Evolution of phosphorus-thioether ligands for asymmetric catalysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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In the early 1990s chiral P–thiother ligands emerged as promising ligands in the field of asymmetric catalysis, with the development of many P-thioether ligand families. However, only few of them have shown a broad reaction and substrate scope. So, compared with other heterodonor ligands such as the widely studied P–N ligands, their impact in asymmetric catalysis was not realised until recently. This has been mainly attributed to the difficulty of controlling the configuration at the sulfur atom when coordinated to the metal. More recently, it has been found that this problem could be solved by a rigorous choice of the ligand scaffold, a process usually aided by mechanistic studies. This allowed the recent discovery of new P–thioether ligand families with a broader versatility, both in reactions and in substrate/reagent scope. This feature article aims to highlight on those new P-thioether ligand libraries and the relationship between structure and catalytic performance.

Introduction

Many pharmaceuticals, agrochemicals, flavours and natural products chiral in nature are marketed in enantioenriched form. The development of efficient synthetic procedures for their preparation is an important field in organic chemistry. Asymmetric catalysis is one of the most powerful approaches to achieve this goal in a sustainable way, and the research for catalysts depicting improved activity and selectivity is nowadays a very active field.[1] The performance of chiral metal-catalysts depends, to a large extent, on the adequate selection of the chiral ligands that make up the catalyst.[1,2] A common approach to designing efficient catalysts is the use of modular ligands that allow a systematic variation of the ligand parameters that influence the catalysts performance, creating the so called ligand libraries.[1,2] Among the thousands of chiral ligands developed, a few stand out for their versatility and high efficiency in several mechanistically unrelated asymmetric reactions. Broad reaction scope and broad substrate/reagent scope are highly desirable characteristics in catalytic ligands, since they minimize the overall time consumed for ligand discovery and preparation. The most efficient and broad-scope ones, often designated as *privileged ligands*, derive from a few core structures. BINOL derivatives, BINAP, the salens, bisoxazolines, tartrates and TADDOLs, cinchona alkaloids, DuPhos phospholanes, PHOX, DSM phosphoramidites, Josiphos families, Trost and Reetz ligands are representative examples.[3] These ligand families have been applied successfully in industrial reactions such as hydrogenations, aldol reactions and asymmetric allylic substitutions among others.[3] Most of them are of bidentate homodonor type, and generally possess C_2 symmetry. Although they have shown to be effective in different reaction types, the substrate/reagent scope for some processes is still rather limited. Research in asymmetric catalysis for the seek ideal, all-purpose ligands, commonly starts by evaluating these privileged structures followed by structural optimization using mechanistically or theoretically gathered knowledge on the relationship between structure and catalytic performance.

In the last decades, heterodonor ligands containing dual, strongly and weakly donor heteroatom pairs, have emerged as an increasingly used ligand class, since the different electronic and steric properties of these heteroatoms are powerful stereocontrol elements.[2,4] The two functionalities also facilitate catalyst optimization, since both functionalities can be independently modified for improved performance. Among them, P–N ligands have been the most commonly used, P–oxazoline being the most studied combination.[4] P–thioether ligands have also attracted attention since they take advantage of the electronic disparity between the two donor atoms: sulphur is a poor σ-donor and a poor π-acceptor in comparison with the better σ-donor and π-acceptor nature of phosphorus.[5] In addition, the thioether group adds the advantage of higher chemical stability when compared with oxazolines and phosphines. The early successful work by Pregosin[6] and Evans[7], among others[5], with P–thioether ligands in Pd-catalysed allylic alkylation and other asymmetric reactions put the focus on this type of ligands and spurred their development. Since then, many P–S ligands have been developed, but only a few of them have shown to be successfully applicable to mechanistically unrelated asymmetric reactions and with high substrate/reagent scope.[5g] Compared to P–N ligands, the lower impact of P–S analogues in metal-catalysed asymmetric reactions has been mainly attributed to the difficulty to control the diastereomeric at sulphur mixtures formed in solution. Some pertinent reviews describing the use of these first generations of P–thioether ligand families in asymmetric catalysis have appeared in the literature.[5] However, only advances prior to 2011 are covered.[5e,g]

After 2011, it has been revealed that the configuration at the thioether sulphur atom can be controlled by the

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correct choice of the ligand scaffold, and this has led to the recent discovery of P–thioether ligand families with broader versatility, both in reaction types and in substrate/reagent scope. Over this period, catalyst design has also been aided by advances in computational DFT studies, both from the methodological (new functionals, better suited for the description of metalloorganic species have been developed) and the practical (real systems can be now treated at full DFT level in a considerable reduced time) perspectives. Remarkable progress has also been made in tandem reactions, which have been efficiently applied to prepare chiral (poly)carbo- and heterocyclic compounds. In addition, these P–S thioether-based ligands are readily available from inexpensive sources and are highly stable, allowing easy storage and handling. At this point, it seems important to summarize and organize the latest advances in catalytic results, mechanistic studies and synthetic applications, and to delineate the possibilities of future research in the field. In this context, this feature article discusses the new P–thioether ligand libraries that appeared since 2011, their applicability, and the relationship between structure and performance. For each ligand family we will first offer an overview of the historical context at the time of the discovery of the ligand library.

Ligand design and application in metal-catalysed asymmetric reactions

1,1'-Binaphthalene-based ligands have been used in asymmetric catalysis for more than three decades, with BINAP being the leading ligand in this family.[3d,8] Since the pioneering work of Hayashi et al. in Pd-catalysed asymmetric hydrosilylation with 2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl, heterodonor versions of BINAP have also proved to be widely applicable to asymmetric catalysis.[9] In 1994, Gladiali et al. reported the first application of chiral heterodonor P–S ligands in asymmetric catalysis. They applied phosphine-thioether ligands **L1** (R= Me and ^{i}Pr), analogue to (*R*)-BINAP, to hydroformylation and transfer hydrogenation with moderate success (Figure 1).[10] In 1995, Kang et al. reported the application of the P–S ligand **L1** (R= Me) in the Pd-catalysed allylic alkylation of the benchmark substrate **S1** with dimethyl malonate (Figure 1) with more success (65% yield and 91% ee).[11] The group of Shi et al. could increase the catalytic performance of **L1** (R= Me) (96% yield and 96% ee) after optimizing the conditions of use.[12]

Ferrocene-based compounds have also been widely employed as ligands in asymmetric catalysis. In 1996, the groups of Pregosin[6] and Togni[13] were the first to develop heterodonor P–S ferrocene-based ligands (Figure 2, ligands **L2**-**L4**). Ligand **L2**, with a thioglucoside moiety, provided 88% ee in the alkylation of **S1** with dimethyl malonate as nucleophile.[6]

After these promising early results, chiral P–thioether ligands attracted increasing interest and examples of their

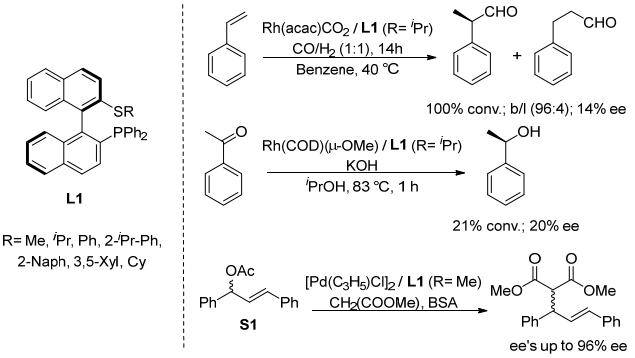


Figure 1 1,1'-Binaphthalene-based phosphine–thioether ligands **L1** and their application in the asymmetric hydroformylation of styrene, transfer hydrogenation of acetophenone and alkylation of **S1** using dimethyl malonate as nucleophile.

application in asymmetric catalysis appeared.[5] These new P–S ligands encompass diverse ligand backbones and stereogenic elements, as well as different distances between the two donor functionalities.

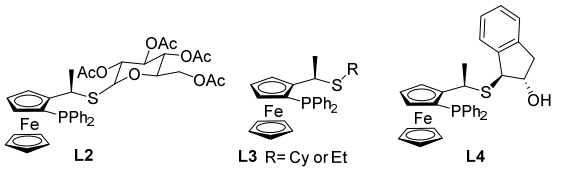
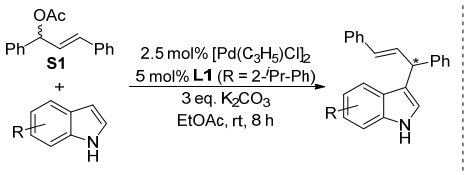


Figure 2 First ferrocene containing phosphine-thioether ligands **L2**-**L4** developed.

Binaphthyl-based P–thioether ligands, where the chiral axis is the only stereogenic element, have found limited application and only Hagiwara *et al.* have reported some further applications. They prepared a range of BINAPS ligands with new thioether alkyl and aryl substituent, ligands **L1** (R = Ph, 2-^{i}PrPh, 2-Naph, 3,5-Xyl and Cy, Figure 1) that allowed to extend the range of nucleophiles used in the Pd-catalysed allylic alkylation to the less studied indoles (Figure 3).[14] Despite indoles are present in many relevant compounds with biological and synthetic interest,[15] only a few successful examples of its use as nucleophiles in the Pd-AAA can be found in the literature.[16] With ligand **L1** (R= 2-^{i}PrPh), a broad range of simple and substituted indoles could be successfully introduced (up to 95% ee, Figure 3), although the substrate scope was still limited to **S1**.



R	% ee (% yield)
5-Br	78 (67)
5-Cl	83 (88)
5-Me	95 (85)
5-OMe	93 (84)
7-Me	90 (76)
2-Ph	66 (66)

Figure 3 Scope of indoles in the Pd-catalysed allylic substitution of **S1** using ligand **L1** (R= 2-^{i}PrPh).

In contrast, since the first application of the previously commented ferrocene based P–S ligands **L2**-**L3**, a broad range of P–thioether ferrocenyl ligands have been developed, frequently combining central and planar chirality, and a few of them stand out for their versatility.[5f]

Among them, three families can be highlighted: the N–phosphine-thioether FerroNPS type ligands **L5**-**L7** (Figure 4),[16b,17] the phosphine-thioether Fesulphos ligands **L8**-**L9** (Figure 5), having only planar chirality,[18] and the phosphine-thioether ThioClick-Ferrophos **L10**-**L11** (Figure 6)[19].

The N–phosphine-thioether FerroNPS ligands (**L5**), with mixed planar/central chirality, have shown efficiency in the Pd-catalysed allylic substitution of **S1** with dimethyl malonate, a number of amines and less studied oxygen nucleophiles (Figure 4).[5e,17] More recently ligands **L6**-**L7**, related to FerroNPS and bearing imidazole or benzimidazole moieties, were applied in the allylic alkylation of not only the model substrate **S1** but also two cyclic substrates (**S2**-**S3**, up to 87% ee) with nucleophiles such as indoles, achieving enantioselectivities up to 96% ee (Figure 4).[16b,17c] Although the problem of substrate and nucleophile scope in Pd-catalysed allylic alkylation was not fully solved, the promising results with other substrates different from the model substrate **S1** and with other nucleophiles, by modification of the ligand, indicated that P–S ligands could be good candidates for further optimisation.

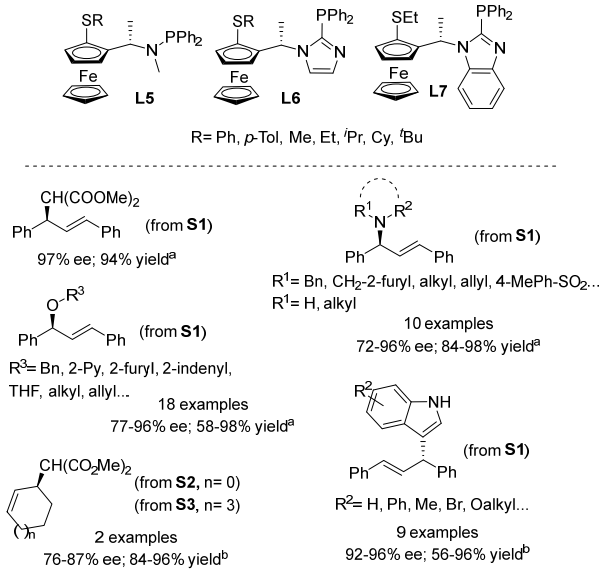


Figure 4 FerroNPS ligands **L5**-**L7** and a summary of their catalytic results in the Pd-allylic substitution of substrates **S1**-**S3** with dimethyl malonate, indole, several amines and ethers as nucleophiles. [a]Results using **L5** (R= Cy). [b]Results using **L7**.

Fesulphos ligands **L8**-**L9** turned out to be one of the more versatile P–S families for asymmetric catalysis (Figure 5). They have been effectively applied in relevant C–C bond forming reactions. The first application was reported in 2002 in the Pd-catalysed allylic substitution of **S1** providing high enantioselectivities (up to 98% at -20 °C) using either carbon or nitrogen nucleophiles.[18a-b] Sterically demanding thioethers and electronically poor phosphines provided the best results (ligands **L8**, R= 4-FPh, 4-CF_3Ph). Since then, Carretero's group has reported their successful application in a very broad range of other asymmetric processes such as the desymmetrisation of bicyclic alkenes (Figure 5a),

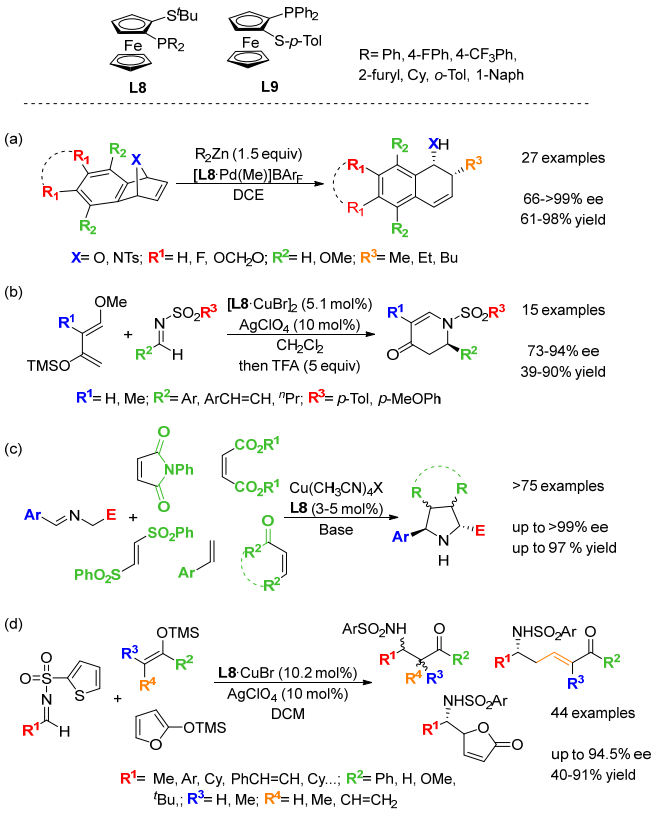


Figure 5 Fesulphos ligands **L8**-**L9** and a summary of their application on several metal-catalysed catalytic asymmetric reactions.

including less reactive substrates such as azabenzonorbornadienes and oxabicyclic alkenes, with organozinc reagents (ee's up to 99%),[18c,f] and in many asymmetric cycloaddition reactions. For instance, Cu(I)/FeSulphos catalytic systems were used in the Diels-Alder reaction of cyclopentadiene with N–acryloyl oxazolidinone[18g] and the aza-Diels-Alder reaction of electron-rich dienes with aldimines (Figure 5b) (ee's up to 95% and up to 97%, respectively)[18d]. These catalytic systems were also very efficient in the 1,3-dipolar cycloaddition of azomethine ylides with several di- and monoactivated alkenes[18e,i,k,o-q] and later, with α,β-unsaturated ketones[18m,r], giving access to a variety of highly functionalized pyrrolidines with enantioselectivities up to >99% ee (Figure 5c). In addition to cycloaddition processes, they were also effective in the asymmetric Mannich-type reaction of a broad range of N–sulfonyl imines and silyl enol ethers (ee's up to 94.5%, Figure 5d).[18h,l] Glycine Schiff bases could be also used as electrophiles to give β-alkyl-α,β-diamino acid derivatives in excellent levels of diastereo- (syn/anti >90:10) and enantioselectivity (≥ 90% ee, Figure 5d).[18n] Finally, **L8**-type ligands were successfully supported onto polystyrene resins, and the immobilised catalysts were successfully used in enantioselective Cu(I)-catalysed 1,3-dipolar cycloadditions and enantioselective Pd-catalysed allylic substitution reactions. This strategy allowed their recovery and reuse for up to three times, without erosion in their excellent catalytic activities and enantioselectivities (91 to >99% ee). [18j]

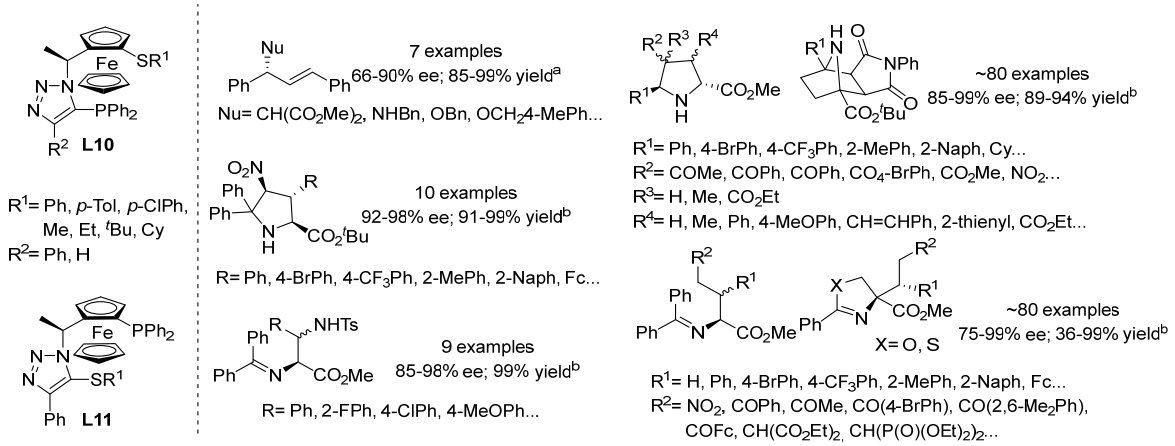


Figure 6 ThioClick-Ferrophos ligands **L10**-**L11** and a summary of the catalytic results obtained in their application on several metal-catalysed asymmetric transformations. [a]Results using **L10** (R= Et). [b]Results using **L11** (R^1 = ^{t}Bu)

ThioClick-Ferrophos ligands **L10**-**L11** (Figure 6) were first applied in the Pd-allylic substitution of **S1** with dimethyl malonate, benzylamine and some benzylic alcohols. Ligands bearing a phosphine directly attached to the triazole ring and a thioether bonded to a ferrocene moiety (**L10**) performed better than **L11**; however, only moderate to good enantioselectivities were achieved (66-90% ee).[19a] In contrast ligands **L11**, with the positions of the phosphine and thioether groups exchanged, were found to be very efficient in other asymmetric transformations. In particular, **L11** (R^1 = ^{t}Bu) was successfully applied in 1,3-dipolar cycloadditions of azomethine ylides with several activated alkenes (ee's up to 99%)[19b-c,g-h,j], in conjugate additions of different imino esters and azomethine ylides to a range of Michael acceptors (ee's up to 99, Figure 6)[19e-f,l,k-m] and also in the Mannich reaction of glycine Schiff base (ee's up to 98%, Figure 6).[19d]

Another group of relevant P–S ligands are those involving two carbon atoms between the two donor functionalities.[5,20] Among them we can highlight the early family of phosphinite-thioether ligands **L12**-**L13**[7,21] (Figure 7), and the much more recent families of phosphite/phosphinite–thioethers **L14**[22] (Figure 7), **L15**-**L17**[23] (Figure 9) and **L18**[24] (Figure 12) ligands and the phosphoramidite-thioether ligands **L19**-**L21**[25] (Figure 15). All of them have the advantage that are modular and are synthesized in few steps from readily available starting materials. In addition, they have a simple backbone that renders simple NMR spectra, which facilitates the identification of relevant intermediates and accelerate DFT calculations to rationalize the behaviour of the system. The Evans' ligands **L12** and **L13** was the first family of P–thioether ligands successfully applied to several asymmetric transformations. A systematic optimization of the substituents at the thioether, phosphinite and backbone led to efficient applications in Rh-catalysed hydrogenation of functionalized olefins (amidoacrylate derivatives, ee's up to 97%), Rh-catalysed hydrosilylation of ketones (ee's up to >99%) and in the Pd-catalysed allylic alkylation and amination.[7,21] Low temperatures (-20 °C) were needed in the Pd-substitution and enantioselectivities were high for the model substrate rac-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) and some cyclic substrates (ee's up to 98%). However, only moderate enantioselectivity (ee up to 65%) could be achieved for the less hindered linear substrate, *rac*-1,3-dimethyl-3-acetoxyprop-1-ene (**S5**).

Over the last decades, it has been consistently shown that the presence in ligands of a biaryl phosphite moiety favours ligand's efficiency and a broader substrate scope in some metal-catalysed asymmetric processes. The main reason is that the biaryl phosphite group is flexible enough to allow accommodation in the chiral pocket of the catalyst of substrates with broadly different steric demands.[26] Moreover, phosphite ligands are less sensitive to air than phosphines, they are easy to prepare from commercial alcohols and their preparation is amenable to parallel synthesis. All this facilitates the preparation of large series of ligands in the quest to maximize catalytic performance for each particular reaction and substrate. Our group has shown the benefits of using biaryl phosphite–N ligands for the hydrogenation of unfunctionalized olefins, with results that are among the best reported so far.[26b,d,e,h] In a similar way, we have recently replaced the phosphinite moiety in the Evans' cyclohexane-based ligand **L13** by diverse biaryl phosphite moieties (Figure 7, ligands **L14**).[22]

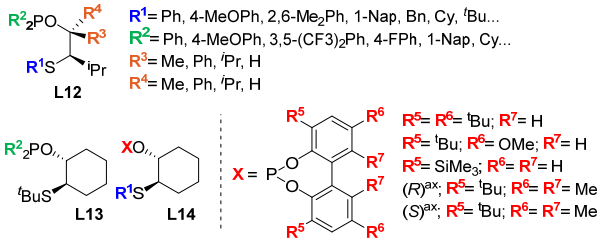


Figure 7 Phosphinite/phosphite-thioether ligands **L12**-**L14**.

The new air stable phosphite-thioether ligands were successfully used in the Ir-catalysed hydrogenation of a broad range of unfunctionalized alkenes. It is worth recalling here that the reduction of unfunctionalized alkenes is underdeveloped in comparison with the reduction of functionalized olefins.[27] The reason for this difference is that most catalysts used in the past were too specific for a certain double bond geometry and substitution pattern of the olefin. For example, the most successful cases have been reported for trisubstituted (*E*)-unfunctionalized alkenes and to a lesser extent for (*Z*)-trisubstituted and 1,1-disubstituted. Advantageously, the new phosphite-thioether ligands could hydrogenate not only (*E*)-trisubstituted olefins including both unfunctionalized and with poorly coordinative groups, but also a variety of 1,1-disubstituted alkenes (Figure 8, ee's up to 99%). Noteworthy, ligands **L14** extended the state-of-the-art with the successful reduction, for the first time, of terminal aryl-substituted boronic esters. It was found that enantioselectivity in these reactions depended on the type of thioether substituent and the configuration of the phosphite group, whereas the substituents of the biaryl phosphite moiety had little impact on the stereochemical outcome of the reactions. The replacement of the phosphite moiety by several phosphinite units resulted in lower enantioselectivities.[22]

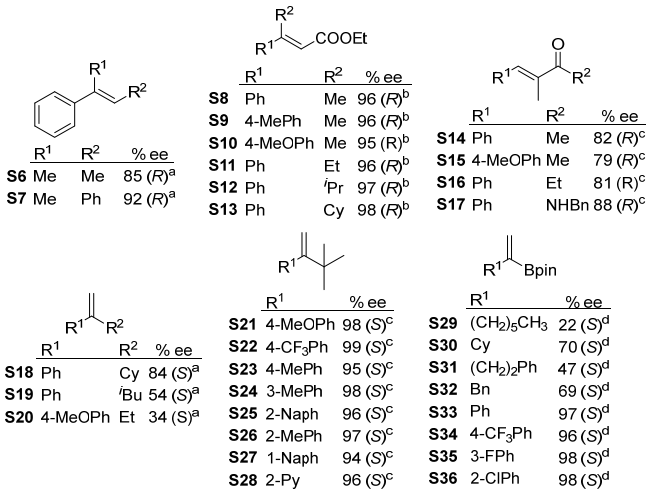


Figure 8 Summary of the enantioselectivities achieved in the Ir-hydrogenation of (*E*)-trisubstituted olefins **S6**-**S17** and 1,1'-disubstituted olefins **S18**-**S36** using [Ir(**L14**)(cod)]BArF catalysts. Reaction conditions: 1 mol% of catalyst, DCM as solvent, 100 bar of H_2 for substrates **S6**-**S17** or 1 bar for substrates **S18**-**S36**, 4 h and rt. Full conversions were achieved in all cases except for substrates **S25**-**S28** and **S36**. [a] Results using **L14** (R^1= ^{t}Bu; (*S*)^{ax}; R^5= ^{t}Bu; R^6=R^7= Me). [b]Results using **L14** (R^1=R^5=R^6= ^{t}Bu; R^7=H). [c]Results using **L14** (R^1= 2,6-Me_2Ph; (*R*)^{ax}; R^5=^{t}Bu; R^6=R^7= Me). [d]Results using **L14** (R^1= 2,6-Me_2Ph; (*S*)^{ax}; R^5=^{t}Bu; R^6=R^7= Me).

The high enantioselectivities achieved with **L14** could be explained thanks to the identification of the catalytically competent Ir-dihydride alkene species by HP-NMR spectroscopy and DFT studies. It was found that the minor intermediate,[27h] which is less stable, was converted to the major product enantiomer, similarly to what happens in the classical Halpern-mechanism for hydrogenation with Rh-catalysts. Therefore, for enantioselectivities to be high, the ligand parameters needed to be correctly combined to enhance the amount of the minor faster reacting intermediate in the catalytic cycle.

The phosphinite/phosphite–thioether ligands **L15**-**L16** synthesized from arylglycidols (in only three steps) have been successfully applied in the Pd-catalysed allylic substitution and hydrogenation of functionalized and unfunctionalized olefins (Figure 9).[23] High enantioselectivities (up to 96% ee) were achieved in the substitution reactions of linear, 1,3-disubstituted **S1** with C, N–, and the less studied O–nucleophiles, but also in the alkylation of the more challenging trisubstituted substrates rac-1,3,3-triphenylallyl acetate and 4,4-diphenylbut-3-en-2-yl acetate (up to 97% ee). Compared with the Evan's ligands, the optimized ligand **L17** provided comparable enantioselectivities working at room temperature with shorter reaction times.[23a]

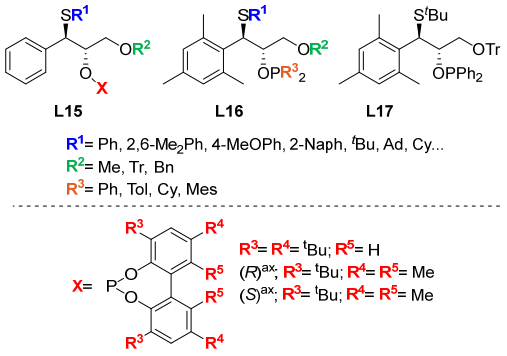


Figure 9 Arylglycidol-based phosphorus/thioether ligands **L15**-**L17**.

Even more remarkable are the results achieved in the hydrogenation of unfunctionalized olefins (ee's up to 99% in 43 hydrogenated products, Figure 10), that surpass the above mentioned phosphite-thioether ligands **L14** and are comparable to the best one reported in the literature with the commonly used Ir-P,N catalysts.[27] In contrast to the cyclohexane-based ligands mentioned above (**L13**-**L14**), the best enantioselectivities were obtained with the phosphinite–S ligands, while results achieved with the phosphite–S analogues were less optimal in this case. The crystal structures of some Ir-catalyst precursors involving these ligands could be determined and confirmed the bidentate coordination of the P–S ligand by both donor atoms, with a chair conformation of the six-membered chelate ring. However, while ligands with a phosphite moiety (**L15**) presented the thioether substituent in an equatorial arrangement, in ligands with a phosphinite group (**L16**-**L17**) the thioether substituent was in axial disposition. This behaviour contrasts with the pseudoaxial disposition of the thioether substituent in the Ir-structures with cyclohexane-based phosphite–thioether mentioned above (ligands **L14**), which also form a six-membered chelate ring. The differential results obtained with **L15** and **L16**-**L17** indicate that the disposition of the thioether substituent (in this case, axial disposition) is important to obtain high enantioselectivity. The modularity of the phosphinite–thioether ligands **L15**-**L17** together with the hints gathered

from DFT studies were crucial to find which ligand parameters could be modified in order to generate more selective catalysts. In this respect, the use of a bulky mesityl group (ligands **L16**) instead of a phenyl group (ligands **L15**) in the ligand backbone improved enantioselectivity. It was also found that the rest of ligand components must be selected for each substrate type, which shows the advantages of working with modular ligands. Thus, excellent enantioselectivities (ee's up to >99%) were recorded for many trisubstituted olefins, including olefins with relevant neighbouring polar groups such as α,β-unsaturated esters, ketones, vinyl boronates and allylic alcohols (**S8**-**S11**, **S14**-**S17**, **S37**-**S43**). In addition, for each type of neighbouring group, the enantioselectivities were quite independent on the electronic and steric nature of the olefin substituents. The effective hydrogenation of such a wide range of olefins is of great importance since their reduction products are key structural chiral units in many high value chemicals (e.g. α- and β-chiral ketones and carboxylic acid derivatives are ubiquitous in natural products, fragrances, agrochemicals, and drugs).

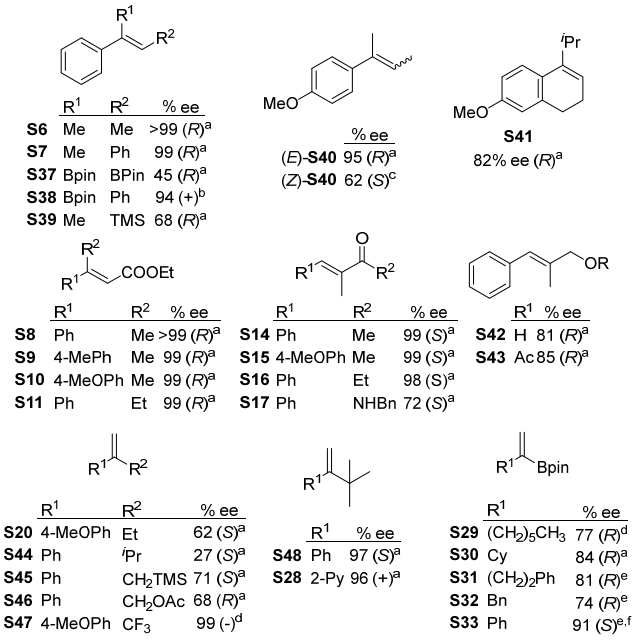


Figure 10 Summary of the enantioselectivities obtained in the Ir-hydrogenation of several (*E*)-trisubstituted olefins and 1,1'-disubstituted olefins using [Ir(**L15**-**L17**)(cod)]BAr_F catalysts. Reaction conditions: 2 mol% of catalyst, DCM as solvent, 100 bar of H_2 for trisubstituted olefins or 1 bar 1,1'-disubstituted olefins, 4 h and rt. Full conversions were achieved in all cases. [a]Results using **L16** (R^1= 2,6-Me_2Ph, R^2= Me, R^3= Tol). [b]Results using **L15** (R^1= Ph, R^2= Tr). [c]Results using **L15** (R^1= 2,6-Me_2Ph, R^2= Me). [d]Results using **L15** (R^1= Ph, R^2= Me). [e]Results using **L15** (R^1= 1-Naph, R^2= Me). [f]Reaction carried out at -20 °C.

High enantioselectivities were also achieved in the hydrogenation of 1,1'-disubstituted alkenes. Unlike trisubstituted olefins, at that moment disubstituted substrates had not been successfully hydrogenated probably because the catalyst must control not only the face selectivity for coordination, but also the isomerization of the 1,1'-disubstituted olefins to form the more stable (*E*)-trisubstituted substrates, which are hydrogenated giving the opposite enantiomer.[27c,f] Hence, it was highly gratifying to find a ligand with a broad substrate scope that could achieve high enantioselectivities (up to 99% ee) in the reduction of 1,1-disubstituted (hetero)aryl/alkyl olefins, alkenylboronic esters and olefins bearing trifluoromethyl substituents (**S20**, **S28**-**S33**, **S44**-**S48**). Excellent enantioselectivities were maintained while using propylene carbonate as an environmentally benign solvent, which allowed the Ir-catalyst to be reused up to three times.[23c] However, the reduction of α-alkylstyrenes with less sterically demanding alkyl substituents proceeded with lower enantioselectivities, like in previous reports.[27f] DFT studies confirmed that the preferred reaction path is an Ir^{III}/Ir^{V} cycle where the selectivity-determining step is the migratory insertion of a hydride. DFT results also allowed the formulation of a quadrant model which explains the effect of the ligand parameters on enantioselectivities (Figure 11). In this model the thioether substituent blocks the upper left quadrant and one of the P–aryl groups partly occupies the lower right one, making it semihindered. The other two quadrants are open (Figure 11(a)). The DFT optimized structures thus show that these Ir-PS catalysts generate a pocket that is well suited for olefins with large trans substituents ((*E*)-olefins; Figure 11(b)). This fully explains the high enantioselectivities obtained with the DFT-guided design of thioether–phosphinite ligands in the reduction of (*E*)-olefins. In the case of the analogous phosphite–thioether ligands, the upper left quadrant is not enough blocked due to the equatorial arrangement of the thioether group, which explains the low enantioselectivities achieved with **L15**.

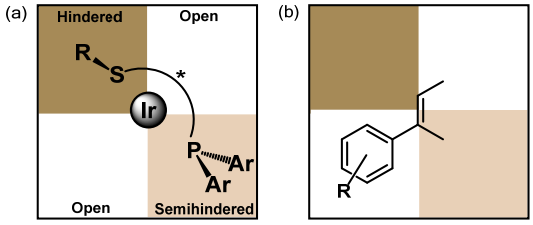


Figure 11 Quadrant diagram describing the substrate-ligand interactions.

Phosphite–thioether ligands **L18** (Figure 12), synthesized in only three steps from cheap indene, were recently proposed to overcome the limited substrate scope in Pd-catalysed allylic substitution.[24] For this process, ligands that tolerate a wide range of substrates and nucleophiles are indeed rare.[28] However, Diéguez *et al*. provided a hint for successful design when showing that biaryl phosphite moieties in P–N ligands are beneficial for the Pd-catalysed allylic substitution.[26a,b,c,e,f,g] The modular architecture of the air stable phosphite–thioether ligands **L18** allowed an iterative optimization of the ligands to adapt the size of the chiral cavity to the substrate type. The combination of experimental results and DFT calculations led to the discovery of the anthracenethiol derivative phosphite-thioether ligand **L18** (Figure 12(b)) that provided excellent enantioselectivities for 40 compounds, covering linear (un)hindered and cyclic substrates and a broad range of C, N and O–nucleophiles (Figure 12).[24]

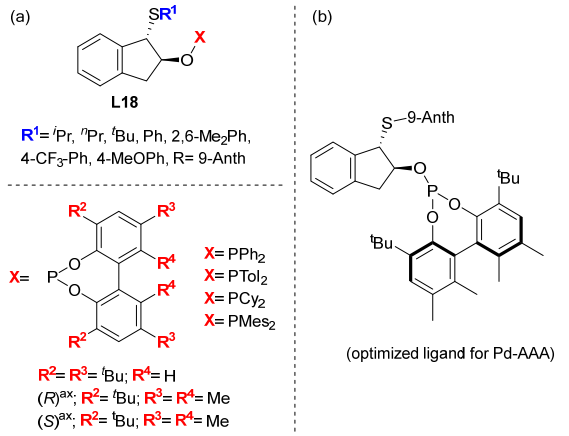


Figure 12 (a) Indene-derived phosphorus-thioether ligands **L18**. (b) Ligand with the right combination of ligand parameters to maximized catalytic performance in the Pd-AAA.

Thus, a variety of malonates, including the allyl-, butenyl-, pentenyl- and propargyl-substituted ones, reacted with **S1** to provide the substituted products in high yields and enantioselectivities (up to 99% ee). These substituted malonates are known to be challenging nucleophiles. They are, however, important from a synthetic point of view since they give rise to very interesting products (Figure 14). Substitution with acetylacetone also proceeded with high enantiocontrol (ee's up to 98%) and pyrroles also provided similarly high enantioselectivities (ee's up to 99%). The difficulty of this last transformation is evident if we consider that even two of the most successful ligands developed for this process, such as Trost diphosphines and Pfaltz phosphinooxazolines (PHOX),[29] did not work with pyrroles.

The use of amines as nucleophiles also gave excellent enantioselectivities (ee's up to 99%). This included primary amines (such as benzylamine, p-methoxy- and p-trifluoromethyl benzylamines and furfurylamine), secondary amines and the allylamine. The high enantiocontrol observed for C– and N–nucleophiles was also extended to aliphatic alcohols (ee's up to 99%). It is worth noting that the effective allylic substitution with this type of O–nucleophiles opened up new synthetic avenues towards chiral ethers, which are important structural motifs in the synthesis of biologically active molecules. Pd/**L18** was also successfully applied to other symmetrical linear substrates with steric and electronic requirements (substrates **S49**-**S53**) different from those of **S1**. A wide range of C–nucleophiles, including the less studied α-substituted malonates, could also be efficiently reacted with the more demanding cyclic substrate **S4** (Figure 13). The main exception in this otherwise excellent performance was noted with acetylacetone, that led to somewhat lower enantioselectivity. As a general trend, high enantioselectivities in both enantiomers of the substitution products were achieved using methyl-, allyl- and propargyl-substituted malonates. Furthermore, the biaryl phosphite group in Pd/**L18** can adapt its chiral pocket to efficiently mediate the substitution of other cyclic substrates. Excellent yields and enantioselectivities, comparable to the best ones reported in the literature, were recorded in the allylic alkylation of a 7-membered cyclic substrate with different C–nucleophiles. Even more interesting is that the good performance could be also extended to the more challenging 5-membered cyclic substrate. These results were maintained when propylene carbonate, a green solvent, was used in the reactions.

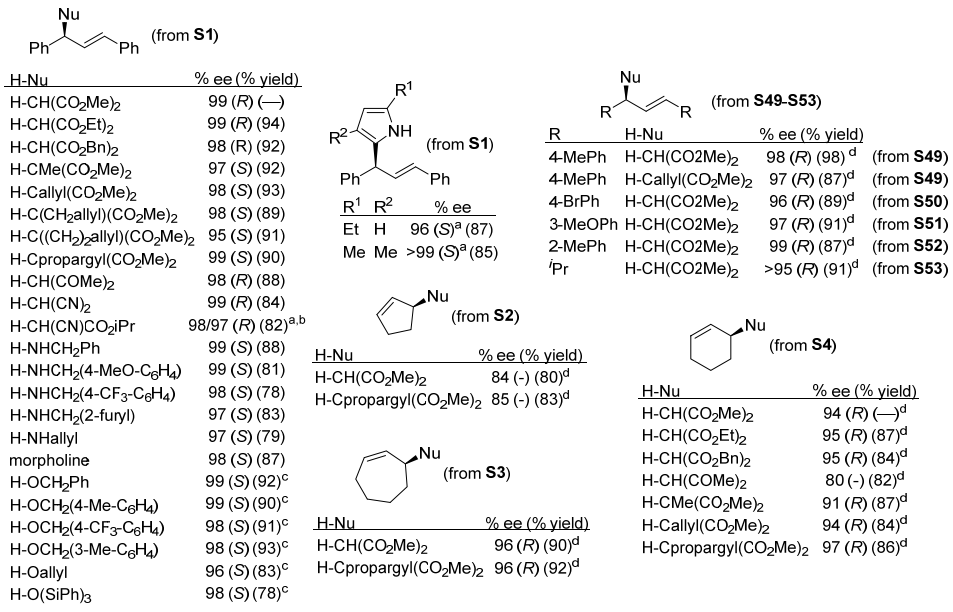


Figure 13 Summary of the catalytic results in the Pd-allylic substitution with Pd/**L18** catalytic system. Reaction conditions: 0.5 mol% of $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1.1 mol% **L18**, DCM (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch), 30 min and rt. [a]2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4.4 mol % ligand, CH_2Cl_2 (2 mL), K_2CO_3 (2 equiv), 18 h and rt. [b]60:40 dr. [c]2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4.4 mol % ligand, CH_2Cl_2 (2 mL), Cs_2CO_3 (2 equiv), 18 h and rt. [d]Reaction stirred for 2h.

Mechanistic studies indicated early TSs for these reactions, so that the stereochemistry of the process is governed by the relative populations of the Pd-η^3-allyl complexes and the electrophilicity of the allylic terminal carbon atoms. Thus, for enantioselectivities to be high, the ligand parameters needed to be chosen to either increase the difference in population of the possible Pd–allyl intermediates (for cyclic substrates) or to increase the relative rates of the nucleophilic attack for each of the possible Pd–allyl complexes (linear substrates).

Finally, a range of chiral functionalized carbocycles (**1**-**4**), heterocycles (**5**-**6**) and polycarbocycles (**7**-**9**) from the enantioenriched allylic substitution products were prepared. These compounds were synthesized by straightforward reaction sequences involving allylic substitution of the appropriate substrates followed by either ring-closing metathesis (Figure 14 (a)) or Pauson-Khand enyne cyclization (Figure 14 (b)).

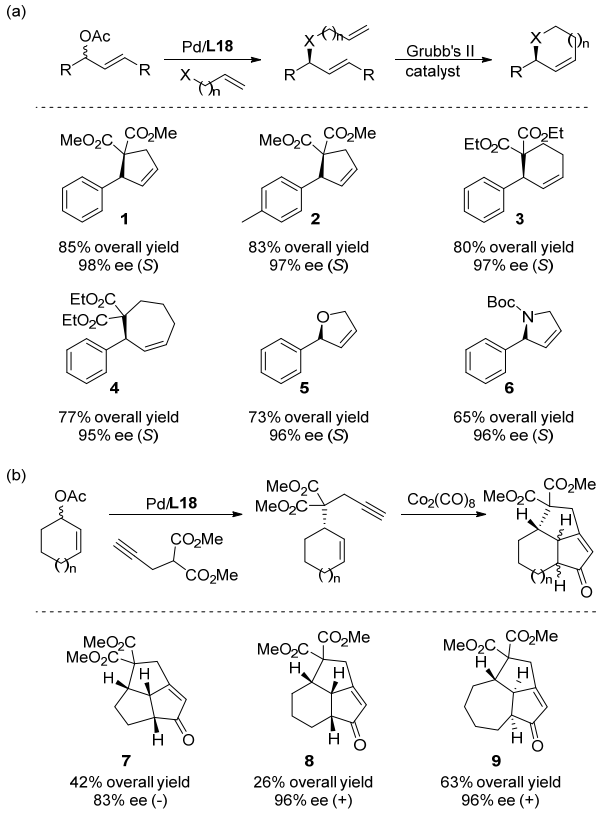


Figure 14 Preparation of chiral functionalized carbo- and heterocyclic compounds **1**-**6** and polycarbocyclic compounds **7**-**9** from the corresponding allylic substitution products followed by ring-closing metathesis (a) or Pauson-Khand cyclization (b).

Thus, the corresponding alkylated compounds underwent clean ring-closing metathesis with no loss of enantiopurity, giving 5, 6 and 7-membered carbocycles, in high yields and enantioselectivities (ee's ranging from 95–98%; Figure 14 (a)). In an analogous manner, the synthesis of dihydrofuran **5** was achieved by sequential allylic etherification of **S1** with allylic alcohol and ring-closing metathesis reaction (Figure 14 (a)) and the corresponding dihydropyrrole **6** could be similarly prepared, although protection of the amine as a N-Boc derivative was required prior to the ring-closing metathesis reaction. The preparation of chiral heterocycles compounds **5** and **6** by sequential allylic substitution/ring-closing metathesis reactions opens up an new route that can advantageously compete with the commonly used intramolecular Pd-catalyzed asymmetric Heck reaction.[30] The Pauson-Khand reaction of the three propargylated derivatives, which differ only in the size of the cycloalkene ring, gave the corresponding complex tricyclic systems (Figure 14 (b)) in high enantioselectivities.

Xiao *et al*. developed the phosphoramidite-thioether ligands **L19**-**L21** (Figure 15) with a β-amino sulphide backbone and successfully applied them in several relevant asymmetric transformations.

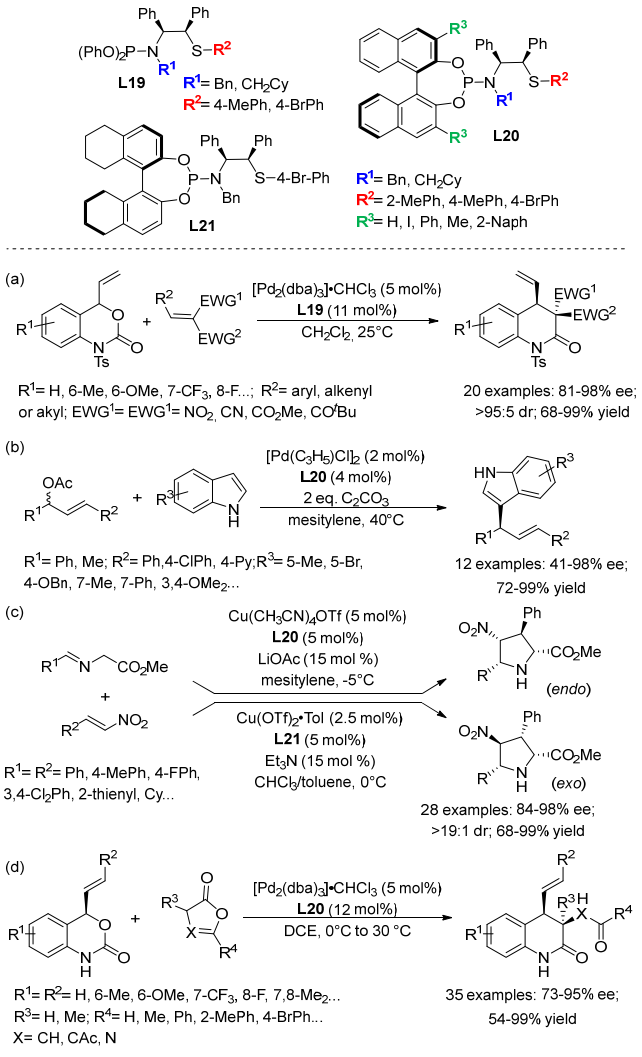


Figure 15 Phosphoramidite-thioether ligands L19-L21 and a summary of their application on several metal-catalysed catalytic asymmetric reactions.

Ligands containing a non-chiral phosphoramidite substituent (**L19**), were initially applied to the asymmetric Pd-catalysed decarboxylative [4+2] cycloaddition between benzoxazinanones and activated alkenes to produce

tetrahydroquinolines with three contiguous stereogenic centres (Figure 15(a)).[25a] Excellent yields, diastereoselectivities and enantioselectivities up to 98% ee were achieved with ligand **L19** (R^1 = Bn, R^2 = 4-MePh). Next, (*R*)-BINOL-containing ligands **L20** were applied in the Pd-allylic alkylation of some disubstituted linear substrates with a range of indoles as nucleophiles (Figure 15(b)).[25b] Ligand **L20** (R^1 = CH_2Cy, R^2 = 4-Br-Ph, R^3 = Ph) provided the best enantioselectivities (up to 98% ee) and it could be also used in the etherification and amination of **S1**, again with very high enantioselectivities (98% an 97% ee, respectively). The same ligand (**L20**) was also found to be effective in the Cu-catalysed 1,3-cycloaddition of azomethine ylides and nitro-alkenes. A wide range of highly functionalized *endo*-pyrrolidines was obtained with high enantioselectivities and diastereoselectivities. The use of ligand **L21** allowed the preparation of the analogous *exo*-products in also high levels of asymmetric induction (Figure 15(c)).[25c] Finally, ligand **L20** (R^1= CH_2Cy, R^2= 4-Br-Ph, R^3= 2-Naphthyl) was used in the unprecedented Pd-catalysed [4+2]-cycloaddition of deconjugated butenolides with vinyl carbamates (Figure 15(d)).[25d] This transformation provided a new approach towards highly functionalized dihydroquinol-2-ones in high yields, enantioselectivities and diastereoselectivities.

Two other family of P–thioether ligands have been recently developed: ligands **L22**-**L25**[31] (Figure 17) and **L26**-**L31**[32] (Figure 20), both of them derived from carbohydrates. Carbohydrates are a cheap and a readily available source of chiral scaffolds for ligand synthesis. Their polyfunctionality and well-established chemistry facilitate their modularity and the subsequent adaptation of the derived ligands to each particular reaction and substrate.33 Actually, the use of sugar P–thioether ligands in asymmetric catalysis was already introduced by Khiar et al. in 2005, with phosphinite-thioether ligands **L32**-**L33** (Figure 16). They successfully applied them in the Pd-catalysed allylic substitution of the model substrate S1 (ee's up to 96%) and the Rh-catalysed hydrogenation of some enamides (ee's up to 98%).[32] In addition, both enantiomers of the products could be obtained by using pseudo-enantiomeric ligands (**L32** vs **L33**), rather than preparing the corresponding P–S ligand from the expensive L-sugar derivative. However, still a narrow substrate and reagents scope was observed.

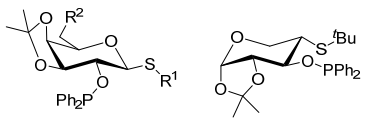


Figure 16 Phosphinite-thioglycoside ligands **L32**-**L33**.

The large library of furanoside phosphite/phosphinite/phosphine-thioether ligands **L22**-**L25** (Figure 17)[31a-b] represented the first application of non-N–donor heterodonor ligands in the challenging Ir-hydrogenation of unfunctionalized olefins.[31c] They present three carbon atoms between the two donor functionalities, and this is probably reflected in their coordination to metals (in P–thioethers **L12**-**L21**, for instance, only two carbon atoms separate the two functions). The structural variety of this library (108 ligands) allowed to investigate the effect on catalytic performance of systematically varying the position of the thioether group at either C-5 or C-3 of the furanoside backbone (ligands **L22**-**L23** vs **L24**-**L25**) and the effect of the configuration at C-3 (ligands **L22**, **L24** vs **L23**,**L25**). The effect of varying the substituent at the thioether group, the configuration of the biaryl phosphite moiety and of their substituents, and the replacement of the phosphite moiety by either a phosphinite group or a phosphine group, were also studied.

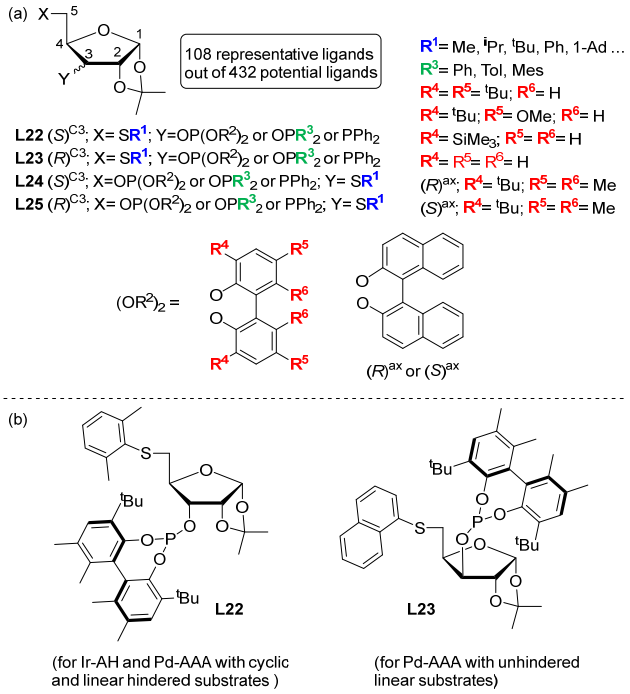


Figure 17 (a) Furanoside-based phosphorus-thioether ligand family **L22**-**L25**. (b) Ligands with the right combination of ligand parameters to maximized catalytic performance in the Ir-AH and Pd-AAA.

Excellent enantioselectivities were achieved (ee's up to 99%) in the reduction of a very broad range of (*E*)- and (*Z*)-unfunctionalized alkenes (Figure 18, 17 alkenes), including relevant examples with poorly coordinative groups (such us, α,β-unsaturated esters and vinylboronates; Figure 18) with the 5-deoxy-ribofuranoside backbone ligand **L22** (Figure 17(b)). For the 1,1'-disubstituted olefins, both enantiomers of the reduction products can be obtained in high enantioselectivities by changing the configuration of the biaryl phosphite group. The asymmetric hydrogenation was also performed using propylene carbonate as solvent, which allowed the Ir-catalysts to be reused while maintaining the excellent enantioselectivities. Replacing the phosphite moiety by a phosphinite or a phosphine group had a negative effect on enantioselectivity (data not shown). In general, the results obtained with **L22** are comparable to the best ones reported in the literature except for the

hydrogenation of terminal disubstituted aryl/alkyl olefins, where enantioselectivity is dependent on the nature of the alkyl substrate substituent. Thus, the reduction of alkenes where one of the double bond substituents is a *tert*-butyl group and isomerization cannot occur, provides high levels of enantioselectivity (ee's up to 99%). In line with this result, the best enantioselectivities were recorded in the reduction of aryl and heteroaryl/tert-butyl substrates.

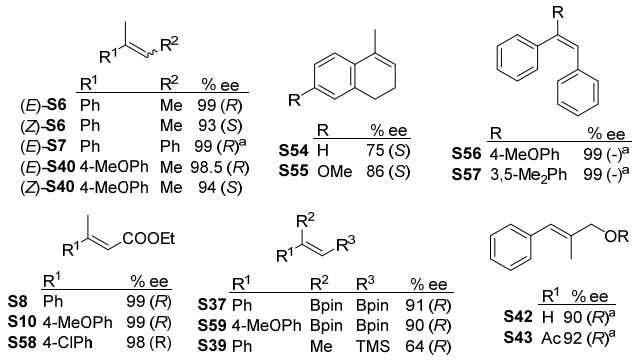


Figure 18 Summary of the enantioselectivities obtained in the Ir-hydrogenation of (*E*)- and (*Z*)-trisubstituted olefins using [Ir**L22**(cod)]BAr_F catalysts. Reaction conditions: 2 mol% of catalyst, DCM as solvent, 100 bar of H_2 for trisubstituted olefins, 4 h and rt. Full conversions were achieved in all cases except for substrate **S42**. [a]The reaction was stirred for 8h

By selecting the ligand parameters it was also possible to apply with success these furanoside phosphite-thioether ligand libraries in the Pd-allylic substitution on a range of substrate types (hindered and unhindered, cyclic and linear) using a wide range of C–, N– and O–nucleophiles (Figure 19, 38 compounds).[31c-d] with both phosphite-thioether ligands **L22** and **L23** (ee's up to >99%, Figure 17(b)). While ligand **L22** provided the best enantioselectivities in the alkylation of cyclic and hindered linear substrates, for unhindered linear substrates the best enantioselectivities were achieved with ligand **L23**, which differs from **L22** in the configuration at C-3 in the sugar backbone. So, the configuration of C-3 help to adjust the size of the chiral pocked to the steric demands of the substrate. Of particular note are the excellent enantioselectivities recorded in the etherification of linear and cyclic substrates, which represent the first example of successful etherification of both substrate types. A DFT computational study of the key intermediates and transition states involved in the enantiodetermining steps is in agreement with an early transition state. Further studies on the π-allylpalladium intermediates indicated that for the achievement of high enantioselectivities, the ligand parameters need to be correctly combined so that either the fastest reacting Pd-intermediate is predominantly formed (for linear hindered **S1** and unhindered linear substrates, such as **S5**) and/or one of the *syn*/*syn* (endo or exo) isomers is predominantly formed (for unhindered cyclic **S4**).

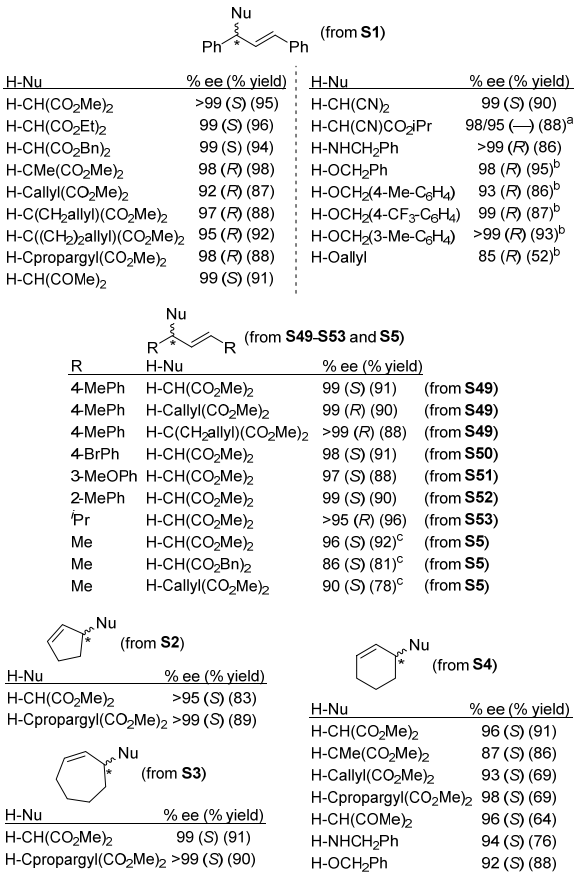


Figure 19 Summary of the catalytic results in the allylic substitution with Pd/**L23** catalyst for substrates **S1**-**S4** and **S49**-**S53** and Pd/**L22** catalyst for **S5**. Reaction conditions: 0.5 mol% of $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1.1 mol% **L23**, DCM (2 mL), BSA (3 equiv), nucleophile (3 equiv), KOAc (pinch), 3 h and rt. [a]55:45 dr. [b]2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol % ligand, CH_2Cl_2 (2 mL), K_2CO_3 (2 equiv), 18 h and rt. [c]Reaction carried out at 0 °C.

The last family of phosphite-thioether ligands was prepared from available L-(+)-tartaric acid and D-(+)-mannitol (Figure 20). These ligands are also highly modular and, therefore, up to 61 ligands could be readily prepared by combining different thioether groups (R^1), different substituents in the alkyl backbone chain next to both coordinating functions (R^2, R^3), which in some cases generate a new stereogenic centre (R^4, R^5), and different substituents and configurations in the biaryl phosphite moiety. The proper choice of the ligand parameters made possible to identify ligands (**L26**-**L30**, Figure 20(b)) that provided for the first time excellent enantioselectivities in the hydrogenation of both, unfunctionalized and functionalized olefins (ee's up to 99% ee, Figure 21, 40 alkenes in total).[32a-b] Moreover, both enantiomers of the hydrogenated products could be obtained by using diastereomeric ligands. The catalytic performance was maintained when using the environmentally benign 1,2-propylene carbonate as solvent. Among these substrates, the results obtained in the reduction of the challenging β-cyclic enamides should be highlighted. Their hydrogenation products, such as 2-aminotetralines and 3-aminochromanes, are structural fragments found in biologically active natural products and therapeutic agents.[35] At that moment, only few examples of their successful hydrogenation had been reported, most of them based on Rh- and Ru-catalysts.[36] In 2016, Riera's group found for the first time that Ir-PN systems can also be effective catalysts for the reduction of several cyclic β-enamides from 2-tetralones, surpassing the

Rh/Ru-catalysts.[37] At the same time we were studying the application of Ir/phosphite-oxazoline[38] and Ir/P–thioether[32a] systems in the reduction of these substrates. We were pleased to see that with phosphite-thioether ligand **L28**, a range of cyclic β-enamides could be reduced in high yields and enantioselectivities, independently of the aryl substituent and the nature of the amido group (ee values up to 99 %, Figure 21). Enamides derived from 3-chromanones could also be reduced in enantioselectivities up to 98% ee. In addition, both enantiomers of the reduction products were accessible in high enantioselectivities by simple switching from Rh to Ir. These results opened up the use of phosphite-thioether ligands in the challenging enantioselective metal-catalysed hydrogenation of cyclic β-enamides.

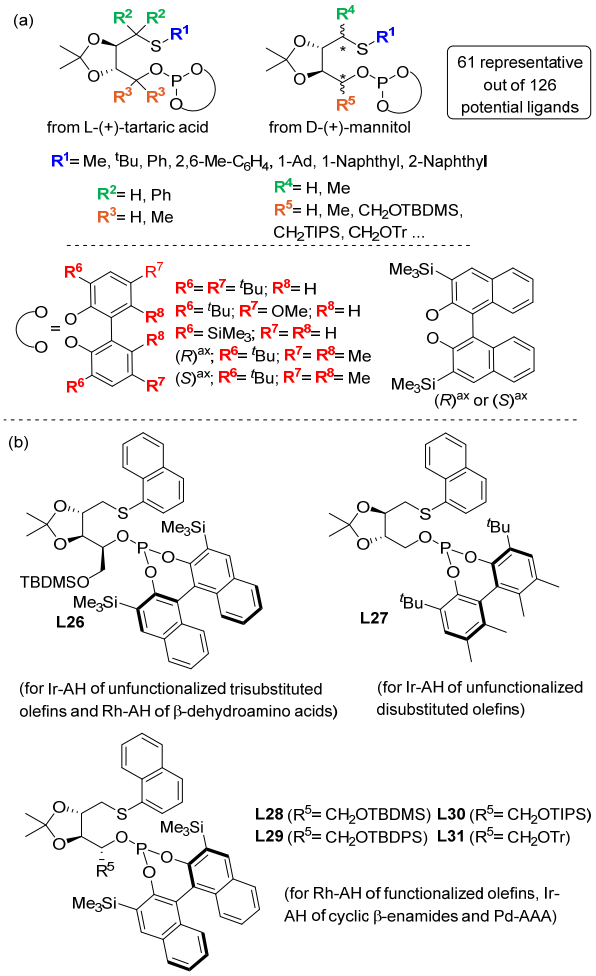


Figure 20 (a) Phosphite-thioether ligand library derived from L-(+)-tartaric acid and D-(+)-mannitol. (b) Ligands with the right combination of ligand parameters to maximized catalytic performance in the Ir/Rh-AH and Pd-AAA

In the application of these ligands to the Pd-catalysed allylic substitution reaction, the best results were achieved with ligands that contain a chiral chain with a silyl group next to an enantiopure biaryl phosphite moiety. With the appropriate choice of this chiral chain, high enantioselectivities could be achieved for a range of hindered and unhindered substrates (ee's up to 99% and 91%, respectively, Figure 22).[32c] In addition, twelve C–, N– and O–nucleophiles could be efficiently introduced,

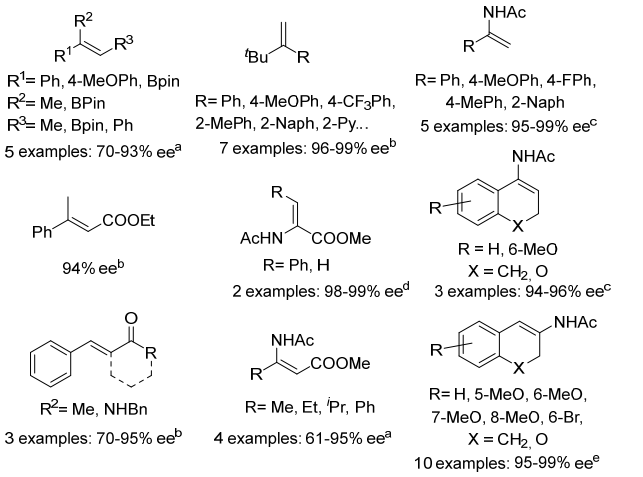


Figure 21 Summary of the enantioselectivities obtained in the Ir- and Rh-hydrogenation of several unfunctionalized and functionalized olefins using [Ir(**L26**-**L30**)(cod)]BArF catalysts precursors. Reaction conditions: 1-2 mol% of catalyst, DCM as solvent, 10-100 bar of H_2, 4-36 h at 5 C° (for Rh catalyst) or at RT (for Ir catalyst). Conversions ≥98% were achieved in all cases. [a]Results using **L26**. [b]Results using **L27**. [c]Results using **L29**. [d]Results using **L30**. [e]Results using **L28**.

independently of their nature. To obtain the highest enantioselectivities, an (*R*)-configured bulky alkyl group next to the phosphite moiety and an enantiopure biaryl phosphite moiety were needed. However, while an (*S*)-biaryl phosphite group was needed for hindered linear substrates (Ligand **L31**), an (*R*)-chiral biaryl phosphite group was preferred, for the less sterically demanding linear substrate **S5** (Figure 22, ligand **L32**). Moreover, for cyclic substrates both enantiomers of the product could be obtained by setting up the desired configuration of the biaryl phosphite group. Finally, studies of the key π-allylpalladium intermediates showed that for high enantioselectivity, the ligand parameters needed to be properly combined to either enhancing the difference in the population of π-allylpalladium isomers formed or enhancing the electronic differentiation between the most electrophilic allylic terminus carbon atoms of the isomeric intermediates formed. The study also showed that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located *trans* to the phosphite functionality.

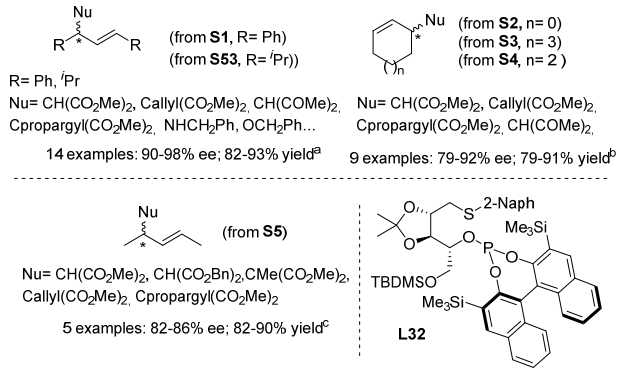


Figure 22 Summary of the catalytic results in the allylic substitution of several substrates using Pd/(**L30**-**L32**) catalysts. Reaction conditions: 0.5 mol% of $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 1.1 mol% **L**, DCM as solvent, BSA (3 equiv), nucleophile (3 equiv), KOAc (3 mol%), 4 h (for S1), 6 h (for **S2**-**S5**) or 24 h (for **S53**) and rt. [a]Results using **L31**. [b]Results using **L30**. [c]Results using **L32**.

Conclusions

In this feature article we have summarized the most relevant progress achieved in recent years in the design and use in asymmetric catalysis of P-thioethers. We have illustrated how, through an appropriate ligand design, P-thioethers can be an excellent source of versatile ligands for enantioselective metal-catalysed reactions, with comparable catalytic performance than the best heterotopic ligands reported so far. In this respect, the new generation of P–thioether ligands collected in this feature article have provided excellent results in several asymmetric transformations with a variety of metals (Pd, Cu, Rh and Ir). Their high modularity was crucial to identify the optimal ligand parameters and to reach the highest catalytic performance for each transformation. In this optimization process, mechanistic NMR and DFT studies, facilitated by the structural simplicity of these modular molecules, have played a crucial role. In summary, the excellent results obtained with its use together with their facile synthesis are expected to lead to new P-thioether ligands and to a further broadening in the scope of metal-mediated processes catalysed by them. This will hopefully contribute to the expansion of asymmetric catalysis as a key tool for the sustainable preparation of enantiopure compounds in forthcoming years.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We all acknowledge MINECO for the INTECAT network CTQ2016-81293-REDC/AEI. The URV members gratefully acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CTQ2016-74878-P and PID2019-104904GB-I00) and European Regional Development Fund (AEI/FEDER, UE), the Catalan Government (2014SGR670), and the ICREA Foundation (ICREA Academia award to M.D). The ICIQ members gratefully acknowledge financial support from CERCA Programme/Generalitat de Catalunya, the Spanish Ministry of Economy and Competitiveness (CTQ2015-69136-R, CTQ2017-87792-R, AEI/MINECO/FEDER, UE and Severo Ochoa Excellence Accreditation 2014–2018, SEV-2013-0319) and DEC Generalitat de Catalunya (Grant 2014SGR827). The CELLEX Foundation is also acknowledged for financing the High Throughput Experimentation (HTE) laboratory.

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