1-MeC₃H₄)(**9c**)]PF₆ were prepared and both the solution and solid-state species were analysed in order to understand the catalytic performance. For the latter complex, the most important catalytic fact was the preference to yield the branched product, and also there was good agreement between the diastereomeric ratio of the two Pd isomers (1.3/1) and the regioselectivity of the process (b/l-**16** = 1.6/1).

A series of chiral dithioethers containing rigid cyclopentane and heterocyclic analogues (**17**,**18**) were prepared and tested in the allylic alkylation of **5** (Fig. 3). The most efficient systems were the ligands containing pyrrolidine moieties (**17**), achieving enantiomeric excesses up to 90%. The authors, however, suggest that alkyl-3,4-bis-(aryltio)pyrrolidine derivatives behave as (N,S)-donating ligands more than (S,S)-donating ligands. Monothioethers **19**–**21** bearing benzylpyrrolidine groups were also considered as (N,S)-ligands because of the high e.e.'s obtained (79–90%). Only ligands **18** were considered (S,S)-homodonor ligands,

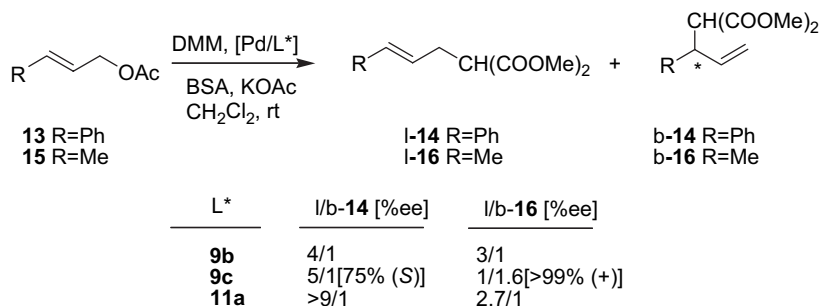


Fig. 2. Selected data of allylic alkylation of unsymmetrical substrates **13** and **15** using Pd/dithioether catalytic systems.

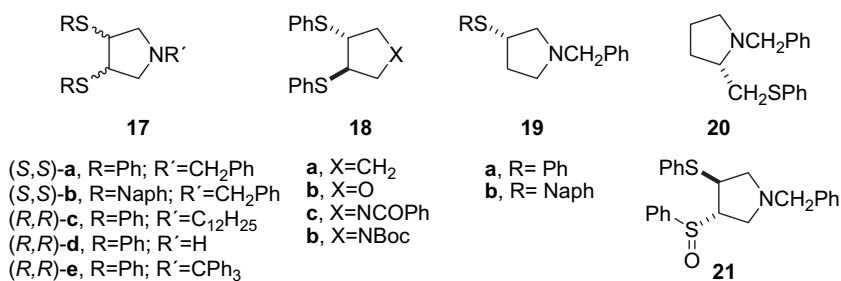
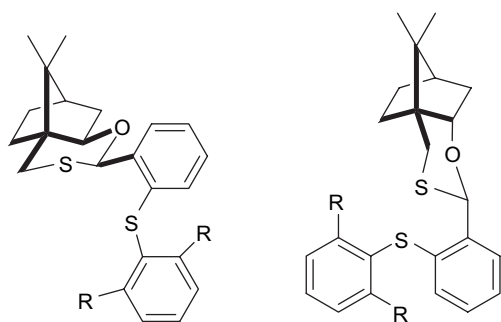


Fig. 3. Chiral heterocyclopentanyl thioethers.



22a, R= H [57% ee(R)] **23a**, R= H [49% ee(S)]
22b, R= Me [94% ee(R)] **23b**, R= Me [75% ee(S)]

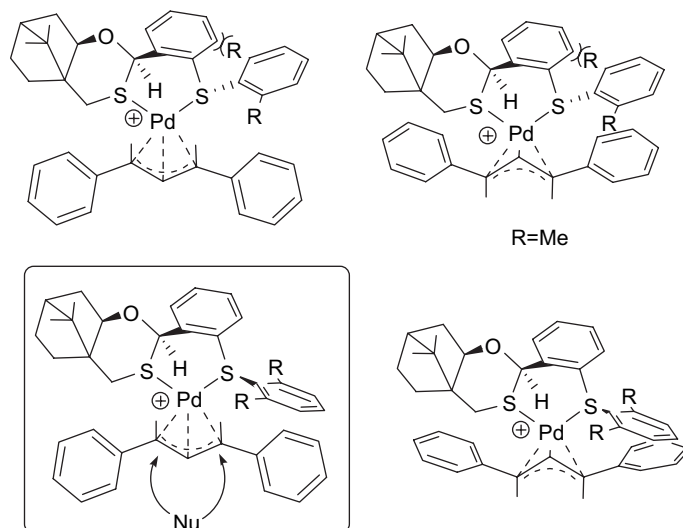
Fig. 4. Chiral sulfideoxathianes **22–23**. In brackets, the enantiomeric excesses of alkylated product **6** are shown.

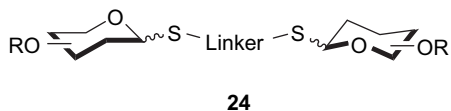
but low-to-modest enantioselectivities were attained in the alkylation [11].

Chiral sulfideoxathianes **22–23** have proved to be effective asymmetric inductors for palladium-catalysed allylic alkylation of substrate **5** with dimethyl malonate (Fig. 4).

Enantiomeric excesses up to 99% were achieved with ligand **22b**, using the same substrate and dimethyl and diethyl methylmalonates as nucleophiles. MO calculations give a rational explanation for the different catalytic behaviour between Pd/**22a** and Pd/**22b**. The palladium allyl optimised structure indicates that the steric hindrance of the methyl group on the phenyl ring in [Pd(η^3 -1,3-PhC₃H₃Ph)(**22b**)] favours one of the four possible isomers (Scheme 3). This result was related to the high enantioselectivity obtained using **22b** [12].

Sugar-based modular ligands (Fig. 5) provided low-to-good enantioselectivities (4–88% e.e.) in allylic alkylation of **5**, depending on the sugar, linker and protecting group used [13]. β -D-glucose, β -D-galactose,

Scheme 3. Possible isomers for [Pd(η^3 -1,3-PhC₃H₃Ph)(**22b**)].



	Sugar	Linker	R	%ee (S)
a	β -D glucose	ethanodithiol	OAc	64
b	β -D galactose	ethanodithiol	OAc	63
c	β -D glucose	ethanodithiol	OBz	66
d	β -D glucose	ethanodithiol	OPiv	86
e	β -D galactose	ethanodithiol	OPiv	88

Fig. 5. Bis-thioglycoside ligands **24**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

α -D-mannose or a glucosamine derivatives were used as sugar residues, 1,2-ethanodithiol, 1,3 propanodithiol, 1,2 benzyldithiol or 1,2 benzenedithiol as linkers and acetyl, benzyl, benzoyl and pivaloyl as protecting groups R. The (*S*)-alkylated product **6** (Scheme 2a) was obtained with high e.e.'s (86% at 293 K, 90% at 273 K) when the bis-thioglycoside contained β -D-glucose, 1,2-ethanodithiol and pivaloyl groups. In general, the best results were achieved using 1,2-ethanodithiol as a linker and β -D-glucose or β -D-galactose as the sugar base. The observed enantiomeric discrimination in the catalytic reaction seems to be related to the steric hindrance of protecting groups in sugars and not to the high stereocontrol of sulphur inversion by *exo*-anomeric effect [14].

2.2. (*S,S*)-heterodonor

2.2.1. Thioether–thiophosphines

C_1 -symmetric binaphthyl (*S,S*)-heterodonor ligands **25** were synthesised and tested in allylic alkylation of **5**, giving moderate-to-good enantiomeric excesses of alkylated product **6** (31% **25a**; 74% **25b**) at 273 K. The coordination to Pd(II) was investigated by NMR and the preliminary results suggest that both sulphur atoms are coordinated to the metal centre [15].

New chiral ferrocenyl thioether–thiophosphine ligands with a stereogenic plane were prepared and applied in allylic asymmetric reactions. These (*S,S*)-ligands proved to be efficient asymmetric inductors, giving good yields and excellent enantioselectivities (88–99% of e.e.). The level of enantioselectivity achieved with **26a–f** is amongst the best in allylic substitution reactions using (*S,S*)-heterodonor ligands [16] (Fig. 6).

3. (*S,X*)-donor bidentate ligands

Several types of heterodonor chiral ligands containing a thioether group have been developed for application in asymmetric allylic substitutions. Mixed

(*S,N*)- and to a lesser extent (*S,P*)-donor ligands have played a dominant role.

3.1. (*S,N*)-donor ligands

3.1.1. Thioether–oxazolines

Some of the most successful mixed (*S,N*)-donor ligands have been the thioglucose-derived ligands containing a chiral oxazoline moiety (**27a–d**) (Fig. 7). These ligands afforded e.e.'s between 90 and 97% in the palladium allylic alkylation of dimethyl malonate to **5**. The effects of the thiosugar substituents on enantioselectivity were mild. However, if a thiocyclohexyl group replaces the thiosugar (**27e**), the enantiomeric excess falls to 75% [17]. Ligand **27f**, related to **27e**, but generating a smaller chelate complex after coordination to Pd, produced higher enantioselectivity (81%) [18].

Uemura and co-workers also reported the synthesis of ligands **28** and **29** (Fig. 8). Their use as chiral auxiliaries in the Pd-catalysed asymmetric allylic alkylation reactions provided e.e.'s up to 90%. The best enantiomeric excess was obtained with ligand **28** for substrate 3-acetoxy-1,3-diphenyl-1-propene. These ligands were also applied in allylic alkylation of 3-acetoxy-1,3-dimethyl-1-propene and 3-acetoxy-1-cyclohexene with low enantioselectivities (e.e.'s up to 49%) [18].

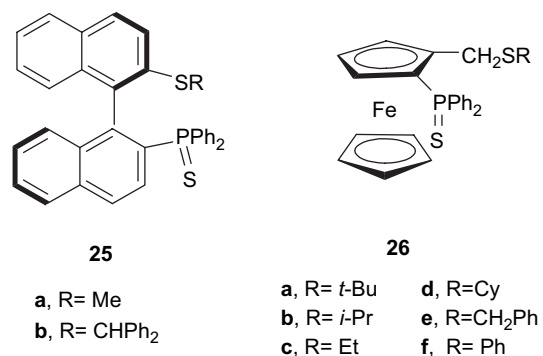


Fig. 6. Chiral thioether–thiophosphines.

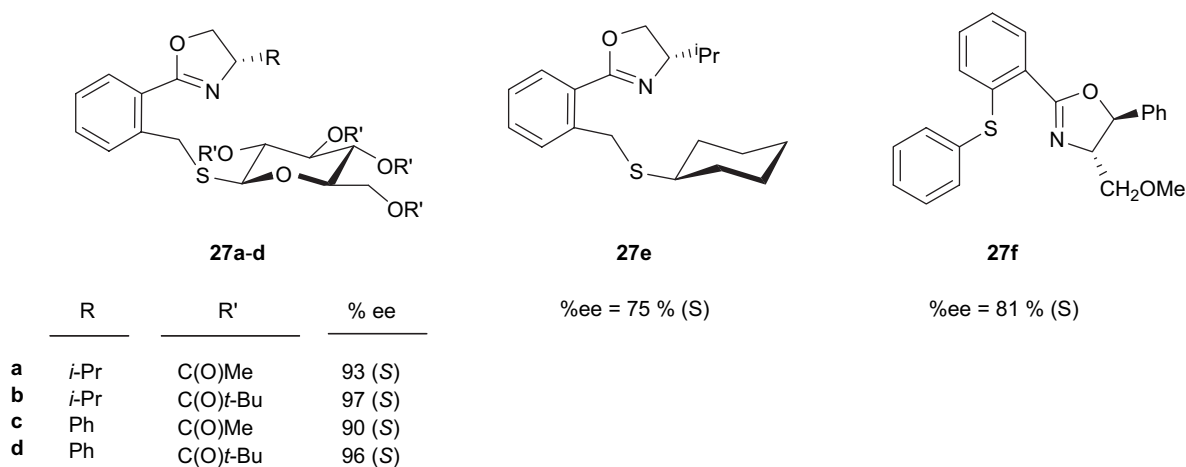


Fig. 7. Thioether–oxazoline ligands **27**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

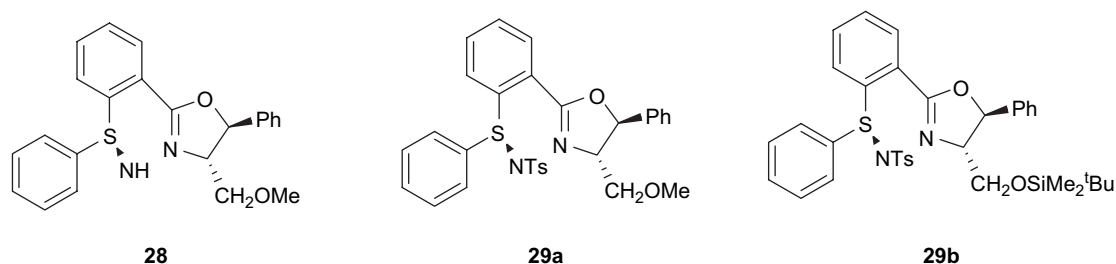


Fig. 8. Ligands developed by Uemura and co-workers.

Several groups have developed chiral ferrocenyl ligands for application in asymmetric catalysis. In particular, three different kinds of thioether derivatives of ferrocenyloxazolines have been tested in asymmetric allylic alkylations.

The first kind of ferrocenyloxazoline ligands contains the thioether group tethered to the oxazoline moiety (ligands **30**, Fig. 9). These ligands were applied in the model Pd-catalysed asymmetric allylic alkylation of **5** and the best asymmetric induction was obtained using **30b** [19]. This is probably due to the increase in tether length between the donor atoms, which coordinate to palladium and bring the asymmetric environment closer to the allylic ligand in the catalytic species.

The second kind of ferrocenyloxazolines applied to this process contains the thioether group attached to the cyclopentadienyl rings producing 1,2- or 1,1'-disubstituted ferrocene derivatives (ligands **31**–**33**, Fig. 10). These ligands were applied in the Pd-catalysed asymmetric allylic alkylation of **5** (Scheme 2a). The results indicated that the chiral stereocentre in the oxazoline moiety is necessary to obtain high enantioselectivities.

Therefore, ligands **31a**–**e**, **32** and **33** containing one chiral stereocentre on the oxazoline ring produced better enantioselectivities (e.e.'s up to 98%) than ligands **31f**–**h** bearing achiral oxazoline substituents (e.e.'s up to 72%) [20].

The NMR study of the 1,3-diphenylallyl palladium complexes **34** and **35**, containing the thioether–ferrocenyloxazoline ligands **31b** and **33b**, respectively, shows a mixture of two isomers. These studies reveal that the major structure is the M-type (Scheme 4), which is the same conformation as the X-ray solid-state structure for the palladium complex **34**. The structural data are in agreement with the absolute configuration

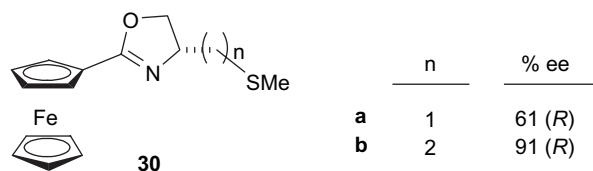
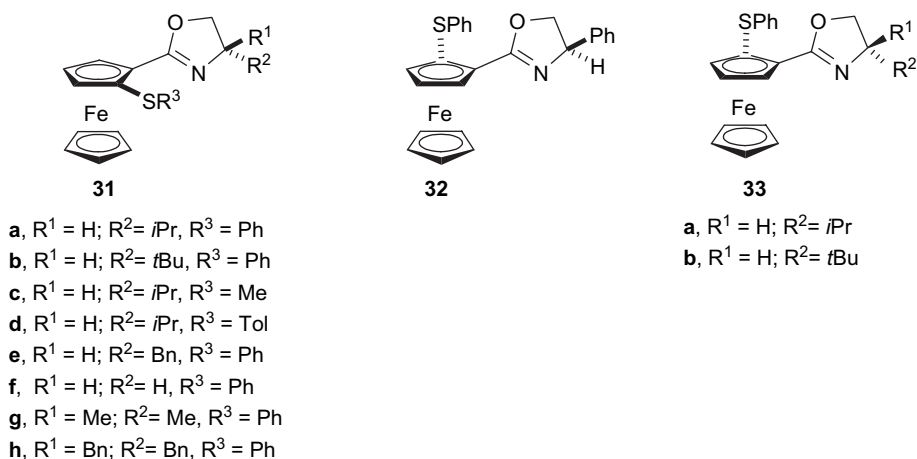
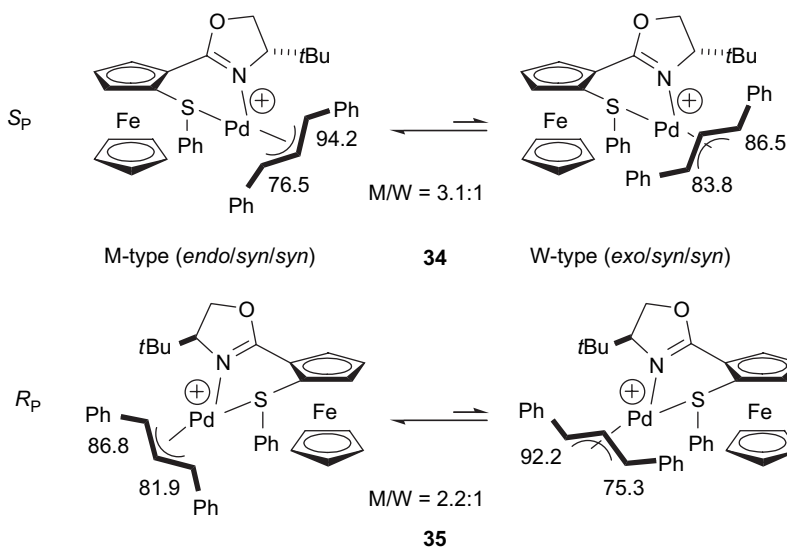


Fig. 9. Thioether–ferrocenyloxazoline ligands **30**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

Fig. 10. Thioether–ferrocenyloxazoline ligands **31–33**.Scheme 4. 1,3-Diphenylallyl palladium isomers for cations **34** and **35**. Figures indicate ¹³C chemical shifts (ppm) of the terminal allyl carbon atoms.

observed for the substitution product. Comparing diastereomeric excesses of the Pd intermediates and enantiomeric excesses of **6**, it has been observed that e.e.'s are higher than d.e.'s, thus M-**34** and W-**35** must react faster than W-**34** and M-**35**, respectively.

The third kind of ferrocenyloxazoline ligands developed for the Pd-catalysed asymmetric allylic substitution reactions are compounds **36** (Fig. 11). These thioether–ferrocenyloxazolines, without a stereogenic plane, afforded low-to-moderate enantioselectivities and poor yields [21]. These catalytic results indicate that the matching effect between stereocentre and stereogenic plane in ferrocene-based S,N-donor ligands may provide high levels of asymmetric induction in palladium-catalysed allylic substitutions.

Another group of ligands containing a stereogenic plane are ligands **37–39** (Fig. 12). These ligands are based on the [2,2]paracyclophane backbone containing both a stereogenic centre and plane. The best enantioselectivity was obtained with ligand **39** that contains the

	R	% ee
	a	20 (S)
	b	60 (S)
	c	75 (S)

36

Fig. 11. Thioether–ferrocenyloxazoline ligands **36**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

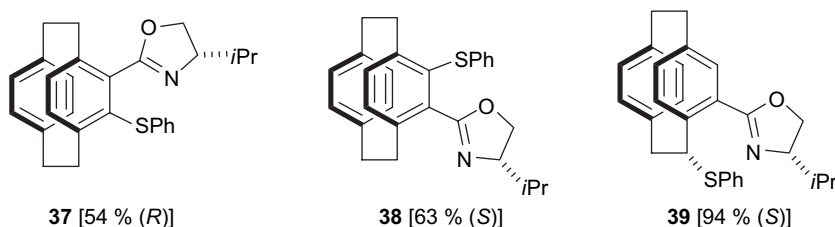


Fig. 12. [2,2]Paracyclophane-based thioether–oxazoline ligands **37**–**39**. In brackets, the enantiomeric excesses of alkylated product **6** are shown.

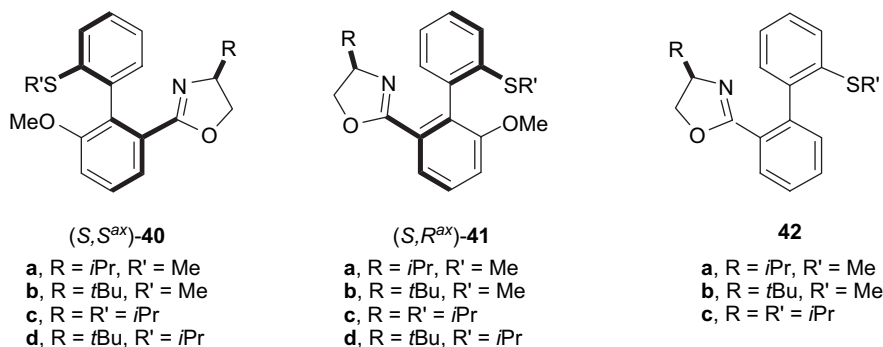


Fig. 13. Biphenyl-based thioether–oxazoline ligands **40**–**42**.

thioether groups attached to the alkyl chain backbone. It is interesting to note that the planar chirality controls the sense of enantioselectivity. Therefore, **37** with S_p planar chirality afforded the alkylated product in (*R*)-configuration, whereas **38** with R_p planar chirality provided the (*S*)-enantiomer [22].

Chiral oxazoline thioether ligands with an axis-fixed (**40** and **41**) and -unfixed (**42**) biphenyl backbone have been prepared and applied in alkylation of **5** catalysed by palladium complexes (Fig. 13). In general, the activity of the catalytic systems with **40** and **41** was low; however, with (*R*)-axial ligands, the activity improved. The best enantioselectivity (e.e.'s up to 81%) was obtained using ligand **42a**, which has a free rotation biphenyl axis [23].

Dithioether–bis(oxazoline) ligand (**43**) with an unfixed biphenyl backbone has also been tested in the Pd-catalysed allylic alkylation reaction (Fig. 14). In

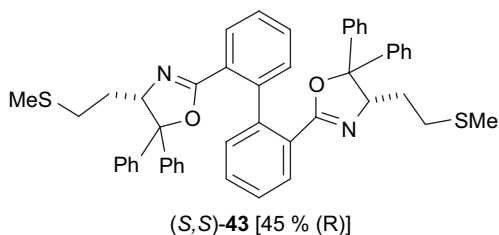


Fig. 14. Dithioether–bis(oxazoline) ligand **43**. In brackets, the enantiomeric excesses of alkylated product **6** are shown.

contrast to other analogous biphenyl derivatives, such as type-**42** ligands, the selectivity was lower (45% e.e. vs. 81% e.e.) [4d].

Gladiali and co-workers developed the thioether–oxazoline ligands **44** with chiral binaphthyl backbones as chiral auxiliaries for Pd-catalysed asymmetric allylic alkylation of 1,3-diphenylallyl esters (Fig. 15). In this reaction, the methyl-substituted ligand **44a** led to complete conversion in a few hours with e.e. up to 66%, whereas the *i*-propyl analogue **44b** produced a catalyst of poor activity (50% conversion within 22 h), which gave rise to a racemic product [24].

Recently, a new series of oxazoline-1,3-dithianes **45** have been developed and applied in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5** (Fig. 16). Enantiomeric excess depends strongly on the steric properties of the substituent in the oxazoline moiety, while the substituents on the dithianyl ring have no influence on the reaction outcome. Therefore,

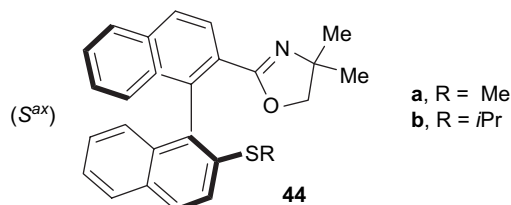


Fig. 15. Thioether–oxazoline ligands **44a** and **44b**.

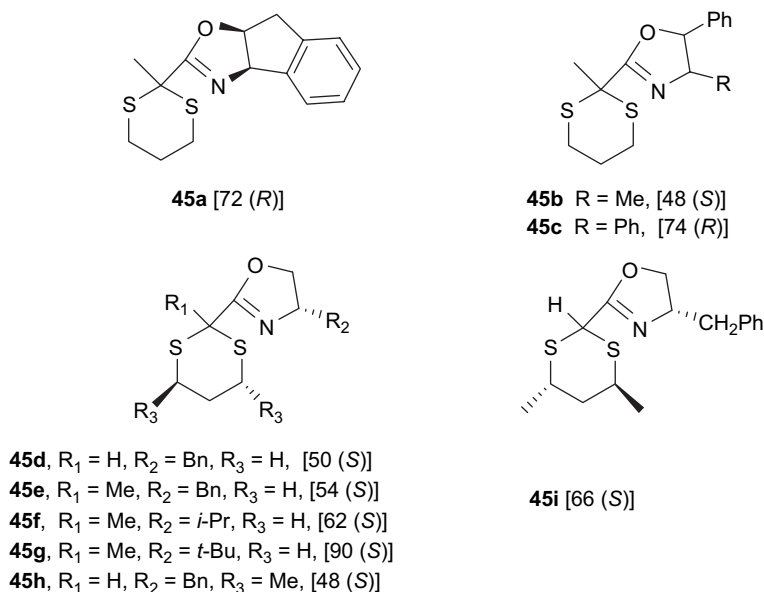


Fig. 16. Oxazoline-1,3-dithiane ligands **45**. In brackets, the enantiomeric excesses of alkylated product **6** are shown.

the best enantioselectivities were obtained with ligand **45g** (e.e.'s up to 90%) [25].

3.1.2. Thioether–pyridines

Chelucci and co-workers developed a series of epimeric phenylthiotetrahydroquinolines **46a** and **46b** as chiral auxiliaries for Pd-catalysed asymmetric allylic alkylation of **5** with e.e.'s up to 83% [26] (Fig. 17).

Chiral thioalkyl-pyridine ligands containing a (*R*)- (–)-fenchone-derived moiety (**47**) have proven to be effective asymmetric inductors in the palladium-catalysed allylic alkylation (Fig. 18). The results indicated an effect of the thioether substituent on enantioselectivity. Therefore, the best enantioselectivities were obtained with ligands that contain an ethyl or benzyl thioether substituent. Enantioselectivities were further increased using the (–)- or (+)-benzyl derivatives (up to 98%) by lowering the reaction temperature to 0 °C [27].

Palladium catalytic systems with thiophenyl-pyridine ligands **48–50** bearing a (+)-camphor-derived

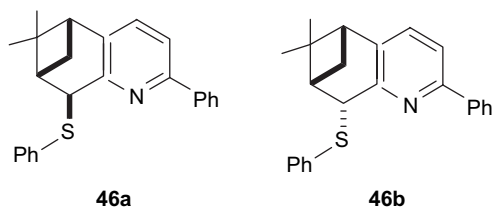


Fig. 17. Thioether–pyridine ligands **46**.

moiety were applied in the asymmetric allylic alkylation of **5** with dimethyl malonate (Fig. 19). The best enantioselectivity (e.e.'s up to 77%) was obtained with ligand **48** with a phenyl group at the 6-position of the pyridine ring [28].

The chiral ligand 1-(2-thiomethyl-1-naphthyl)isoquinoline **51** (Fig. 20) has been synthesised and tested in allylic alkylation of substrate **5** with poor success (total conversion in two weeks with 2% e.e.) [29].

3.1.3. Thioether–imines

A series of (*S*)-valinol (**52**), (*R*)-phenylglycinol (**53**) and (*S*)-*tert*-leucinol (**54**) derived imine ligands containing thioether group have been developed for the palladium-catalysed asymmetric allylic alkylation (Fig. 21). Excellent enantioselectivities were obtained (e.e.'s up to 96%) and the results indicated that enantioselectivity is not sensitive to electronic effects caused by substituents on the imine group, whereas the steric

	R	% ee
a	Me	53 (<i>R</i>)
b	Et	91 (<i>R</i>)
c	<i>i</i> -Pr	82 (<i>R</i>)
d	<i>n</i> -Pr	81 (<i>R</i>)
e	Bn	92 (<i>R</i>)

Fig. 18. Thioether–pyridine ligands **47**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

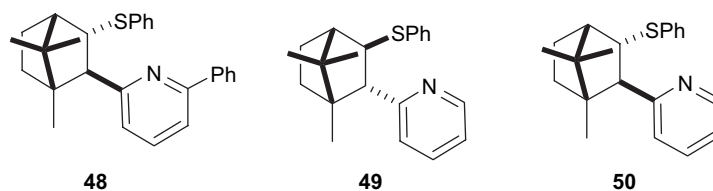


Fig. 19. Thioether–pyridine ligands 48–50.

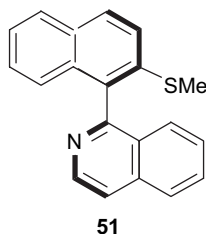


Fig. 20. Thioether–pyridine ligand 51.

bulk in *ortho*-position of the aryl group attached to the imine has a subtle effect. The bulkiness of the aryl substituent at sulphur (ligand **52k**) provided the highest enantioselectivity (96% e.e.). However, the replacement by a methyl group (ligand **52j**) only reduced the enantiomeric excess to 90%. The increase in steric hindrance of the backbone (ligand **54**) caused a decrease in both e.e.'s and yields [30].

In contrast to other chiral (S,N)-donor ligands, the authors have proved that for these systems, the nucleophilic attack on the allyl group is not *trans* to the sulphur atom, but *trans* to the imine donor, and so the enantioselectivity is controlled by the steric environment of the chelate ligand more than by electronic effects. The X-ray structure of complex [Pd(η^3 -1,3-PhC₃H₃Ph)(**52e**)]ClO₄ shows that the allyl group adopted a W conformation and the sulphur phenyl substituent is *trans* to the isopropyl group, avoiding an unfavourable interaction. In addition, one structure is present in solution,

showing a *syn/syn* allyl arrangement with a W conformation.

In 2003, Dai and co-workers developed the ferrocenyl–imino ligands **55** and **56** containing a stereogenic plane (Fig. 22) to be used in allylic alkylation of dimethyl malonate to **5** and 3-acetoxycyclohexene, affording 86 and 82% of enantioselectivity, respectively [31].

Recently, 2-iminoalkyl ferrocenyl derivatives were prepared and tested in asymmetric allylic alkylation, obtaining low-to-modest e.e.'s (15–72%) [32]. Better results (61–95% of e.e.) were obtained by Tokuda, employing sterically congested 2-iminothioethers to alkylate **5** with dimethyl malonate. The authors suggest that the M-type π -allyl palladium intermediate is favoured, since it minimizes the steric hindrance between substrate and ligand aromatic moieties; so the nucleophile preferentially attacks *trans* to sulphur, which explains the high enantiomeric excesses and the configuration of the alkylated product **6** [33].

3.1.4. Thioether–amines

A series of norephedrine-based thioether–amine ligands **57** (Fig. 23) were applied in the model allylic alkylation (Scheme 2a) with low-to-good enantioselectivities (9–72%). The best enantioselectivity was obtained with ligand **57f** with *tert*-butyl group in the thioether moiety [34].

In 2004, Braga and co-workers developed a series of modular thioether–oxazolidine ligands **58** and **59** for

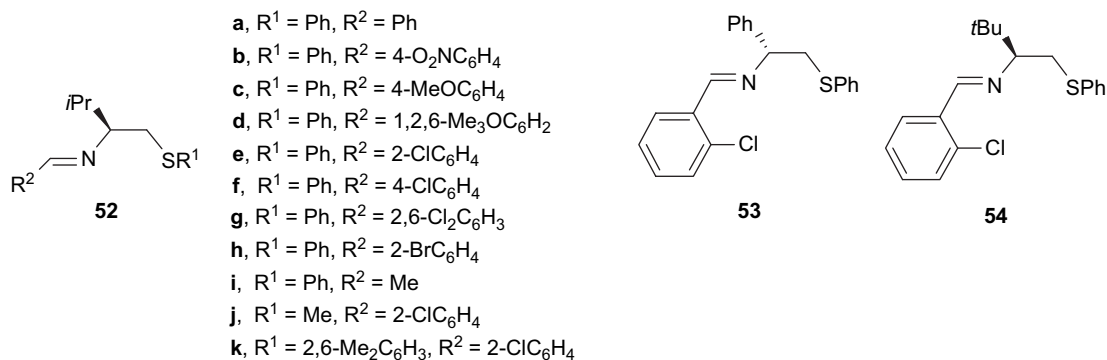
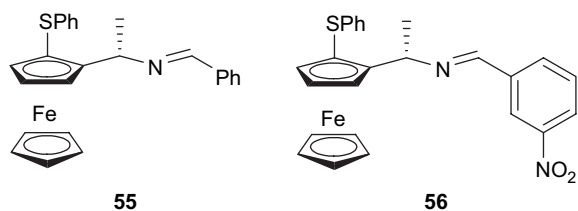
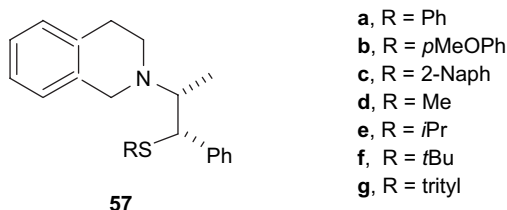


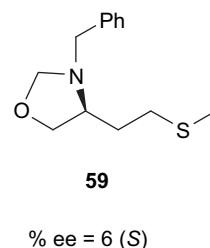
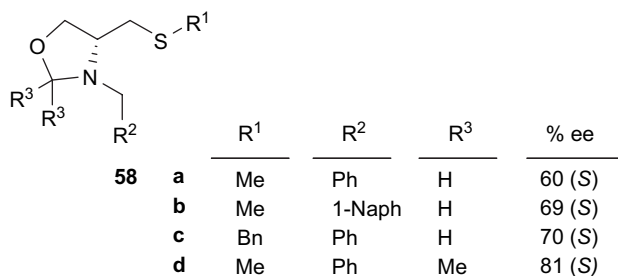
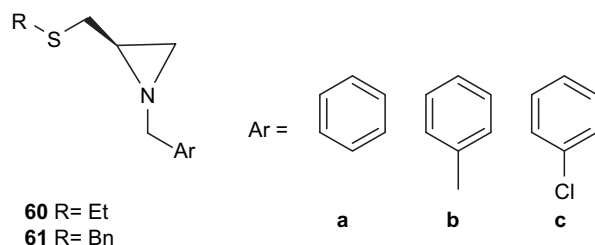
Fig. 21. Thioether–imine ligands 52–54.

Fig. 22. Ferrocenyl thioether-imine ligands **55** and **56**.Fig. 23. Thioether-amine ligands **57** derived from ephedrine.

allylic alkylation of **5** (Fig. 24). By carefully selecting the ligand components, they obtained an enantioselectivity of 81% (*S*) with ligand **58d**. This ligand is an analogue of ligand **58a**, but has more steric crowding in the oxazolidine ring. Ligand **59**, which generates a larger bite angle after coordination to palladium, gave the lowest enantioselectivity (e.e.'s up to 6% (*S*)) [35].

The same authors also reported the synthesis of thioether-aziridine ligands for application in the Pd-catalysed asymmetric allylic alkylation (Fig. 25). The catalytic results indicated that the influence of the benzyl group attached to nitrogen is important in obtaining high asymmetric induction and the substituent at the sulphur atom has a small effect in the conversion. Therefore, the best enantioselectivity (up to 99% (*S*)) was obtained with ligand **61c**, which contains an electron-withdrawing benzyl group attached to nitrogen [36].

Recently, Anderson and co-workers reported the synthesis of a series of ferrocenyl thioether-amine

Fig. 24. Thioether-oxazolidine ligands **58** and **59**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.Fig. 25. Thioether-aziridine ligands **60** and **61**.

ligands **62** for the allylic alkylation of *rac*-3-acetoxy-1,3-diphenyl-1-propene (Fig. 26) with low-to-moderate enantioselectivities. The best e.e.'s (up to 59%) were attained with methyl substituents in the thioether and amine groups (ligand **62c**) [37].

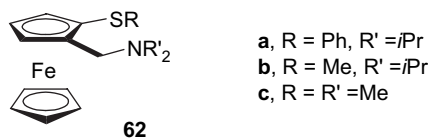
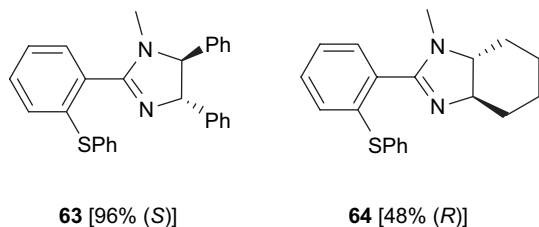
3.1.5. Thioether-imidazolines

Two thioether-imidazoline ligands, **63** and **64**, have been developed and applied in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to 3-pivaloxy-1,3-diphenylpropene (Fig. 27). The best enantioselectivity was obtained with ligand **63** (up to 96%) [38].

3.2. *S,P*-donor ligands

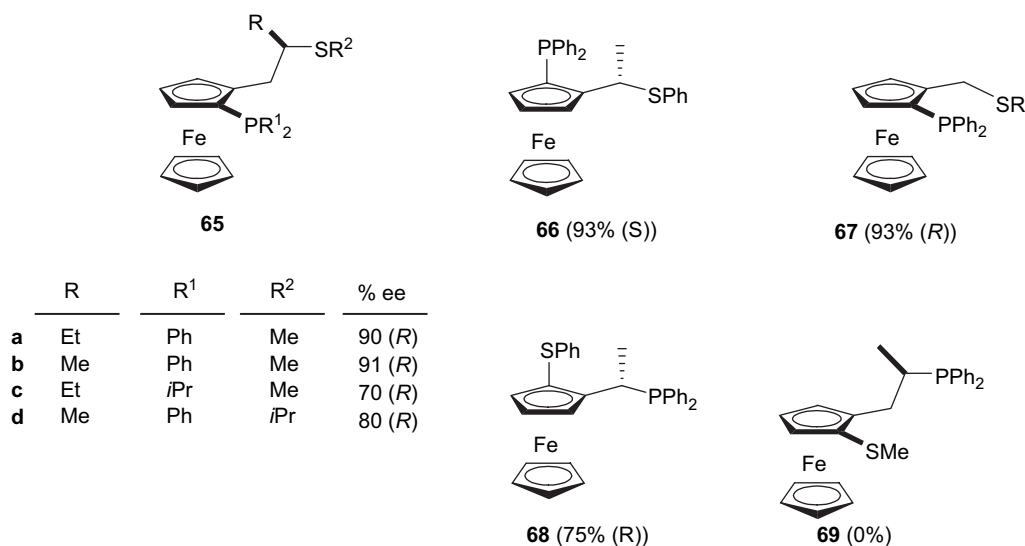
3.2.1. Thioether-phosphines

The catalytic results using ferrocenylphosphine-thioether ligands **65–69** (Fig. 28) indicated that enantioselectivity is better when the phosphine group is attached to the Cp ring (ligands **65–67**) rather than when it is attached to the thioether unit (ligands **68** and **69**). Furthermore, by comparing ligands **65–67**, it can be seen that enantioselectivities are not affected by the presence of an additional stereogenic unit or by the length of the thioether chain. The structural studies of a 1,3-diphenylallyl palladium complex containing ligand **65a**, [Pd(η^3 -1,3-PhC₃H₃Ph)(**65a**)]PF₆, indicate that the small substituents on thioether groups favour

Fig. 26. Ferrocenyl thioether–amine ligands **62**.Fig. 27. Thioether–imidazoline ligands **63** and **64**. In brackets, the enantiomeric excesses of alkylated product **6** are shown.

the nucleophilic attack in the *cis* position to the S-donor moiety [31a,39].

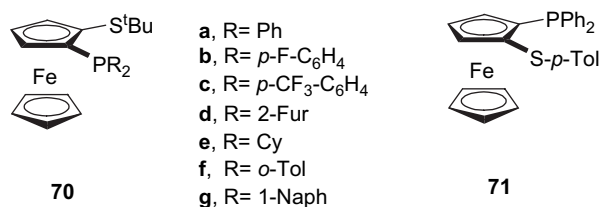
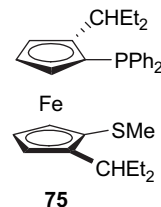
Carretero and co-workers developed a new series of successful ferrocenyl thioether–phosphine ligands **70–71** (Fig. 29) for Pd-catalysed asymmetric allylic substitution of **5** (e.e.'s up to 97%). Enantiomeric excess depends strongly on the steric properties of the substituent in the thioether moiety and the electronic properties of the phosphine group. Therefore, for high enantioselectivities, a bulky group on the thioether moiety and electron-withdrawing substituents on the phosphorus are needed [40].

Fig. 28. Ferrocenyl thioether–phosphine ligands **65–69**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

The ferrocenylphosphine–thiosugar ligand **72** (Fig. 30), with several chiral sources, afforded an e.e. of 88% in the palladium allylic alkylation. However, when the thiosugar moiety is the only source of chirality on (S,P)-ligand (**73a,b**, Fig. 30), only asymmetric inductions of 64% (*R*) and 53% (*R*), respectively, were reached. Good activities but low enantiomeric excesses were obtained with a similar thioether–phosphine ligand using a chiral norborneol fragment (**74**). The authors attributed their performance to the effects of chain size between the sulphur donor and the kind of stereogenic unit [41].

The 1,3-diphenylallyl palladium complexes [Pd(η^3 -1,3-PhC₃H₃Ph)(**74**)]BF₄, [Pd(η^3 -1,3-PhC₃H₃Ph)(**73a**)]BF₄ and [Pd(η^3 -1,3-PhC₃H₃Ph)(**73b**)]BF₄ were obtained as a mixture of isomers. Dynamic studies indicate that the η^3 – η^1 – η^3 isomerisation occurs by dissociation of the carbon *trans* to sulphur and *cis* to phosphorus, in contrast to the *non*-substituted allyl complex [Pd(η^3 -1,3-C₃H₅)(**74**)]BF₄, due to the steric hindrance between the PPh₂ group and the phenyl allyl substituent. From these results, the authors suggest that this isomerisation process is sterically, and not electronically, controlled. For ligand **72**, the study of corresponding 1,3-diphenylallyl palladium complex indicates that the nucleophilic attack takes place *trans* to the phosphine moiety.

The (P,S)-hybrid ferrocenyl ligand **75** was developed by Kang and co-workers and used as chiral auxiliary in the model Pd-catalysed asymmetric allylic alkylation (Scheme 2a), with moderate enantioselectivity (38% e.e.) (Fig. 31) [42].

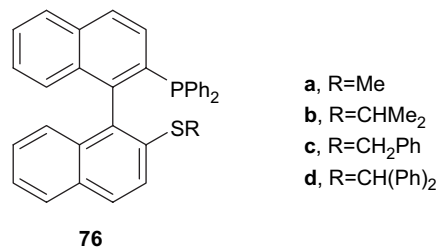
Fig. 29. Ferrocenyl thioether–phosphine ligands **70**–**71**.Fig. 31. Chiral thioether–phosphine ligand **75**.

The thioether–phosphine ligand **76a** (Fig. 32) with a binaphthyl backbone was applied in asymmetric allylic alkylation of dimethyl malonate to **5** with enantioselectivity of 91% [43a]. Later, Gladiali and co-workers proved the ligand **76b** in the same reaction obtaining 60% of e.e [43b].

In 2004, Zhang and Shi tested the ligands **76a**–**d** in asymmetric allylic alkylation of **5** (Scheme 2a) achieving enantiomeric excesses up to 96% (**76a**). The authors observed an interesting reversal of the absolute configuration in the alkylated product **6** by changing of steric bulkiness of ligand **76** [43c].

A series of (*S*)-proline-derived phosphine ligands bearing thioether functionalities (**77**–**79**) were prepared and proved in palladium-catalysed asymmetric allylic alkylation, affording enantioselectivities from 31 to 88%, depending on the steric bulkiness of the sulphur atom substituents (Fig. 33) [44].

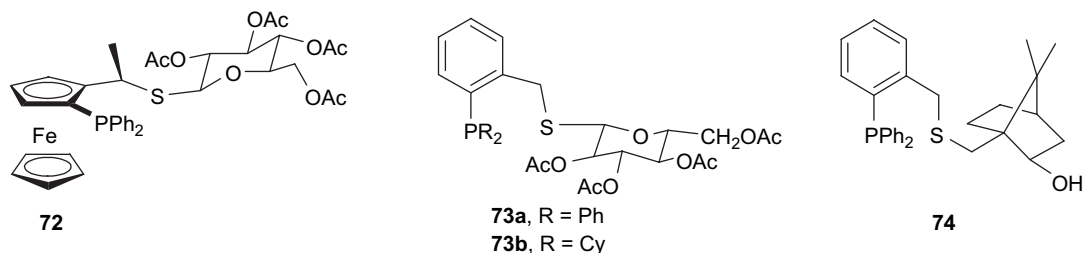
Chiral phosphinoxathiane ligands **80**–**82** have been successfully used in alkylation and amination reactions of substituted allyl acetates (Fig. 34). The chiral norbornane-based phosphinoxathianes provided moderate-to-excellent levels of enantioselectivity (52–94%) in allylic alkylation of **5** with dimethyl malonate and enantioselectivities of 13–85% with low regioselectivities to the branched product in the allylic alkylation of substrate **13** (Fig. 2). The model allylic amination reaction (Scheme 2b) was also explored with these chiral phosphinoxathianes, and asymmetric inductions of 46–86% e.e. were achieved [45].

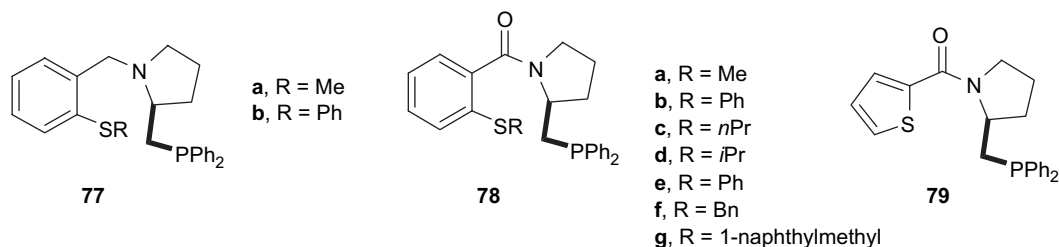
Fig. 32. Thioether–phosphine ligands **76**.

Chiral phosphinoxathiolanes, also norbornane derived, were tested in the same catalytic reactions and conditions. Enantiomeric excesses up to 82 and 66% for alkylation and amination reactions, respectively, were attained using these new ligands [46].

Additionally, Nakano and co-workers developed a new xylofuranose-based phosphinoxathiane ligand, **83**, that provided high enantioselectivities (e.e.'s up to 91%) in the Pd-catalysed asymmetric allylic substitutions of **5** (Fig. 35) [47].

Recently, Molander and co-workers developed a series of cyclopropane-based phosphine–thioether ligands (**84**–**86**) for the palladium-catalysed allylic alkylation of **5** with dimethyl malonate (Fig. 36). Varying the ligand substituents on the phosphorus, sulphur and carbon chain revealed that **86c** provided the optimal configuration for this reaction, producing high yield and enantioselectivity [48].

Fig. 30. Chiral thioether–phosphine ligands **72**–**74**.

Fig. 33. Chiral thioether–phosphine ligands **77–79**.

3.2.2. Thioether–phosphites

To date, two families of thioether–phosphite ligands have been applied to this process.

Thioether–phosphite ligands with furanoside backbone **87** have been applied in the palladium-catalysed allylic alkylation and amination substitution reactions providing up to 58 and 67% e.e., respectively (Fig. 37). The catalytic results reveal that the thioether moiety hardly affects the enantioselectivity. It is thus assumed that the nucleophilic attack takes place *trans* to the thioether group [49].

The allylic alkylation reaction of unsymmetrical substrates catalysed by palladium-containing binaphthylphosphite–thioether ligand **88** as chiral inductor was investigated. Yields up to 70% were reached, but in all cases, both the regio- and enantioselectivities were moderate [50] (Fig. 38).

3.2.3. Thioether–phosphinites

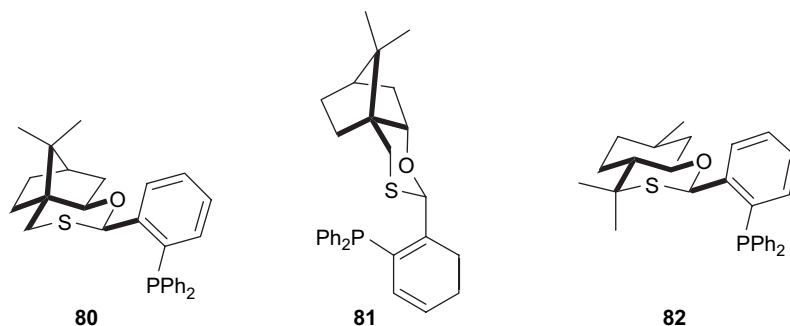
The first family of mixed thioether–phosphinite ligands (**89–95**) was developed by Evans and co-workers, and was successfully applied in enantioselective palladium-catalysed allylic substitutions of several acyclic and cyclic substrates (Fig. 39) [51]. Electronic and steric effects of the ligands on the enantioselectivity of the allylic alkylation reaction (Scheme 2a) were studied by varying sulphur, backbone and phosphorous substituents. The best results were obtained with **89a**

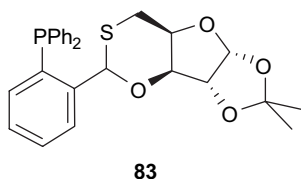
and **90a**, containing bulky alkyl substituents in both backbone and thioether group. In allylic alkylation of **5** with dimethyl malonate, **89a** and **90a** afforded enantiomeric excesses of 90 and 98%, respectively. In contrast, **89a** was superior in the model allylic amination reaction, giving 99% e.e. A variety of other heteroatom nucleophiles in allylic substitution of **5** were investigated, but low yields and enantioselectivities were attained.

The regioselective allylic alkylation of trisubstituted propenyl acetates was also explored with **89a** and **90a**, affording high yields and asymmetric inductions up to 94% of e.e. In addition, this family of ligands was tested in the palladium-catalysed allylic substitution of cyclic substrates. Ligand **91a** afforded enantiomeric excesses of 91–97% in quantitative yields in the alkylation and amination of several cycloalkenyl acetates [51].

Related to these ligands, two allylic palladium intermediates have been characterised, in both the solution and solid state, **96** and **97** containing ligands **90a** and **89a** and the 1,3-diphenylallyl and cyclohexenyl groups, respectively (Fig. 40). The X-ray diffraction data indicate a stronger *trans* influence of the phosphinite group [52].

In solution, **96** exists as a mixture of two diastereomers, in a 2.3:1 ratio, due to the relative position of the central allylic carbon and the *tert*-butyl substituent

Fig. 34. Chiral thioether–phosphine ligands **80–82**.

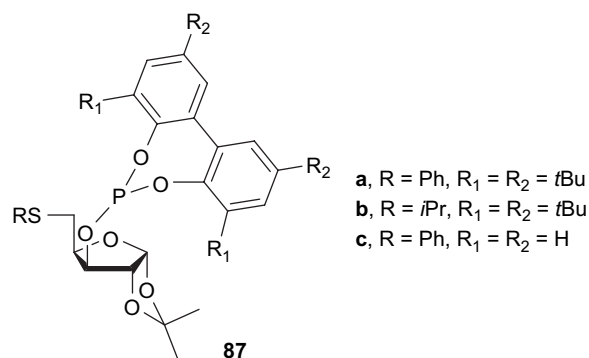


83

Fig. 35. Chiral thioether–phosphine ligand **83**.

on the sulphur moiety. The major isomer was assigned to an *exo* arrangement (both groups pointing in the same direction), which is consistent with the structure observed in solid state. In contrast to **96**, NMR data of complex **97** reveal the presence of mainly one allyl palladium isomer (ratio > 98:2), consistent with the X-ray structure.

Recently, a series of thioether–phosphinite ligands (**98**) with a furanoside backbone have been tested in the Pd-catalysed allylic substitution reactions of several acyclic and cyclic substrates (Fig. 41). The results indicated that enantioselectivity depends strongly on the steric and electronic properties of the substituents in the thioether moiety and the substrate structure. By carefully selecting the ligand parameters, good enantioselectivities were obtained for hindered linear substrates (e.e.'s up to 95%) and for unhindered cyclic substrates (e.e.'s up to 91%). The strong *trans* influence of the phosphinite moiety, together with the effect of the thioether moiety on enantioselectivity, confirms that the nucleophilic attack takes place on the allyl terminus located *trans* to the phosphinite moiety. This



87

Fig. 37. Furanoside thioether–phosphite ligands **87**.

contrasts with related thioether–phosphite ligands **87**, where the nucleophilic attack was *trans* to the thioether group [53].

Phosphinite β -thioglycosides have been prepared and evaluated in allylic alkylation of **5** under Trost conditions. The alkylated product **6** was obtained in high yield in all cases, but with variable e.e.'s (60–92%), depending on the substituent at the sulphur atom. The bulky *t*-butylthioglycoside derivative was also an efficient inductor in the amination reaction (Scheme 2b) affording 94% of e.e. [54].

3.2.4. Thioether–phosphinamidites

Recently, Chan and co-workers developed a series of ferrocene-based thioether–phosphinamidite (Fig. 42), and successfully applied them in the asymmetric allylic

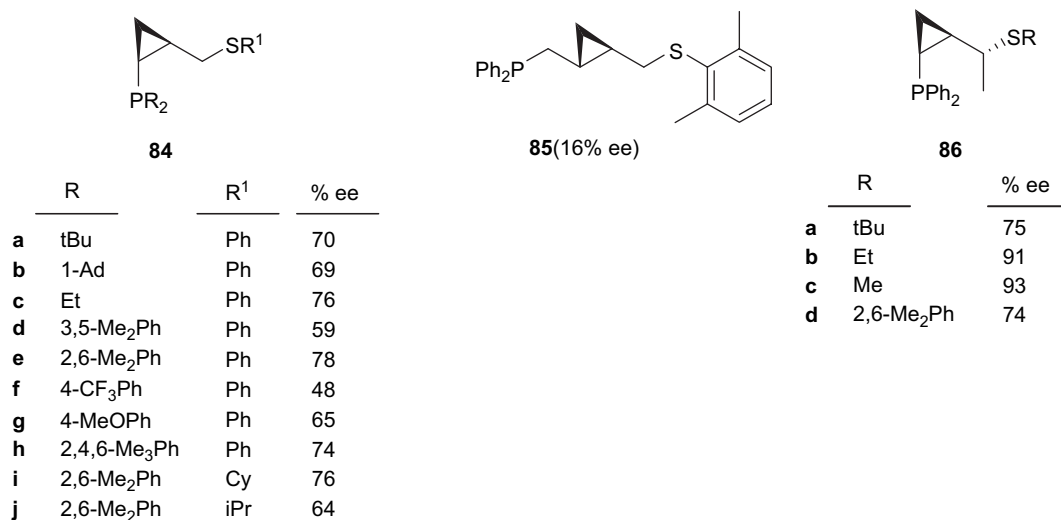
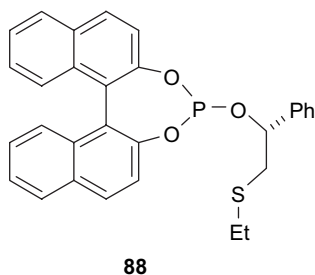


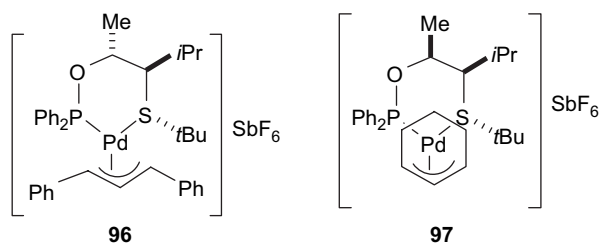
Fig. 36. Thioether–phosphine ligands **84–86**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

Fig. 38. Thioether—phosphite ligand **88**.

substitution of **5** (e.e.'s up to 93%). A mild effect of the thioether substituent on enantioselectivity was observed; however, activities are better when a small ethyl substituent in the thioether group is present [55].

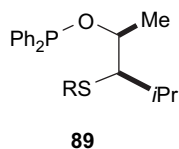
3.3. Other mixed thioether ligands

Other mixed thioether ligands such as (S,Se)-donor [39,56] and (S,X)-polydentate donor ligands [27,28] were applied to this process, but only the tridentate chiral pyridine—dithioether ligands **100a–e** (Fig. 43) provided good enantiomeric excess (78–85% e.e.) [27].

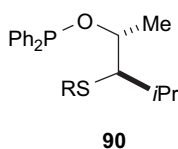
Fig. 40. Allyl palladium complexes **96** and **97**.

4. Final remarks

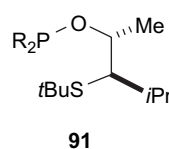
Chiral thioethers are an alternative coordinative group to be successfully applied in asymmetric allylic substitution. Particularly, the use of the chiral heterodonor ligands containing sulphur functionalities is a highly efficient strategy to control the enantioselectivity through the different electronic effects of the donor atoms. Furthermore, the electronic and steric properties of these kinds of ligands can be easily modified by the groups attached at the sulphur atom, modulating in this way, the strength of the M—S bond and changing the thioether *trans* influence in metal complexes. In fact,



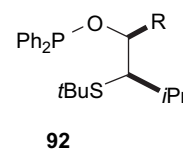
- a, R = *t*Bu
- b, R = Ph
- c, R = 4-MeOPh
- d, R = 2,3,5,6-F₄Ph
- e, R = 4-*t*BuPh
- f, R = 3,5-Me₂Ph
- g, R = 3,5-*t*Bu₂Ph
- h, R = 1-Naph
- i, R = 2-Naph
- j, R = Bn
- k, R = Cy



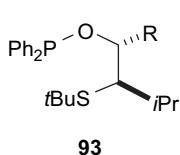
- a, R = *t*Bu
- b, R = Ph
- c, R = 4-MeOPh
- d, R = 2,3,5,6-F₄Ph
- e, R = 4-*t*BuPh
- f, R = 3,5-Me₂Ph
- g, R = 3,5-*t*Bu₂Ph
- h, R = 1-Naph
- i, R = 2-Naph
- j, R = Bn
- k, R = Cy



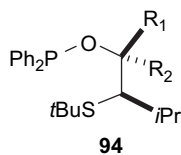
- a, R = α -Naph
- b, R = 4-MeOPh
- c, R = 2-MeOPh
- d, R = 4-FPh
- e, R = 3,5-(CF₃)₂Ph
- f, R = 3,5-Me₂Ph
- g, R = Cy



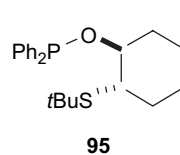
- a, R = Ph
- b, R = *i*Pr



- a, R = Ph
- b, R = *i*Pr



- a, R₁ = R₂ = H
- b, R₁ = R₂ = Me

Fig. 39. Thioether—phosphinite ligands **89–95**.

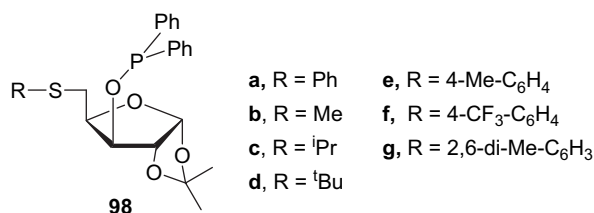


Fig. 41. Sugar-based thioether–phosphinite ligands **98**.

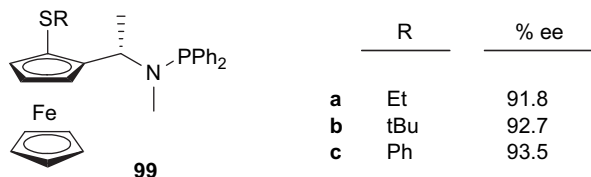


Fig. 42. Thioether–phosphineamidite ligands **99**. This figure also shows the enantioselectivities obtained in the Pd-catalysed asymmetric allylic alkylation of dimethyl malonate to **5**.

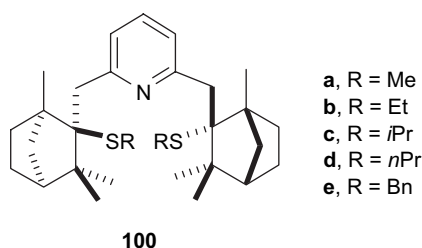


Fig. 43. Tridentate pyridine–dithioether ligands **100**.

different catalytic performances have been obtained due to the variety of electronic combinations of (S,X)-ligands.

An additional feature is the creation of a new chiral sulphur centre upon thioether complexation, which represents an advantage, since it generates a chiral pocket nearer to the metal centre. Nevertheless, the difficulty in controlling the sulphur inversion and therefore, the number of diastereomeric complexes in solution, is the reason for the enantioselectivity erosion in asymmetric reactions using metal–thioether catalysts. However, this problem can be solved by appropriately tuning the ligand, as has been shown in this review.

Acknowledgements

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