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Review

Evolution in heterodonor P-N, P-S and P-O chiral ligands for preparing efficient catalysts for asymmetric catalysis. From design to applications

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ABSTRACT

The success of phosphine-oxazoline ligands (PHOX) inspired the progress in P-oxazoline ligand families by modifying either the ligand backbone, the electronic and/or steric properties of the phosphine group or by exchanging the phosphine to a phosphinite or a phosphite group. In this respect, the structures of chiral P-oxazoline ligands have become more diverse and new families of very efficient ligands have emerged, which have improved catalytic performance in some asymmetric transformations, with an increased versatility, both in the range of reactions and in the range of substrates/reagents. In addition, most of ligands are synthesized from easily accessible chiral amino alcohols, maintaining the short and efficient synthetic route developed for PHOX ligands. New ligands have been developed by replacing the oxazoline functionality with several other N-donor groups, e.g. imidazole, thiazole, oxazole, pyridine, etc., and O- and S-groups. This review offers a critical overview of the utility of these most successful bidentate heterodonor P-N, P-O and P-S ligand families applied in metal-mediated processes. We illustrate how, through proper ligand design, these heterodonor bidentate ligand families can be an excellent source of ligands, with superior catalytic performance in many asymmetric reactions than the best C_2-symmetric N,N and P,P-ligands reported so far.

Contents

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1. Introduction

Enantioselective metal-catalysis is one of the most important synthetic approaches for preparing enantioenriched compounds, which occupy a central position in areas ranging from medicinal chemistry to chiral materials. The performance of chiral metal-catalysts depends, mainly, on the correct choice of the chiral ligand [1]. Among the large amounts and variety of ligands built up, only some have a broad applicability. A large reaction, substrate and/or reagent scope are worthwhile to minimize the time devoted to ligand finding and preparation. The most efficient, called "privileged chiral ligands", derive from a few core structures [2]. Surprisingly, most of them possess C_2 symmetry (e.g. BINOL, BINAP, TADDOL ...). The reason for initially selecting bidentate ligands with C_2-symmetry was to reduce the number of catalyst-substrate arrangements and transition states, helping mechanistic studies and therefore facilitating the understanding of the correlation between ligand architecture and catalytic results crucial to find the optimal catalyst. However, the intermediates that take place in the catalytic cycle may not be symmetric and in these cases the desymmetrization of the ligand has proven to allow a better enantiocontrol in certain reactions. An easy and suitable way to desymmetrize a ligand is to introduce in the ligand design two different donor atoms. In the last decades, heterodonor ligands have therefore increased their use in catalysis, by being able to facilitate the stereocontrol thanks to the different electronic and steric properties of two distinct coordination groups [3]. Moreover, the presence of the two different donor groups facilitates the discovery of highly effective ligands for a given reaction since it is easy to independently tune both donor groups. Among heterodonor ligands, those containing both P- and N-donor groups have a predominant position, with phosphorus-oxazoline ligands the most commonly investigated due to their ready accessibility and modular construction (see Section 2). During the last decade the oxazoline group has been substituted for other more robust N-donor groups (e.g. imines, amines, oxazoles ...) that in some cases have allowed further catalytic improvement (see Section 3). Over the last years, there has been a new renaissance in the use of chiral P,O- and P,S- ligands in asymmetric catalysis, which have led to very interesting new successful applications (see Section 4). We here offer a critical review on the design and application of the most successful bidentate heterodonor P-oxazoline, P-other N, P-O and P-S ligand families in asymmetric processes. In addition to the comprehensive contents, for each group of ligands this review also offers a new perspective of presenting such ligands. While other reviews present the ligands by time or asymmetric reaction, for the first time we grouped them by their relationship between their structure and catalytic performance, which helps to associate the structural characteristics of a set of catalysts with their catalytic capacity and will facilitate further research on the field. Finally, the representative applications of these heterodonor family of ligands in total synthesis are collected at the end of this review (Section 6).

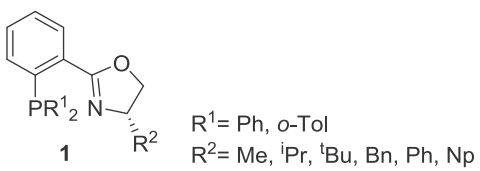


Fig. 1. The phosphine-oxazoline PHOX ligands.

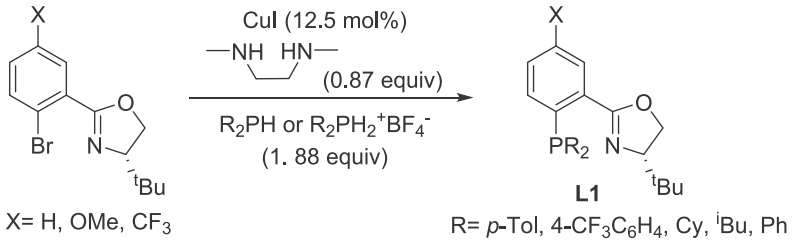
2. Heterodonor P-oxazoline ligands in asymmetric catalysis

Most of P-oxazoline ligands are prepared from easily obtainable chiral amino alcohols in short and efficient synthetic sequences [3a-e]. The beginning of P-oxazoline ligands can be found in 1993, with the preparation of the phosphine-oxazoline PHOX ligands **1** (Fig. 1) [4] that have been applied with huge success to a large variety of asymmetric transformations (e.g. allylic substitution and decarboxylative allylation reactions, hydrogenation, inter- and intramolecular Heck reactions, conjugate additions to enones, Diels-Alder and aza-Diels-Alder reactions, etc.) [2]. Despite being reported >25 years ago, PHOX ligands maintain their success in new enantioselective transformations, emphasizing their category as privileged ligand [5].

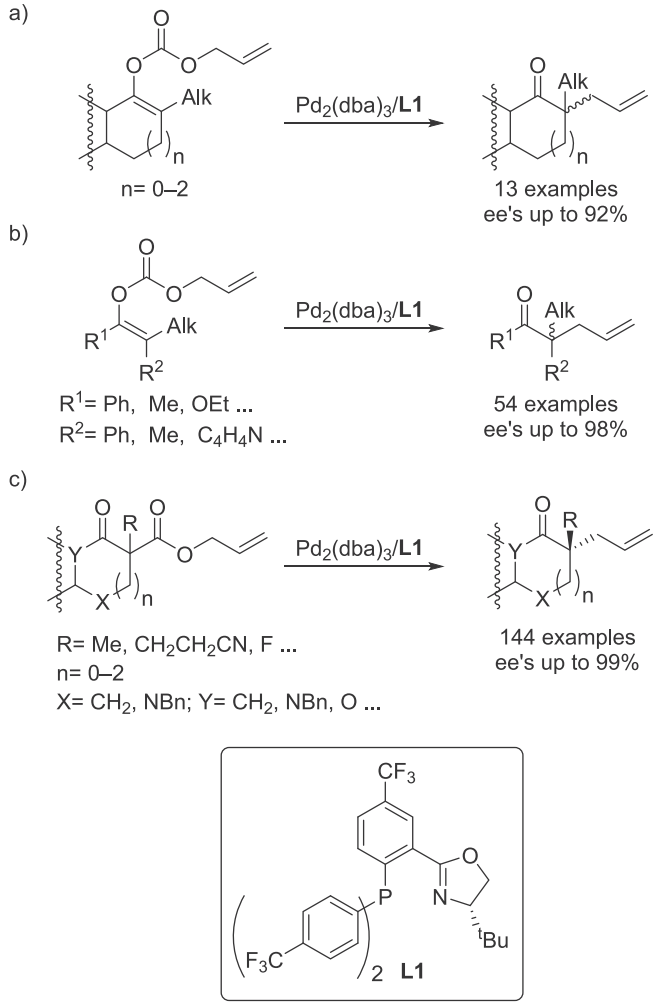
Since then, many new P-oxazoline ligands have been synthesized by varying either the ligand skeleton or the steric/electronic properties of the phosphine group or by swapping the phosphine moiety by other P-donor groups (e.g. phosphoroamidite, phosphinite) [3a-e]. These modifications allowed to improve enantioselectivities in some specific reactions. However, a few of them have been used with success to different asymmetric reactions and have shown a wide substrate and/or reagent scope. Next, we collect the families of P-oxazoline ligands that have successfully showed a large range of reaction and/or substrate scope and the relationship between their structural design and their catalytic performance. We will center on recent works and a quick overview of previous reports will also be incorporated.

Some successful modifications of the PHOX ligands are electronics by introducing withdrawing groups in the phenyl backbone ring or/and in the phosphine moiety. In this respect, it can be highlighted the recent synthesis of ligands **L1** developed by Stoltz's group (Scheme 1). The synthesis of these ligands relies in the Cu-catalyzed Ullmann-type coupling which allows the modular synthesis of ligands **L1** even in demanding steric and electronic cases, avoiding the discrete synthesis of anionic reagents (Scheme 1) [6a].

Stoltz's group found that **L1** (X = CF_3 and R = 4-CF_3-C_6H_4) was highly favorable in the Pd-catalyzed decarboxylative allylation of cyclic allyl carbonates, providing higher catalytic performance than PHOX ligands (Scheme 2a) [6]. This methodology has facilitated the transformation of substituted cyclic allyl enol carbonates into a range of natural products (e. g. (+)-hamigeran, (−)-cephalotaxine and elatol; see Section 6) [7]. The same group has recently expanded this methodology to acyclic enol carbonates, achieving also excellent enantioselectivities (Scheme 2b) [8]. Interestingly, the same catalytic system was also able to achieve excellent enantiocontrol in the decarboxylative allylation of bench-stable β-keto allyl esters. This latter finding has facilitated the synthesis of many quaternary cyclobutanones and cyclopentanones as well as heterocyclic compounds (e.g. piperazines, diazepanones, etc., Scheme 2c) [9]. This methodology has again enabled



Scheme 1. Synthesis of ligands **L1** via Cu-catalyzed phosphine/aryl halide coupling.



Scheme 2. Representative applications of Pd/**L1** (X = CF_3 and R = 4-CF_3-C_6H_4) catalytic system in the asymmetric decarboxylative allylation reactions.

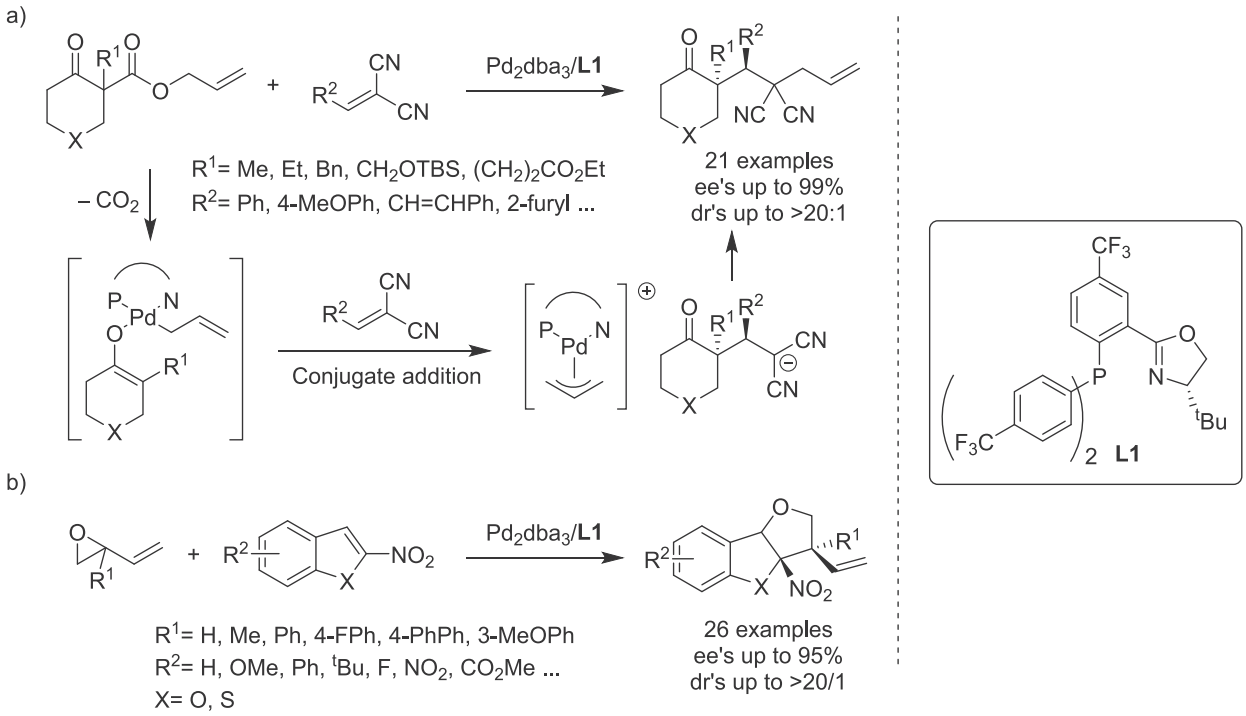
the total synthesis of several natural products (e.g. (+)-sibirinine, (−)-goniomitine, (+)-limaspermidine, nigelladine A, etc; see Section 6) [10].

The Stolz's group also demonstrated the benefits of ligand **L1** in the Pd-catalyzed enolate alkylation cascade procedure that allows the installation of vicinal quaternary and tertiary stereocentres at the α-carbon of a ketone [11]. This multiple bond-forming procedure takes place by conjugate addition of the chiral Pd/**L1**-enolate, generated *in situ* from β-keto allyl esters, to malononitriles (Scheme 3a). More recently, You's group disclosed the usefulness of Pd/**L1** catalyst in the highly diastereo- and enantioselective synthesis of tetrahydrofurobenzofurans and tetrahydrobenzothienofurans through a Pd-catalyzed dearomative [3 + 2] cycloaddition of nitrobenzofurans (Scheme 3b) [12].

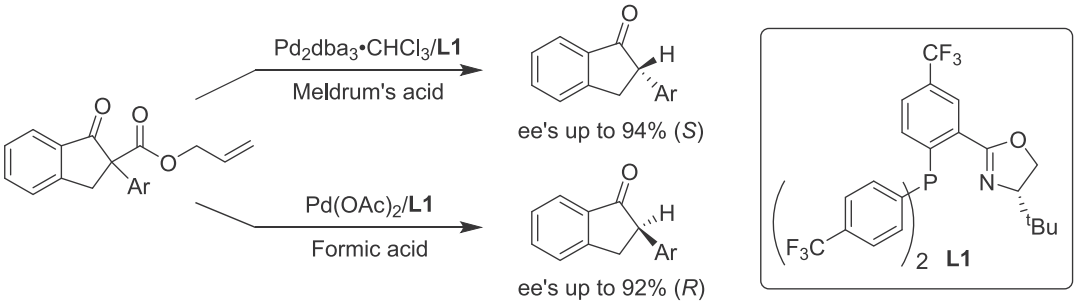
Guiry's group also disclosed the usefulness of ligand **L1** (X = CF_3 and R = 4-CF_3-C_6H_4) in the preparation of sterically demanding tertiary α-aryl ketones, such as isoflavones and α-aryl-1-indanones, via Pd-catalyzed decarboxylative protonation of α-aryl-β-keto allyl esters [13]. Interestingly, they also showed that the nature of the proton source has an impact on enantioselectivity, which clearly indicates that it is involved in the enantioselective determining step. By switching the proton source form Meldrum's acid to formic acid both enantiomers of the α-aryl-1-indanones can be accessed (Scheme 4).

Another notable modification of the PHOX ligands was to add a biaryl phosphite functionality (**a**–**e**) instead of the phosphine moiety, which increases the π-acceptor character of the ligand [14]. Ligands **L2a**–**e** (R = ^{t}Bu, ^{i}Pr, Et, Ph; Scheme 5) have the advantage to be air-stable solids, which are easily prepared by attaching several amino alcohols and phosphorochloridites to the 2-hydroxyphenyl cyanide scaffold (Scheme 5) [15].

Ligands **L2** were initially designed to increase the substrate range of PHOX ligands in Pd-catalyzed allylic substitutions [14,16]. In Pd-catalyzed allylic substitution reactions, ligands able to induce high enantioselectivities in a large range of substrates' type and nucleophiles are exceptional [1c,17]. Improving Pd-PHOX catalysts, which gave excellent enantioselectivities with *rac*-(*E*)-1,3-diarylallyl substrates but low-to-moderate ee's for cyclic and 1,3-dialkylallyl substrates, respectively [2a,3], Pd/**L2** catalysts provided an excellent catalytic performance in the allylic substitution for all of them [14]. Thus, higher activities (TOFs > 2400 mol substrate × (mol Pd × h)$^{-1}$) than with PHOX ligands were achieved due to the π-acceptor character of the phosphite moiety. In addition, the high enantioselectivities (up to 99% ee) were reached not only for disubstituted substrates, but also for tri- and monosubstituted ones (Scheme 6) [15]. The highest enantioselectivities for the benchmark substrate, *rac*-1,3-diphenylallyl acetate, were reached with the simple tropoisomeric ligand **L2b** independent of the oxazoline substituent (R = Ph, Et, ^{i}Pr or ^{t}Bu). Pd/**L2b** was also tolerant with the variation of the type of nucleophile (Scheme 6). In this respect, excellent enantioselectivities were reached with butenyl-, pentenyl-, propargyl and allyl-substituted malonates, fluorobis(phenylsulfonyl)methane (a fluoromethide synthon) and non-aromatic alcohols (ee's up to >99%, Scheme 6), whose resulting substitution products have proved valuable in the preparation of more complex chiral products [18]. Pd/**L2b** was also effectively applied to symmetrical 1,3-diaryl- and 1,3-dialkylallyl acetates with different electronic and steric demands with a large variety of C-nucleophiles (Scheme 6). For cyclic and monosubstituted substrates, the highest ee's (up to >99% and 92%, respectively; Scheme 6) were achieved using ligands **L2b** and **L2e**. It should be noted the high regioselectivities in favor to the branched chiral product attained in the allylic alkylation of monosubstituted substrates, since most of the Pd-catalyst led to the preferential formation of the achiral linear isomer [16,19]. The phosphite moiety of the ligand is key to understand the high regioselectivities achieved towards the branched isomer. Thus, the phosphite group favors the nucleophilic attack at the



Scheme 3. Pd/**L1**-catalyzed a) enolate alkylation cascade reaction and b) [3 + 2]-cycloaddition reaction.



Ar= Ph, 4-OMePh, 2,4,6-$(OMe)_3$Ph, 2,4-$(OMe)_2$Ph, 2,6-$(OMe)_2$Ph, 2,3,6-$(OMe)_3$Ph, 2,3,4-$(OMe)_3$, 2,6-Me_2Ph

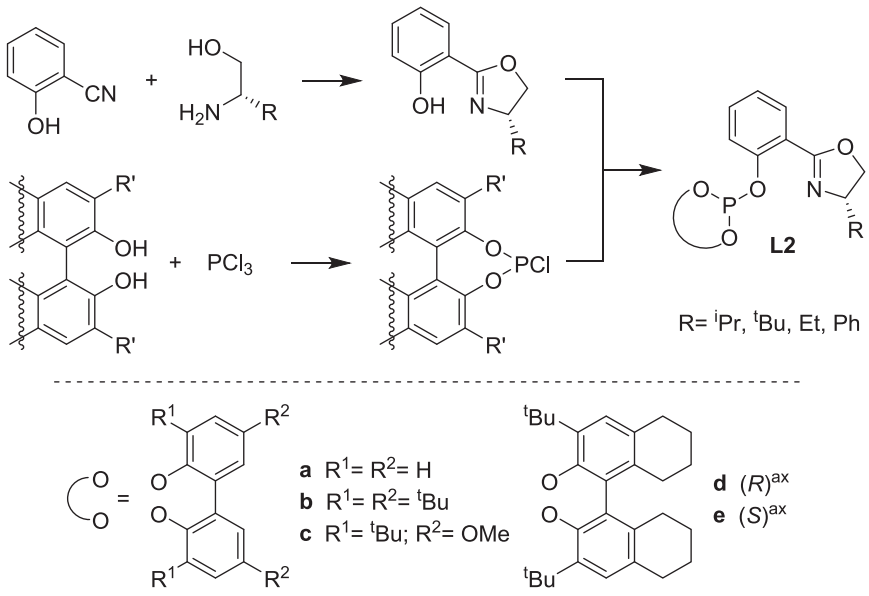
Scheme 4. Enantiodivergent preparation of tertiary α-aryl-1-indanones through Pd/**L1**-catalyzed decarboxylative asymmetric protonation.

most substituted allylic terminal carbon atom thanks to the *trans*-influence [14]. Excellent results were also reached in alkylation of 1,3,3′-trisubstituted allylic acetates (Scheme 6).

The broad substrate scope of the Pd/**L2b** catalyst system was rationalized by NMR studies and DFT calculations of their Pd-η^2-olefin and Pd-η^3-allyl intermediates complexes [14b]. These studies indicated that: (a) the tropoisomeric biphenyl phosphite group in ligand **L2b** adopts an (*S*)-configuration in the Pd-η^3-allyl intermediates with hindered as well as unhindered substrates (Fig. 2); and (b) the Pd/**L2** catalysts are able to readjust the binding chiral pocket's size to the substrate requirements, which explains the high ee's achieved in a very diverse set of substrates. This latter feature is crucial to explain the success of Pd/**L2** catalytic system in other asymmetric transformations, such as hydrogenation of unfunctionalized olefins [20], intermolecular Heck reactions, with results comparable to Pd/PHOX catalyst, using ligand **L2b** (R = Ph) [21], and in the hydroboration of olefins [22]. Interestingly, for the latter transformation Ir/**L2b** (R = ^{i}Pr) catalyst proved to be of an exceptional effectiveness, attaining higher ee's (up to 94%) than phosphine-oxazoline PHOX ligands [23]. These results are specially remarkable because achieving high selectivities in the hydroboration of 1,1′-disubstiuted alkenes is difficult, due to face selectivity issues and the difficulties in controlling the regiospecific boration in the terminal β-position [24]. Particularly, Pd/**L2b** is the only catalytic system able to hydroborate α-*tert*-butylstyrenes, thus complementing Cu-NHC catalysts, the only other system able to hydroborate α-alkyl styrenes with high ee's [25].

A final benefit of the new phosphite-oxazoline **L2** ligands compared to the PHOX ligands is that the most efficient ligand in all of the catalytic asymmetric reactions discussed above are derived from affordable (*S*)-phenylglycinol or (*S*)-valinol (R = Ph or ^{i}Pr) instead of the more costly (*S*)-*tert*-leucinol found in PHOX ligands.

Other modifications of the PHOX ligands are on the oxazoline group, by attaching the phenyl backbone ring to the stereogenic center next to the oxazoline (ligands **L3**; Fig. 3) [26], or introducing other oxazoline substituents such as, ferrocene, tricyclic and sugar oxazoline groups (e.g. ligands **L4** and **L5**; Fig. 3) [27]. However, in any case the enantioselectivities and the substrate scope improved



Scheme 5. Synthesis of phosphite-oxazoline ligands **L2a**–**e**.

those attained with the PHOX ligands. Thus, ligands **L3** (R^1 = Cy or Ph and R^2 = ^{t}Bu) led to high enantioselectivities in the Ir-catalyzed hydrogenation of unfunctionalized olefins but only in the reduction of some methylstilbenes (ee's up to 99% ee) and a range of β-methylcinnamic esters with enantioselectivities up to 99% [26]. Ligand **L3** (R^1 = Ph and R^2 = ^{t}Bu) has also been used with success in the Pd-catalyzed allylic alkylation of benchmark substrate (ee's of 98%) and in the intermolecular Heck reaction of 2,3-dihydrofuran with the phenyl triflate (94% ee) [28]. Ligands **L4** and **L5** followed a similar trend than the PHOX ligands in the Pd-catalyzed allylic alkylation. Thus, they provided high enantioselectivities with *rac*-(*E*)-1,3-diarylallyl substrates, but low for cyclic ones. Ligand **L4** provided also high enantiocontrol in the Pd-catalyzed Heck reaction of 2,3-dihydrofuran using various aryl triflates (ee's up to 98%) [29].

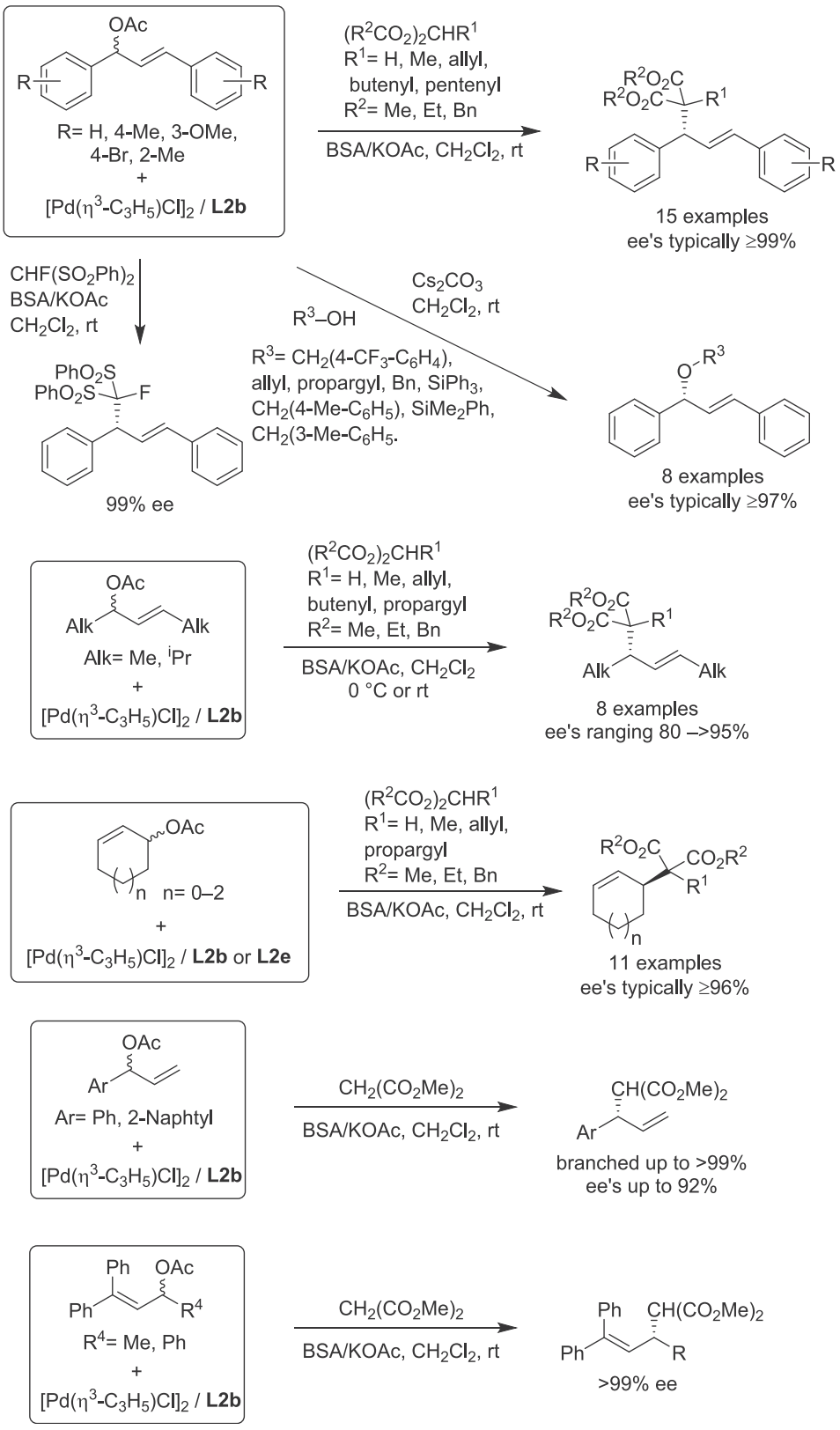
Another modification into the oxazoline ring was to introduce substituents in the 5 and/or 5′ positions (e.g. ligands **L6** and **L7**; Fig. 4) [30] providing similar levels of enantioinduction than the usually most effective PHOX ligand, the ^{t}Bu-PHOX, but with the advantage of being readily accessible as both enantiomers from either the (*S*) or (*R*)-valine rather than from expensive *tert*-leucinol enantiomers.

Besides these modifications on the phosphine and oxazoline moieties and in phenyl backbone ring, many changes on the ligand backbone have been studied. One of these modifications includes a methylene spacer linking the phenyl ring of the ligand backbone and the oxazoline ring (ligands **L8**), forming with the metal a higher seven-membered chelate ring (phosphine-oxazoline ligands **L8**, R^1 = Me, H; R^2 = Me, ^{i}Pr, ^{t}Bu; Scheme 7) [31]. The phosphine moiety in ligands **L8** has also been exchanged for a biaryl phosphite group (ligands **L9**; Scheme 7) [32]. Ligands **L8** and **L9** were synthesized in few steps from easily available starting material, as illustrated in Scheme 7.

Zhou and coworkers used Pd/**L8** catalytic systems in the intermolecular Heck reaction (Scheme 8) [31]. The intermolecular asymmetric Heck reaction is less developed than the intramolecular version due to regioselectivity issues, which hampers its application for the synthesis of more complex molecules [33]. Pfaltz early demonstrated that the use of ^{t}Bu-PHOX ligand can overcome the regioselectivity issue, although it requires from 3 to 7 days for full conversion [34]. Ligands **L8** (R^1 = Me, H and R^2 = ^{t}Bu) provided high regio- and enantioselectivities (up to 95% ee, Scheme 8), with results comparable to PHOX ligands, in the reaction of 2,3-dihydrofuran and various aryl triflates [31]. From these results it should be highlighted that ligands that contained hydrogens in the benzylic position provided the *R*-enantiomer while ligands with methyl substituents at R^1 provided the *S*-enantiomers (Scheme 8).

More recently our group decided to replace the phosphine group in ligands **L8** by several π-acceptor biaryl phosphite moieties (ligands **L9b**, **e**, **f**–**h**; R^1 = Me, H; R^2 = ^{i}Pr, ^{t}Bu, Ph; Scheme 7) [32]. This change increases the activity, because the presence of the phosphite group favors the migratory insertion, which come up to be the rate-determining step. At the same time the substrate scope could be extended to other heterocyclic and carbocyclic olefins and to other triflates including non-aromatic ones (ee's up to 98% and regioselectivities up to 99%). The best results were obtained with the ligand that had biaryl phosphite groups **b**, **e** and **h**, a hydrogen in R^1 positions and an ^{i}Pr oxazoline substituent, avoiding the use of the costly ^{t}Bu substituent required in the analogous phosphine-oxazoline **L8** and PHOX ligands [32].

Advantageously, the same family of P-oxazoline ligands **L8**–**L9** also provided an excellent catalytic performance in the reduction of unfunctionalized olefins or olefins with poorly coordinative groups. This was a relevant finding because the reduction of these type of substrates is underdeveloped compared with the asymmetric hydrogenation of alkenes containing coordinative groups [35]. This is because catalysts able to hydrogenate unfunctionalized olefins are very sensitive to changes in the olefin geometry and to changes in the substitution pattern. Thus, for instance, most of the catalysts perform well for trisubstituted *E*-unfunctionalized alkenes. Only very recently have appeared catalysts able to reduce *Z*-trisubstituted and 1,1′-disubstituted. The asymmetric reduction of tetrasubstituted unfunctionalized olefins still remains a challenge. This substrate-dependent behavior was already displayed with the pioneering Pfaltz's design of [Ir(PHOX)(cod)]BAr_F (cod = 1,5-cyclooctadiene and BAr_F = 3,5-$(F_3C)_2$-$C_6H_3)_4B$) catalyst precursors [36], which mainly provides high ee's in the hydrogenation of a small group of *E*-trisubstituted olefins [37]. The authors first prepared the catalyst precursors [Ir(cod)(**L8**–**L9**)]BAr_F by reaction of the corresponding ligand with $[Ir(\mu\text{-}Cl)(cod)]_2$ and subsequent Cl/BAr_F anion exchange to give air stable red–orange solids in high



Scheme 6. Representative catalytic results in the Pd-catalyzed allylic substitution with Pd/**L2b** (R = Ph) catalyst.

yields (Scheme 9). The VT-NMR spectra (from +35 to −85 °C) showed one single isomer in solution [20,38].

They found that the use of [Ir(cod)(**L8**)]BAr_F (**L8**; R^1 = H and R^2 = ^{i}Pr) allowed to extend the range of *E*-trisubstituted olefins to include allylic alcohols and α,β-unsaturated ketones and esters (ee's up to 98%) [38]. Replacing the phosphine moiety in ligands **L8** by several π-acceptor biaryl phosphite groups (ligands **L9**) further extended the array of substrates successfully hydrogenated,

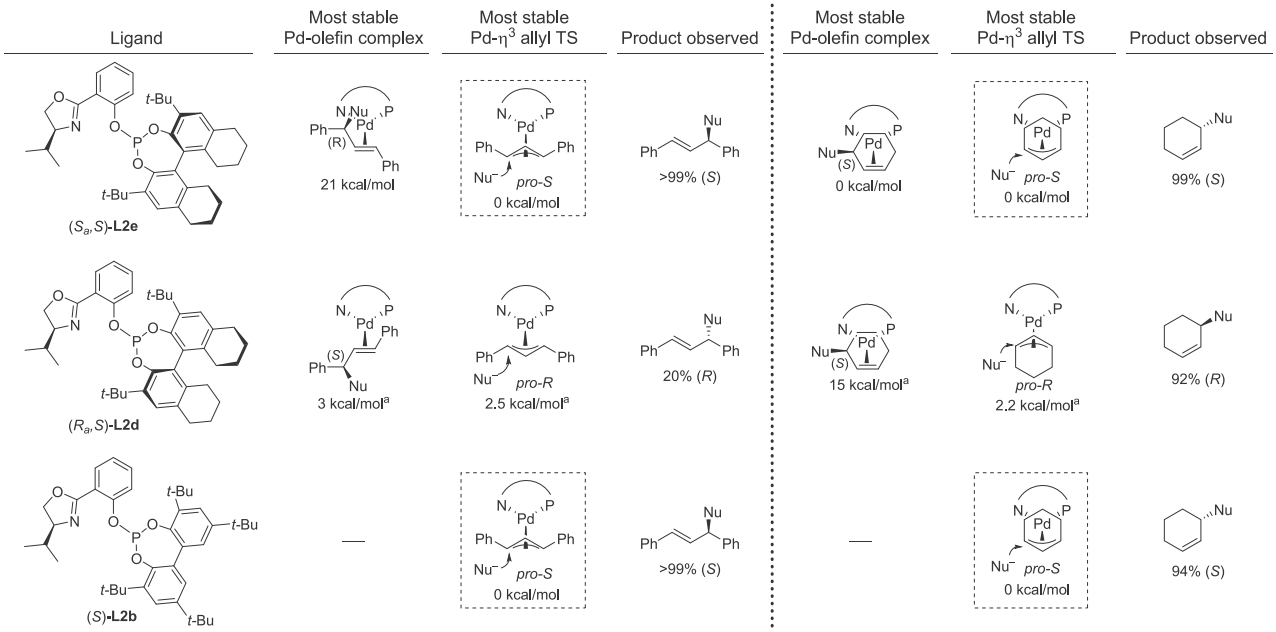


Fig. 2. Calculated relative energies for the most stable Pd-olefin complexes and transition states (TS) for the nuclephilic attack at the Pd-η^3 allyl complexes for model hindered and unhindered substrates. Experimental enantioselectivities for the allylic alkylation products using dimethyl malonate are also shown. [a] Energies relative to those containing ligand (*Sa*,*S*)-**L2e**.

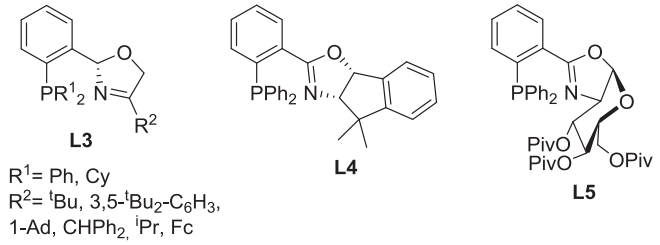


Fig. 3. Phosphine-oxazoline ligands **L3**–**L5**.

including more challenging 1,1′-disubstituted olefins [20]. The highest enantioselectivities were obtained with [Ir(cod)(**L9**)]BAr_F containing the ligand with the less expensive Ph or ^{i}Pr oxazoline substituents and hydrogen atoms in the benzylic position. The phosphite group depended on the substrate to be hydrogenated (a summary of the reduction of 55 olefins with Ir/**L9** are shown in Fig. 5). Interestingly, environmentally friendly solvent 1,2-propylene carbonate (PC) could be used instead of the commonly used dichloromethane without any deleterious effect on enantioselectivity. High enantioselectivities were therefore attained in the reduction of trisubstituted olefins including the more challenging triarylsubstituted substrates ones and those containing several poorly coordinative groups such as α,β-unsaturated ketones, amide, lactones, lactams, alkenyl boronic esters and enol phosphinates (ee's up to >99%). Even thought, highly enantioselective hydrogenation catalysts for 1,1′-disubstituted substrates are very scarce [39], it was gratifying to obtain ee's up to 98% in a large number of *tert*-butyl-aryl 1,1′-disubstituted alkenes (Fig. 5) which differs in the steric and electronic characteristics of the aryl substituent. Decreasing the bulkiness of the alkyl substituent on these α-alkyl-styrenes results in slightly lower enantioselectivities (ee's from 83% to 91%), due to a competing isomerization pathway as it was disclosed by means of deuterium labeling experiments. Similar values of enantioselectivities were found in the hydrogenation of 1,1′-disubstituted alkenyl boronic esters and enol phosphinates (Fig. 5).

In addition, [Ir(cod)(**L9**)]BAr_F were also successfully applied in the reduction of an additional challenging class of substrate; the cyclic β-enamides (Scheme 10) [40]. Despite, there is an important number of therapeutic agents (e.g. robalzotan, rotigotine, terutroban and alnespirone) [41] than can be accessed via their hydrogenation, there are only few catalysts able to hydrogenate such substrate class with high ee's, being the majority based on rhodium and ruthenium [42]. In 2016, Verdaguer's and Riera's group demonstrated that Ir-PN catalyst can also be used, exceeding the scope of Ru/Rh-catalyst [43]. Then, our group decided also to study the application of Ir/**L9** [40]. Enantioselectivities were high for many cyclic β-enamides derived from, 2-tetralones and 3-chromanones when using Ir/**L9f** (R^1 = H; R^2 = ^{i}Pr) catalyst (Scheme 10). To note, the high enantioselectivity achieved in the reduction of *N*-(5-methoxy-3,4-dihydronaphthalen-2-yl)acetamide, which provides a crucial intermediate for the synthesis of rotigotine [40]. We also found that both enantiomers of the products can be accessed by exchange iridium to rhodium. Again, the use of PC has not effect on the enantioselectivities.

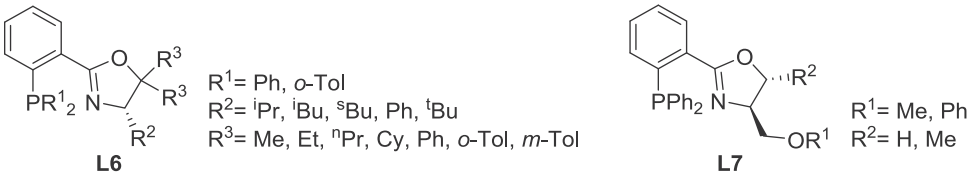
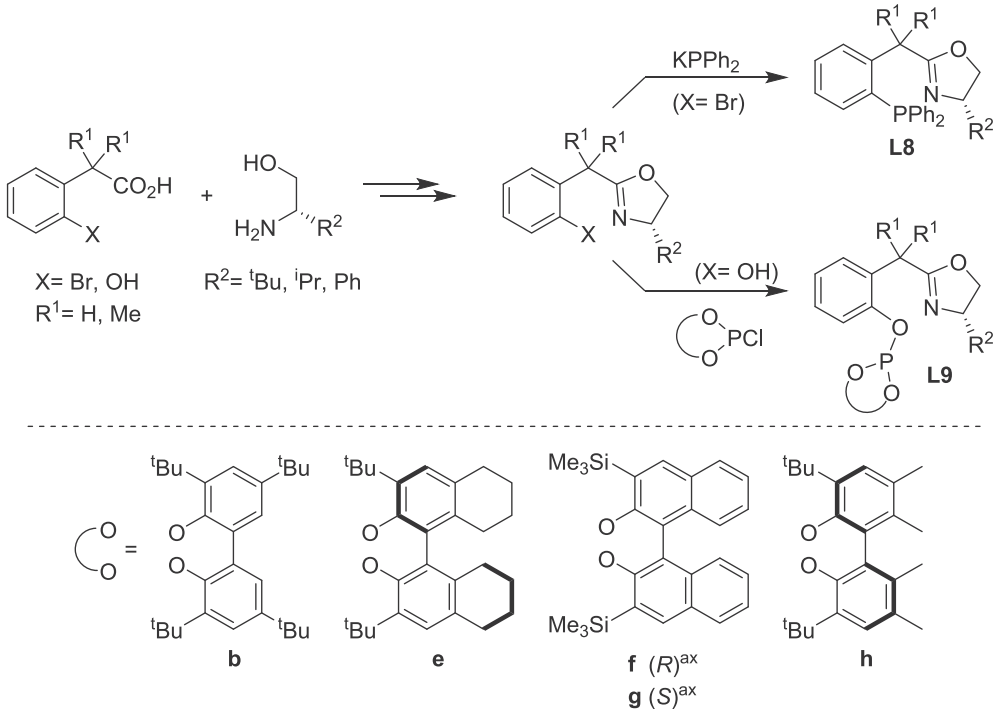
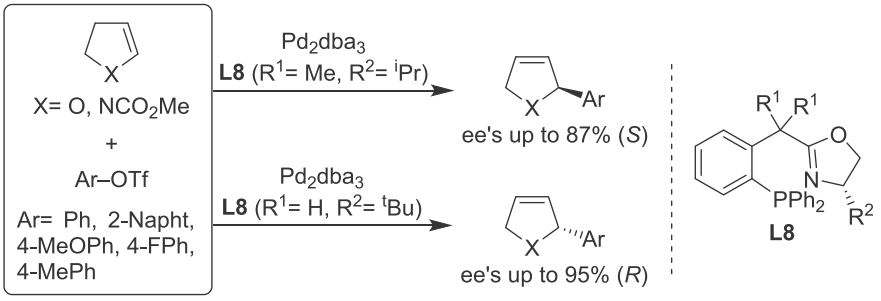


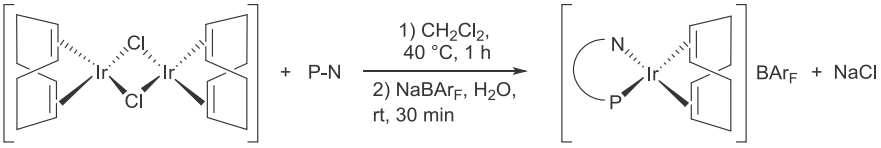
Fig. 4. Phosphine-oxazoline ligands **L6** and **L7** with geminal substituents at C5 as practical substitutes of ^{t}Bu-PHOX.



Scheme 7. Synthesis of P-oxazoline ligands **L8** and **L9**.



Scheme 8. The use of ligands **L8** in the Pd-catalyzed intermolecular Heck reaction.



Scheme 9. Synthesis of [Ir(cod)(**L8**–**L9**)]BAr_F catalyst precursors.

Many of the backbone changes in the PHOX ligands also includes the replacement of phenyl backbone ring of PHOX ligand by other moieties (Fig. 6), such as ferro- and ruthenocene groups (e.g., ligands **L10**–**L14**) [44], biphenyl or binaphthyl groups (e.g., ligands **L15**) [45], several heterocyclic backbones (e. g., ligands **L16**–**L19**) [46], an alkyl chain (e.g., ligands **L20**–**L28**) [47] and bicyclic, sugar, and spiro backbones (e.g., ligands **L29**–**L34**). In many of these latter backbones modifications the phosphine group has also been replaced by a phosphinite, a phosphite, an aminophosphine and an stereogenic P groups. Among them those having two carbons linking the two donor functionalities have been employed with great success to several enantioselective reactions.

In this respect, we can point up the families of phosphinite/phosphite-oxazoline ligands **L22–23** and **L24–27** (Fig. 6), where the *ortho*-phenylene tether of the PHOX has been changed by an alkyl chain. They were initially designed to provide a wider substrate capacity in the asymmetric reduction of unfunctionalized olefins. Starting from different carboxylic acid derivatives, chiral serine or threonine methyl esters, and Grignard reagents a range of hydroxyl-oxazolines were easily attained, which after treatment with the corresponding chlorophosphine or phosphorochloridite gave access to ligands **L22**–**L23** (Scheme 11) [48].

The phosphinite–oxazolines **L22**, developed by Pfaltz, (Fig. 6 and Scheme 11) are one of the most successful ligands for the Ir-catalyzed reduction of unfunctionalized olefins [24]. Unlike the

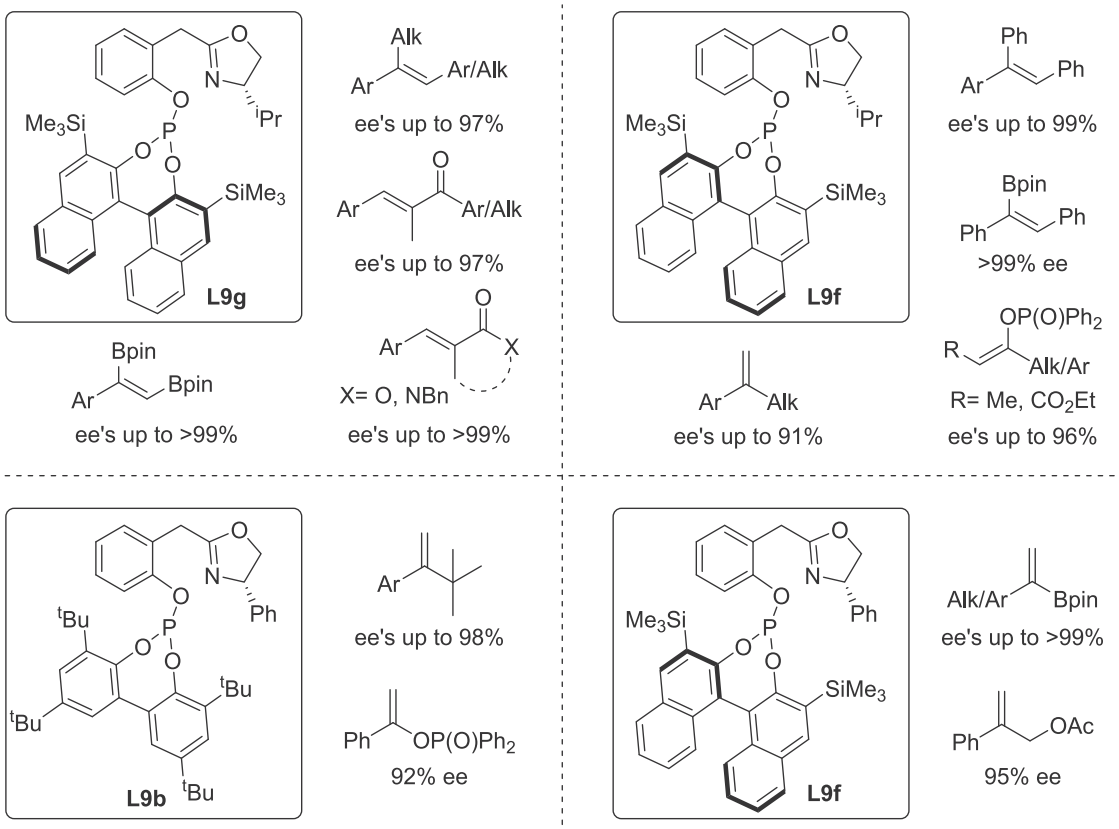
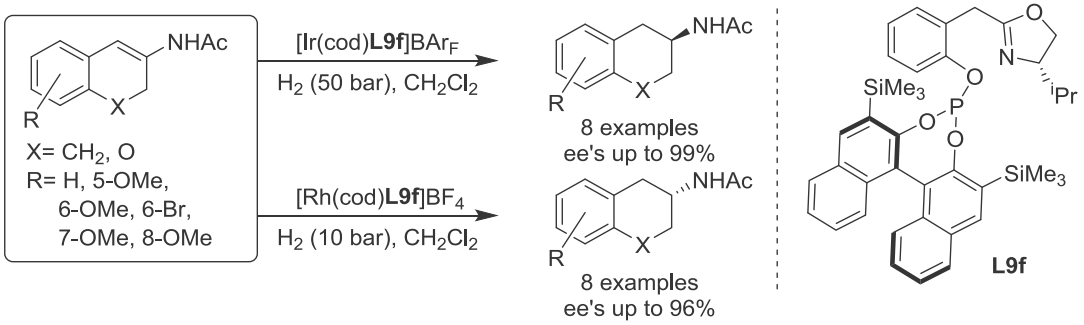


Fig. 5. Representative catalytic results for the hydrogenation of unfunctionalized olefins with [Ir(**L9**)(cod)]BAr_F catalysts precursors.



Scheme 10. Asymmetric hydrogenation of cyclic β-enamides with [Ir(cod)**L9f**]BAr_F and [Rh(cod)**L9f**]BF_4 catalysts.

PHOX ligands, the phosphorus unit is bonded to the stereogenic center next to the oxazoline.

The Ir-catalyst precursors were synthesized using the same process described for previous [Ir(cod)(**L8**–**L9**)]BAr_F complexes, obtaining air-stable orange powders that needed to be purified by column chromatography on silica gel. With [Ir(cod)(**L22**)]BAr_F, they reached excellent enantioselectivities for the first time in the reduction of *E*- and *Z*-2-aryl-2-butenes (Fig. 7) [48a,49]. The author optimized the enantioselectivity for each substrate by systematic modifications of the substituents at the oxazoline ring and ligand skeleton. The best enantioselectivities were achieved with [Ir(cod)(**L22**)]BAr_F, containing diphenylphosphinite ligands **L22** (R^1 = Ph) with a methyl group at R^3 and a benzyl at the alkyl chain (R^4), although, the correct choice of the oxazoline R^2 substituent and the configuration of the carbon of R^3 is determined by olefin geometry. Thus, for *E*-trisubstituted olefins, ee's are highest with a 3,5-Me_2-Ph or a Ph oxazoline R^2 substituent and an *S*-configuration for R^3, while for *Z*-olefins they are best with a Ph oxazoline substituent and an *R*-configuration into the ligand. Further optimization of ligand parameters allowed for the first time to reduce some more challenging terminal olefins and 1,1′-disubstituted enamines (ee's up to 99%; Fig. 7) with the ligand that contains a methyl and a benzyl group at R^3 and at R^4, respectively but a cyclohexenyl at R^1 [49b,c]. More recently, Ir-**L22** also allowed the hydrogenation of α,β-unsaturated nitriles (ee's up to 98%, Fig. 7) [49d]. These catalysts also perform well in 1,2-propylene carbonate, a green solvent, allowing the catalysts to be recycled several times [50].

Then our group synthetized the phosphite-based analogues of ligands **L22**, which broadened the number of 1,1′-disubstituted substrates to be reduced with success [51]. By using [Ir(cod)(**L23j**)]BAr_F and [Ir(cod)(**L23b**)]BAr_F (R^2 = Ph, R^3 = H and R^4 = Me) catalysts high ee's (up to >99%) were therefore attained in the hydrogenation of a range of (het)aryl–alkyl disubstituted olefins,

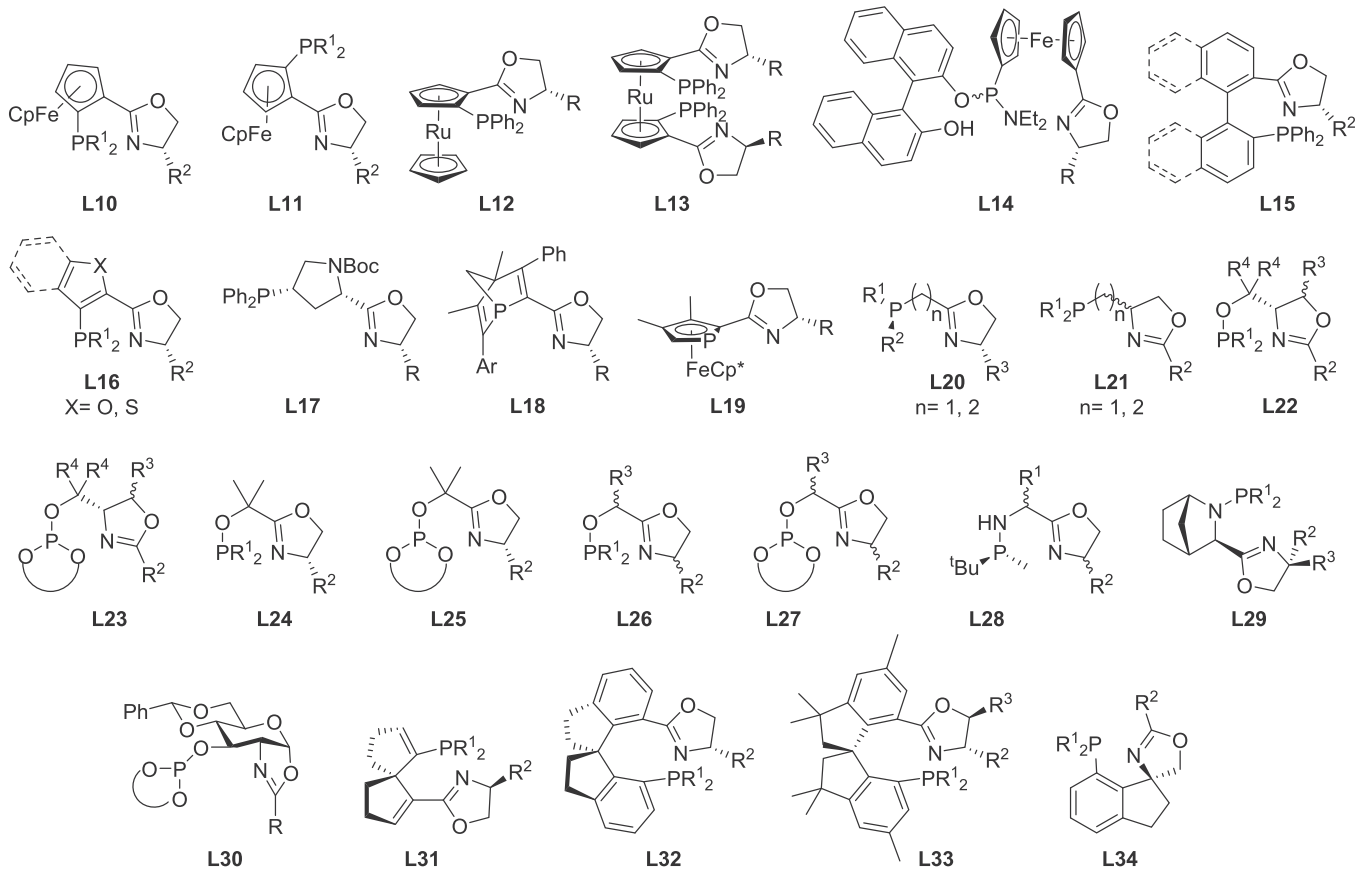
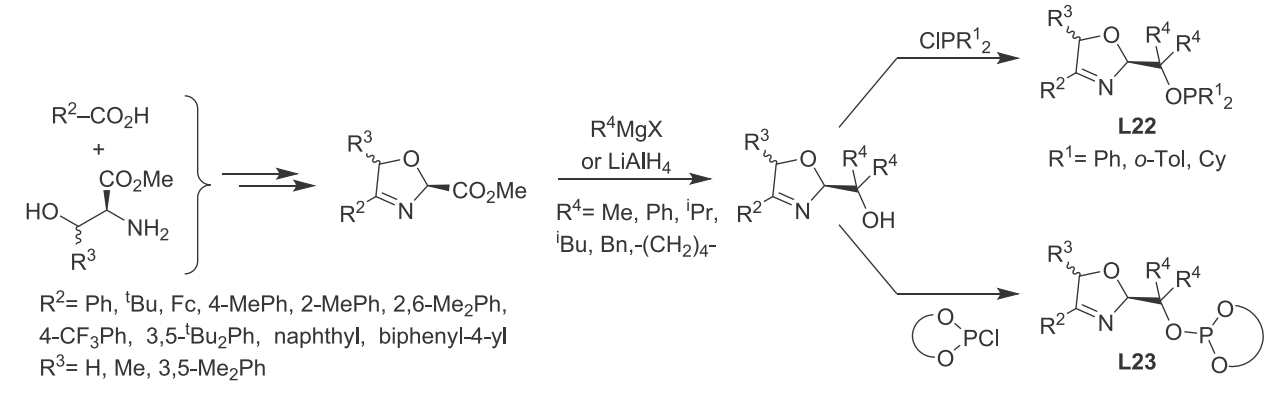
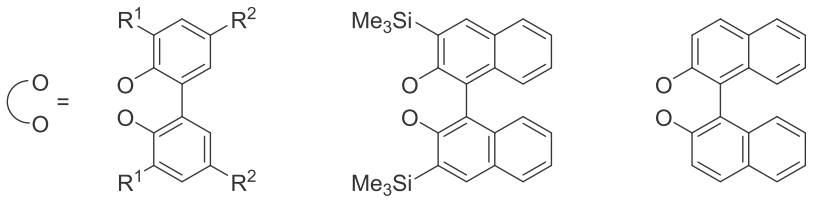


Fig. 6. P-oxazoline ligands **L10**–**L34**.





Scheme 11. Synthesis of phosphinite/phosphite-oxazoline ligands **L22**–**L23**.

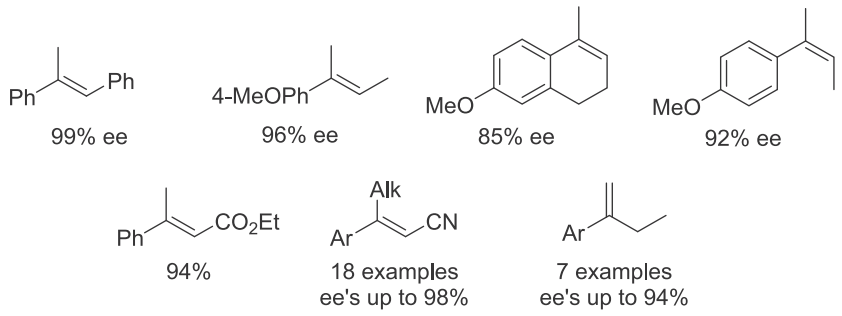


Fig. 7. Selected catalytic hydrogenation results with [Ir(**L22**)(cod)]BAr_F.

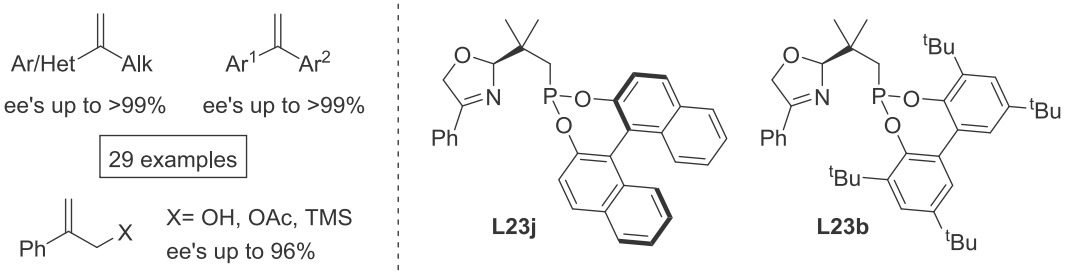
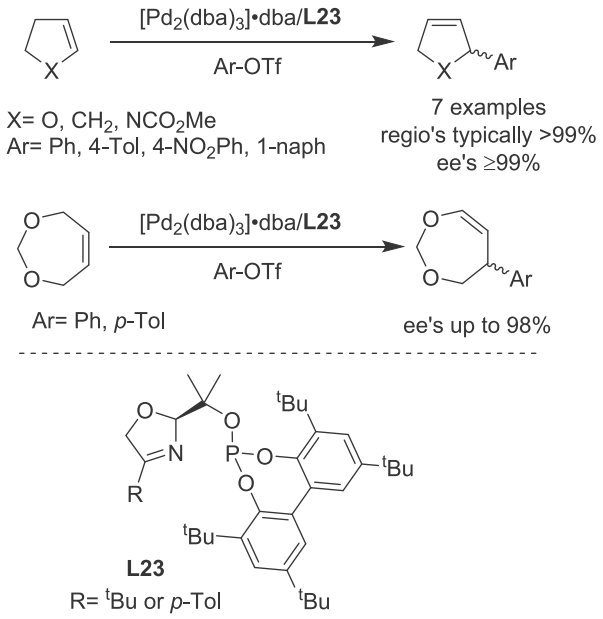


Fig. 8. Selected results achieved with [Ir(**L23j** and/or **L23b**)(cod)]BAr_F catalysts in the asymmetric hydrogenation of 1,1′-disubstituted substrates.



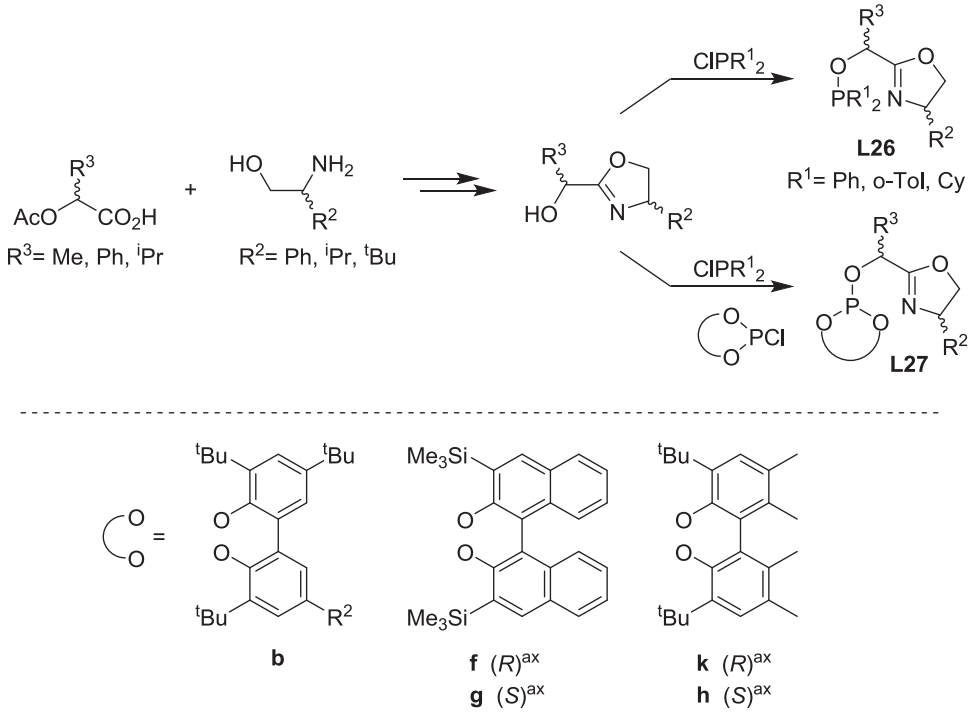
Scheme 12. Pd-catalyzed asymmetric intermolecular Heck reaction using phosphite-oxazoline ligands **L23**.

allylic alcohols and allylic silanes (29 compounds; Fig. 8), surpassing previous successfully Ir/**L9** and Ir/**L22** catalysts [39]. It should point up that Ir/**L23j** (R^2 = Ph, R^3 = H and R^4 = Me) also attained high ee's for trisubstituted olefins and α,β-unsaturated esters. For Z-trisubstituted olefins and allylic alcohols the highest catalytic performance was attained with Ir/**23b** (R^2 = Ph, R^3 = H and R^4 = Me) [51]. Advantageously, the use of PC enabled the recycle of the catalysts until five times.

Useful, ligands **L23** were also used in the allylic substitution of many mono, di- and trisubstituted linear hindered and unhindered linear allylic acetates (up to 99% ee) with C- and N-nucleophiles [48b]. Moreover, reversing the configuration of the alkyl chain or reversing the configuration of the phosphite group led to both enantiomers of the products. The results surpass PHOX ligands and are similar to the best accounted with the previous family of phosphite-oxazoline ligands **L2** except for cyclic substrates (ee's up to 83%). To increase the enantioselectivity in the cyclic substrates the oxazoline group was changed by a thiazoline group (see Section 3) [18c]. With this simple modification the enantioselectivities improved significantly (94% ee). Both families of ligands (phosphite-oxazoline/thiazoline) are complementary. The study of the Pd-π allyl intermediates allowed to explain the catalytic performance. Thus, 1,3-diphenyl allyl and 1,3-cyclohexenyl allyl Pd-complexes showed that the substitutents at the backbone ligand chain and at the oxazoline group have to be correctly combined to give the isomer that reacts faster and to avoid complexes with the ligand coordinated monodentated. However, for the unhindered lineal substrates, the enantioselectivity is explained throught a late transition state were the substituent at the alkyl chain favored to reach a specific Pd-olefin complex [48b].

Ligands **L23** also provided high catalytic performance in the Pd-catalyzed Heck reaction. High regio- and enantioselectivity could be achieved using many substrates and triflate sources, with ligands **L23b** (R^2 = *p*-CH_3-Ph or ^{t}Bu, R^3 = H, R^4 = CH_3, Fig. 6) [21]. Interestingly, the reaction times were considerably reduced by using microwave-irradiation conditions (from the 24 h with PHOX ligands to 10 min with ligand **L23b**) and regio- and enantioselectivities were still high (ee's up to 99%; Scheme 12).

Another modification of ligands **L22** was the development of ligands **L24** (Fig. 6, R1 = *o*-Tol, Ph and R^2 = ^{t}Bu, ^{i}Pr,), with the alkyl chain linked to the C-2 of the oxazoline group as in PHOX ligands [52]. Albeit the substrate range in asymmetric reduction of unfunctionalized olefins is reduced than with Ir/**L22**, they are complementary. Thus, high enantioselectivities were attained in the hydrogenation of allylic alcohols, alkenes with heteroaromatic substituents and the cyclic substrate 6-methoxy-1-methyl-3,4-di hydronaphthalene. Advantageous, Harmata and Hong have also used Ir/**L24** catalyst in the total synthesis of pseudopteroxazole, a natural antitubercular agent (see Section 6). The catalysts was able



Scheme 13. Synthesis of phosphinite/phosphite-oxazoline ligands **L26**–**L27**.

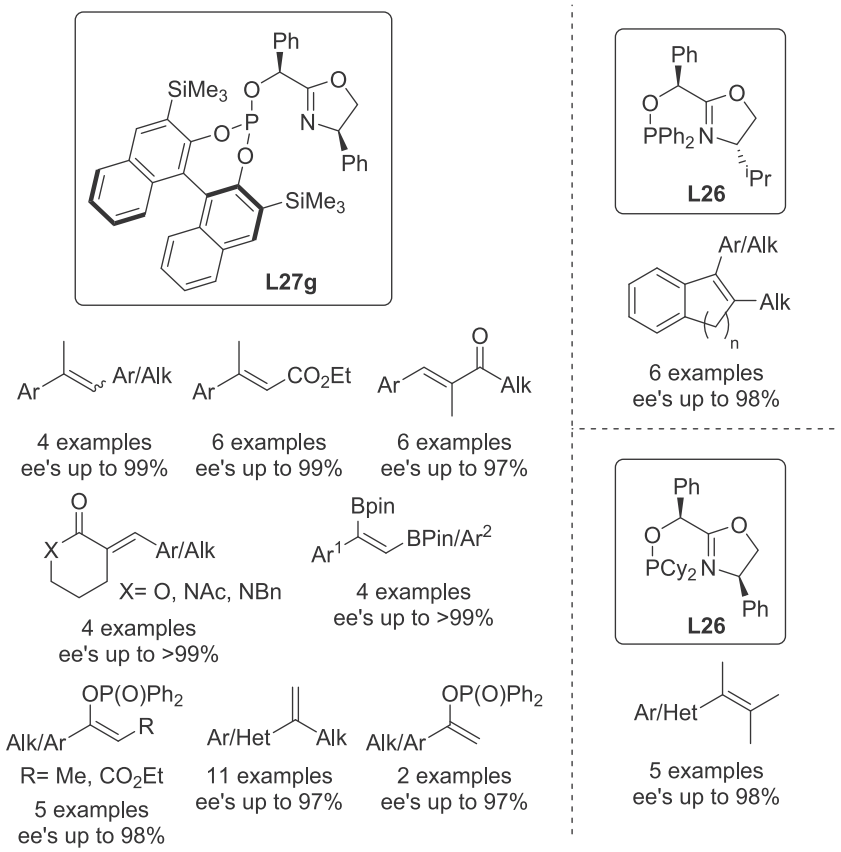


Fig. 9. Chosen results attained with P-oxazoline ligands **L26**–**L27** in the Ir-catalyzed hydrogenation of di-, tri- and tetrasubstituted olefins.

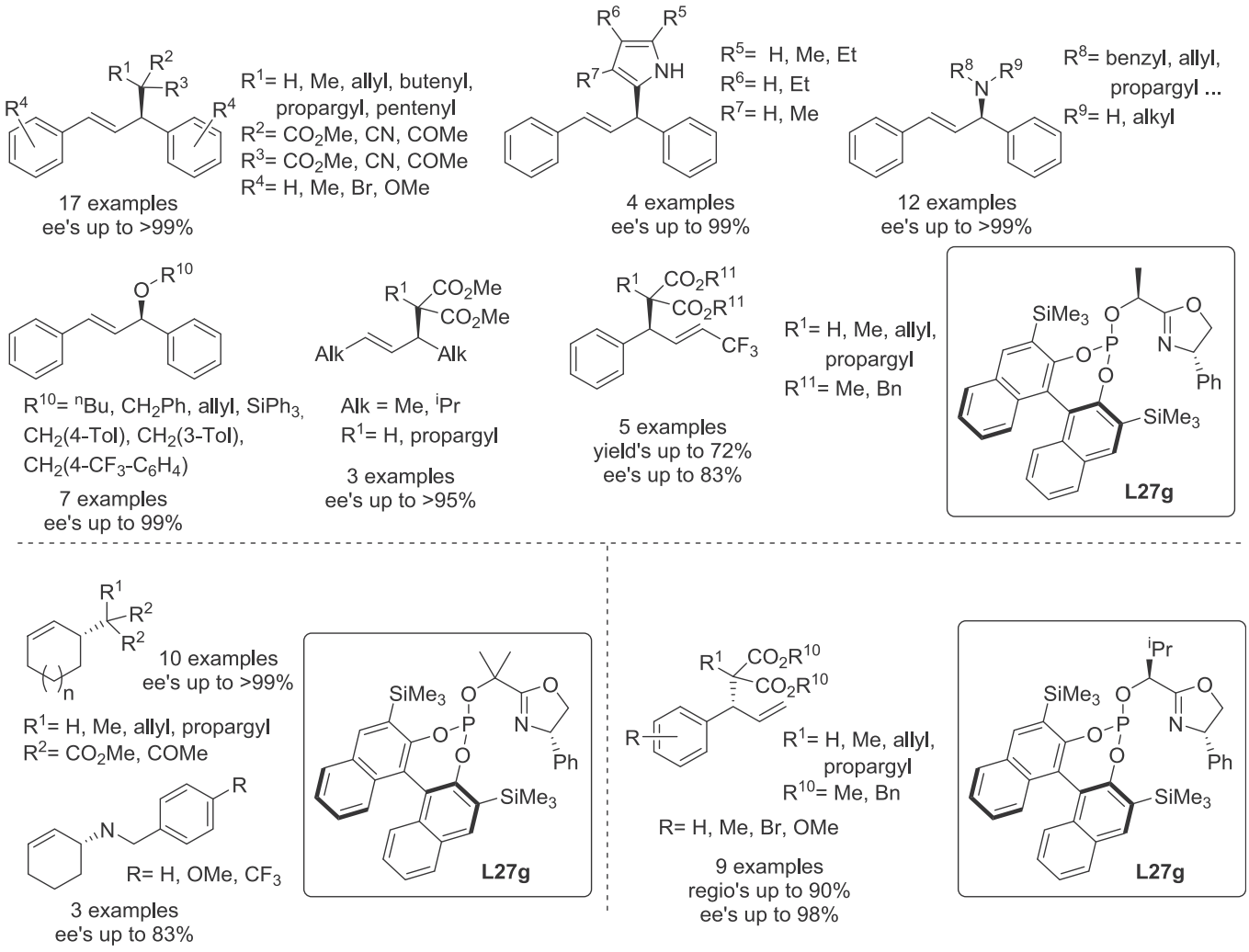


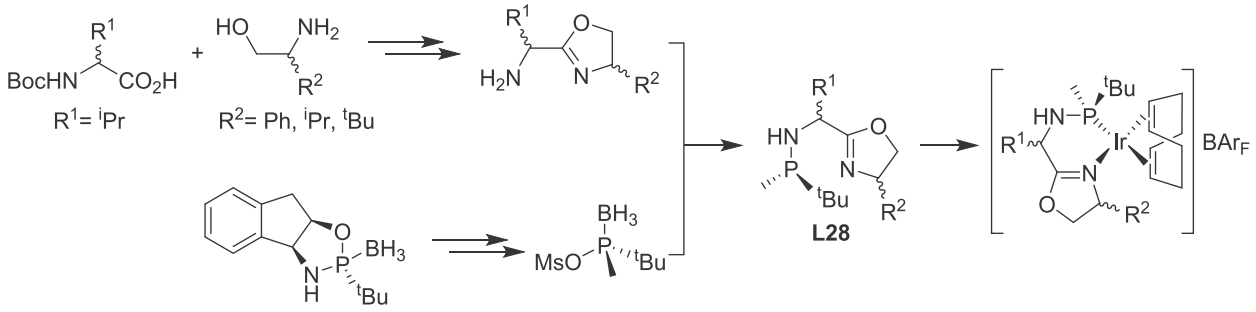
Fig. 10. Selected results in the use of Pd/**L27g** in the Pd-catalyzed allylic substitutions.

to hydrogenate the internal double bond, and not the exocyclic C=C bond, with high regioselectivity in 90% yield [53].

More recently, new families of P-oxazolines (ligands **L25**–**L27**; Fig. 6) analogous to Pfaltz ones, still with two carbon atoms between the P- and N-donor functionalities, have been developed. The phosphite/phosphinite-oxazoline ligands **L25**–**L27** were used in the enantioselective Ir-catalyzed hydrogenation and Pd-catalyzed allylic substitutions. Ligands **L26** and **L27** were prepared in a similar manner than ligand **L24** and **L25** (Scheme 13). Condensation of readily available chiral α-acetoxy acids with a range of chiral aminoalcohols followed by oxazoline formation using diethylaminosulfurtrifluoride (DAST) and subsequent alcohol deprotection yielded a range of hydroxyl-oxazolines. The later were then treated with the corresponding chlorophosphine or phosphorochloridite to give access to ligands **L26**–**L27** (Scheme 13) [40].

About the hydrogenation, air stable orange-solids [Ir(cod)(L)] BAr_F (L = **L26** and **L27b**, **f–h**, **k** complexes were the first catalysts able to successfully hydrogenate di-, tri- and tetrasubstituted unfunctionalized olefins (ee's up to 99% in 62 examples, Fig. 9) [40]. As early stated, the asymmetric hydrogenation of tetrasubstituted olefins is still a challenge [35f,54]. Thus, there are a very limited number of catalyst able to hydrogenate them and those that do shows poor versatility, except for the recent publication with Ir/**L21** catalyst [55] (Fig. 6) [56]. Improving previous reports, high enantioselectivities (up to 98%) were attained in the hydrogenation of several indenes, 1,2-dihydro-napthalene and a broad scope of acyclic tetrasubstituted olefins under mild reaction conditions using Ir-phosphinite-oxazoline **L26** catalysts (Fig. 9) [40]. Significantly, it was also found that the phosphinite-oxazoline ligand **L26** to be used depend on the olefin to be reduced. In this respect, while the highest enantioselectivity in the reduction of the more bulky cyclic indene substrates is obtained with the less bulky phosphinite group (Ph), for the less bulky indenes and acyclic substrates phosphinite ligands with bulkier substituents are needed (*o*-tolyl and cylcohexyl groups, respectively) to reach the highest enantioselectivity. Finally, by simple replacing the phosphinite by the right phosphite moiety (ligands **L27**) the same family of catalysts could also effectively hydrogenated a range of unfunctionalized tri- and disubstituted substrates (Fig. 9). The catalysts could also effectively reduce a variety of olefins with different functional groups from those poorly coordinative (e.g.enones, lactames and vinyl boronates) to highly coordinative ones (e.g. β-enamides) [40].

Compared to Pd/**L2** catalyst Pd/**L27g** (R^2 = R^3 = Ph) also gave higher activities (TOF up to 8000 h^{-1}) and high enantioselectivities in the allylic substitution of a wide number of substrates (ee's up to >99%, 74 examples in total, Fig. 10) [57]. Symmetrically disubstituted linear allylic acetates, containing alkyl or aryl substituents, with a variety of C-nucleophiles, including α-substituted malonates, malononitrile, diketones, 2-cyanoacetates and pyrroles were successfully alkylated with Pd/**27 g**. High enantioselectivities were reached with: i) both alkyl and aryl amines, ii) benzylic, allylic and



Scheme 14. Synthesis of P-stereogenic aminophosphine-oxazoline ligands **L28** and their corresponding Ir-complexes.

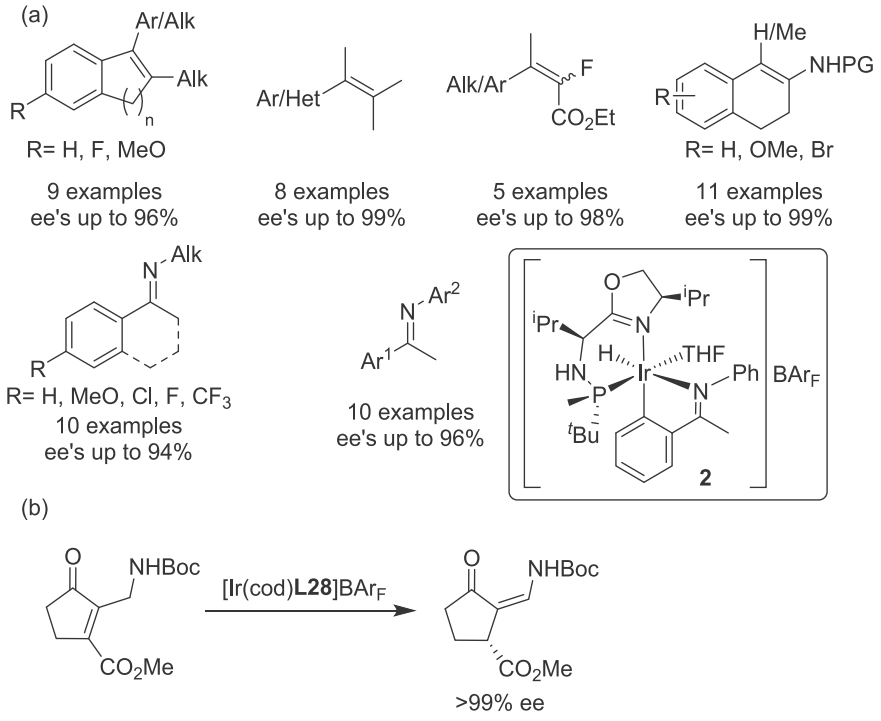
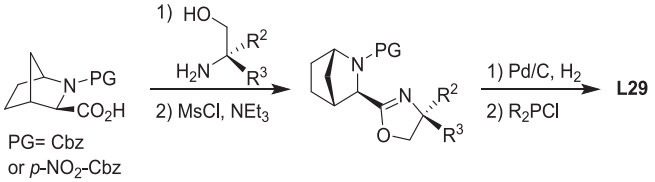


Fig. 11. Representative results in the Ir/**L28**-catalyzed (a) hydrogenation of tetrasubstituted alkenes, β-enamides and imines, and (b) isomerization of *N*-allyl amides.

iii) silanols. By introducing in ligand **L27g** a second methyl group at the alkyl chain, ee's could be improved up to >99% in the alkylation of cyclic substrates (Fig. 10). In addition, the Pd/**L27g** catalyst is one of the few catalyst that can deracemize unsymmetrically disubstituted substrates such as 1,1,1-trifluoro-4-phenylbut-3-en-2-yl acetate via dynamic kinetic asymmetric transformation with several malonates (yield's up to 72% and ee's up to 80%). Regioselectivities up to 90% and ee's up to 98% were offered in the alkylation of 1-arylallyl acetates with malonates. Nevertheless, the regioselectivity into the branched product decreased with α-substituted malonates (e.g. it dropped from 83% using dimethyl malonate to 60% using dimethyl 2-methylmalonate). NMR and DFT studies showed an early TS, in which the enantioselectivity is guided by the ratio of the Pd-η^3-allyl compounds and the relative electrophilicity of the allylic terminal carbon atoms. It was also found that the population of these intermediates is affected by the ligand parameters. Thus, whereas for cyclic substrates the configuration of the phosphite functionality together with the substituents in the alkyl chain guide the population of *exo* and *endo* isomers, for linear substrates its ratio is also affected by the oxazoline group [57].

Most heterodonor P-oxazoline ligands developed have the chirality in the stereogenic carbon centers located on the oxazoline ring and/or in the carbon backbone (Fig. 6). We have also showed ligands that combines a chiral oxazoline or/and chiral carbon backbone with a phosphite with axial chirality (Fig. 6). However, few P-oxazoline ligands with a P-sterogenic center have been published, mainly due by the complexity of preparing bulky P-stereogenic phosphines in optically pure form (e.g. ligands **L18** [46b], **L19** [46c], **L20** [58] and **L28** [59]; Fig. 6). Verdaguer and Riera's have recently reported a simpler protocol for the synthesis of P-stereogenic aminophosphine-oxazoline ligands **L28** (MaxPHOX ; R^2 = Ph, ^{i}Pr, ^{t}Bu; R^3 = ^{i}Pr; Scheme 14). The synthesis of **L28** relies in the fact that upon activation enantioenriched *tert*-butylphenyl phosphinous acid borane undergoes stereospecific nucleophilic substitution with a range of amino-oxazoline compounds (Scheme 14) [59b]. Reaction of **L28** with $[Ir(\mu\text{-}Cl)(cod)]_2$ and



Scheme 15. Synthesis of phosphinite-oxazoline ligands **L29**.

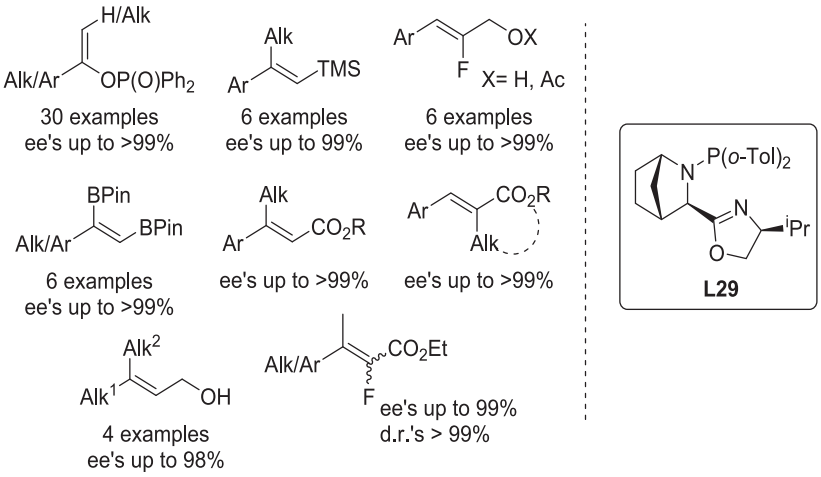
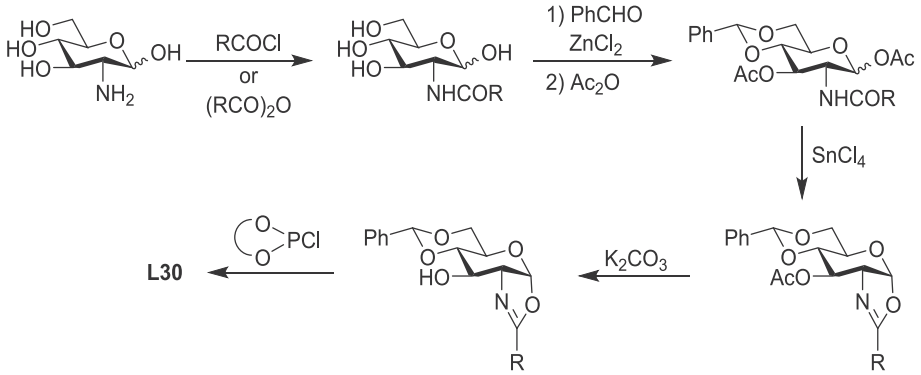


Fig. 12. Representative hydrogenation results with Ir/**L29** catalysts.

$NaBAr_F$ using the above mentioned standard protocol led to [Ir(cod)(**L28**)]BAr_F catalyst precursors [59b]. Actually, ligands **L28** only differ from ligands **L26** and **L27**, in the replacement of phosphinite/phosphite groups by an aminophosphine group, so ligands **L28** still have two carbon atoms linking the two donor groups.

Usefully, these catalysts were able to efficiently hydrogenate a variety of tetrasubstituted olefins: indenes and 1,2-dihydronapthalene derivatives (ee's up to 96%) and also acyclic tetrasubstituted olefins (ee's up to 99%; Fig. 11) [59a]. These excellent results were also attained in the reduction of tetrasubstituted vinyl fluorides (dr's >99% and ee's up to 98%) [59a]. Catalysts Ir/**L28** (R^1 = (*S*)-^{i}Pr and R^2 = (*R*)-^{t}Bu or (*R*)-^{i}Pr), which have the oxazoline substituent and the bulky group at the P-center *cis* to each other, also reached excellent results (>99% ee) for cyclic β-enamides (10 examples; Fig. 11) using only 3 bar of hydrogen pressure [43]. The process could also be performed with greener solvents such as ethyl acetate and methanol. Ir/**L28** (R^1 = (*R*)-^{i}Pr and R^2 = (*S*)-^{i}Pr) catalyst also provided comparable results than the best Ir–P,N systems reported in the hydrogenation of challenging *N*-aryl imines (Fig. 11) [60]. The reaction was performed with a balloon of H_2 at −20 °C, achieving up to 96% ee. The authors found that the configuration at the P*-center had almost no effect on the enantioselectivity of the catalyst. Useful, the authors were able to isolate the active specie, complex **2**, which was efficiently used to the direct hydrogenation of *N*-methyl ketimines (Fig. 11) [61]. Both, *N*-methyl imines and *N*-alkyl imines were hydrogenated with ee's up to 94% using only 1 mol % of catalyst and 3 bar of H_2, at 0 °C. The effective hydrogenation of this class of substrates had not yet been achieved, maybe due to the higher basicity of *N*-methyl amines than the *N*-aryl amines, which may lead to catalyst deactivation [62]. Ir/**L28** (R^1 = (*R*)-^{i}Pr and R^2 = (*R*)-Ph) catalyst was also used with effectiveness in the enantioselective isomerization of *N*-allyl amides to enamides (Fig. 11), which allowed to shorter the reported synthetic route for obtaining the antibiotic *R*-sarkomycin methyl ester (See Section 6) [63].

Andersson group was one of the few pioneering researchers in designing suitable ligands for the challenging Ir-catalyzed enantioselective reduction of unfunctionalized olefins. They synthesized an aminophosphine-oxazoline family of ligands **L29** (R^1 = Cy, *o*-Tol, Ph; R^2 = ^{t}Bu, H, Ph; R^3 = Ph, H, Fig. 6), with a rigid bicyclic backbone, to overcome the limited substrate scope in this process [64]. Ligands **L29** have also two carbons atoms linking the two donor functionalities. Ligands **L29** were prepared in a multigram scale from (1*S*,3*R*,4*R*)-2-((benzyloxy)carbonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid or (1*S*,3*R*,4*R*)-2-(((4-nitrobenzyl)oxy)carbonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid, which are accessible via stereoselective aza-Diels Alder reaction [65] followed by Cbz- or *p*-NO_2-Cbz-protection of the free amine. The oxazoline moiety was introduced via amide coupling with the desired 1,2-aminoalcohol followed by addition of mesyl chloride and base. Amine deprotection by hydrogenolysis using Pd/C followed by reaction with the appropriate chlorophosphine completes the synthesis of ligands **L29** (Scheme 15). The Ir-catalyst precursors [Ir(cod)(**L29**)]BAr_F were then prepared as previously described (see Scheme 9). For first time, Ir/**L29** catalysts furnished high enantioselectivities in the reduction of enol phosphinates [64b,c], vinyl silanes [64d], vinyl boronates [64f], fluorinated olefins [64e], α,β-unsaturated lactones [64g], α,β-unsaturated acrylic esters [64g]



Scheme 16. Synthesis of phosphinite-oxazoline ligands **L30**.

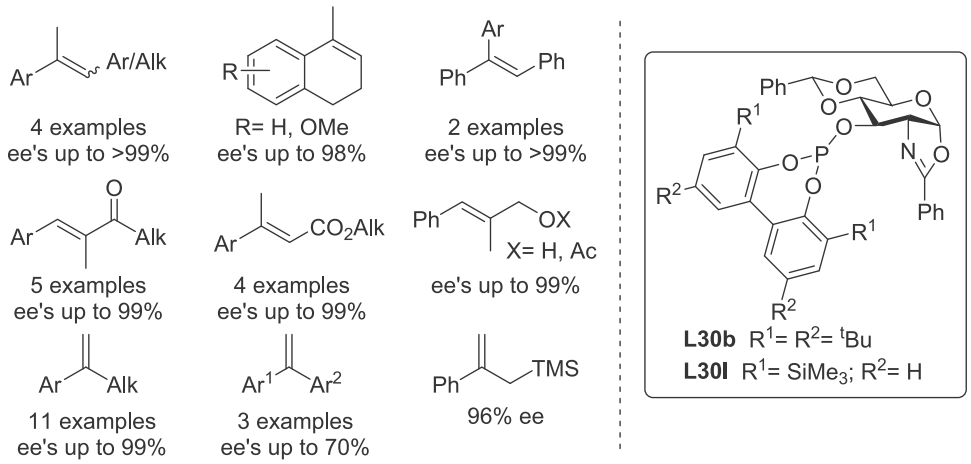


Fig. 13. Summary of the hydrogenation results with [Ir(**L30b,l**)(cod)]BAr_F catalysts.

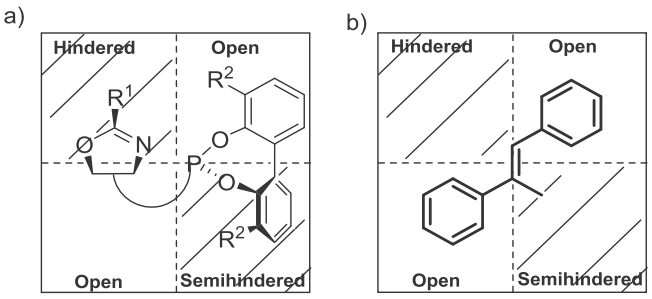


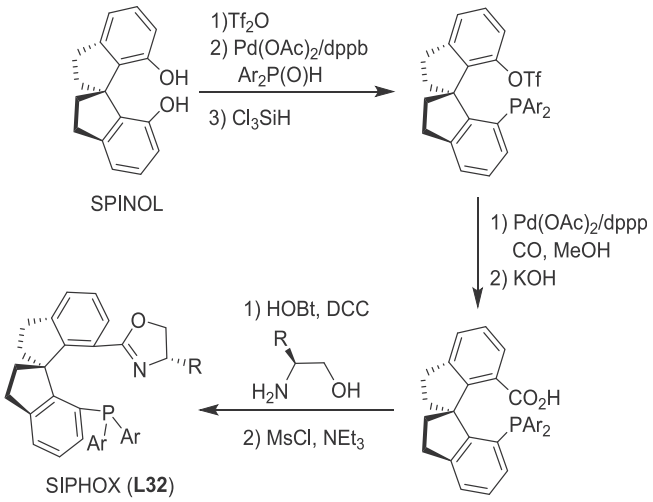
Fig. 14. Model diagram explaining the enantioselective substrate–ligand relationship.

and γ,γ-di- and β,γ-disubstituted allylic alcohols [64h] (Fig. 12). The related aminophosphite-oxazoline/thiazole ligands extended the number of substrates that could be reduced with selectivities similar to the best published (see Section 3) [66]. They successfully reduced *E*- and *Z*-tri- and disubstituted olefins (ee's up to 99%), including those with poorly coordinative groups (e.g. alkenylboronic esters, enones, vinylsilanes . . .) [66].

Another notable family of P-oxazoline ligands with two carbon atoms linking the two donor functionalities, are the pyranoside ligands **L30** (R = Me, ^{i}Pr, ^{t}Bu, Ph, Bn; Fig. 6). As with ligands **L22**–**L23** the P is bonded to the stereogenic center next to the oxazoline nitrogen atom but differs in the presence of a more rigid sugar backbone. Ligands **L30** were efficiently synthesized from D-glucosamine, an inexpensive natural feedstock (Scheme 16). D-glucosamine was first treated with the desired acid chloride or anhydride to form the corresponding amide [67]. Then, the hydroxyls groups at C-4 and C-5 position were protected with a benzaldehyde, to provide more rigidity to the backbone, and the rest of alcohols were acetylated. Formation of the oxazoline group was then achieved in the presence of anhydrous $SnCl_4$. Deacetylation followed by treatment with the corresponding phosphorochloridite led to ligands **L30**. Ligand **L30** provided high catalytic performance in the hydrogenation of unfunctionalized olefins, allylic substitutions and intermolecular Heck reactions [68]. In fact, [Ir(cod)(**L30**)]BAr_F were the first fruitful use of catalyst precursors with biaryl-based phosphite ligand in the hydrogenation of unfunctionalized alkenes [68a]. These Ir catalyst precursors were prepared straightforward as a single isomer following the previously described methodology (Scheme 9) as orange air-stable solids [68a,b]. The use of [Ir(cod)(**L30b**)]BAr_F and [Ir(cod)(**L30l**)]BAr_F (R = Ph) complexes containing bulky groups in the biaryl phosphite functionality led to high enantioselectivities (ee's between 91% and >99%) in trisubstituted olefins (until 25 examples, Fig. 13), including triarylsubstituted substrates, α,β-unsaturated ketones and esters and vinylboronates among other type of olefins. High enantioselectivities were also reached in a range of terminal olefins (19 examples, Fig. 13) including heteroaromatic ones (ee's up to 99%). Note that lower ee's were achieved when using the phosphinite-oxazoline analogues.

A computational study showed that the reaction proceed through an Ir^{III}/Ir^{V} catalytic cycle where the migratory insertion of the hydride is the step that control the selectivity [68b]. From the calculated TSs structures, a quadrant model describing the ligand-substrate interactions was developed. The occupance in this quadrant model suited perfectly for olefins containing *E*-geometry (Fig. 14). Calculations also shown that by varying the biaryl-phosphite substituents it is possible to modulate the occupance of the semihindered quadrant allowing the coordination of *Z*-olefins as well.

Ligands **L30l** (R = Me) and **L30b** (R = Ph) were also used in the intermolecular Heck reaction [68e,f]. They provided high activities (full conversions in minutes with microwave irradiation) and enantio- and regioselectivities (up to 99%) for a range of carbo- and heterocyclic olefins and triflate sources. In contrast to PHOX ligands, having non-bulky substituents at the oxazoline has a



Scheme 17. Synthesis of phosphinite-oxazoline SIPHOX ligands **L32**.

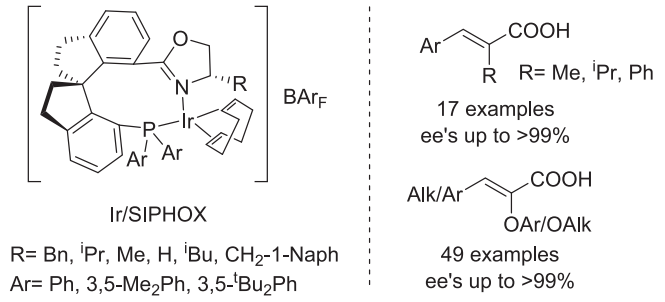


Fig. 15. Application of Ir/SIPHOX catalysts in hydrogenation.

positive effect on both, selectivities and activities. Finally, good activities and high enantioselectivities (up to 99%) have also been reached in the substitution of tri- di- and monosubstituted linear substrates and cyclic substrates [68c,d]. For hindered linear substrate ligand **L30b** (R = Ph) provided the best results, while for unhindered linear substrates ligand **L30g** (R = Me) provided the best results, and ligand **L30f** (R = ^{i}Pr) was the best for cyclic substrates. The related phosphinite-oxazoline analogues reached lower enantioselectivities [67]. The elucidation of NMR of the Pd-η^3 allyl intermediates allowed the rationalization of the experimental catalytic results. They showed that the substituents at both the oxazoline and the phosphite moieties are crucial for high ee's by enhancing the amount of the faster Pd-η^3 allyl isomer and, at the same time, eluding the presence of species with the ligand coordinated as monodentated. They also corroborated that the nucleophile attacks the allylic terminal carbon which is *trans* to the phosphite functionality [68].

Since the pioneering work of Chan and coworkers, the spiro backbone has been identified as a privileged arrangement for ligand families and catalysts [69,70]. We can highlight four main types of spiro phosphine-oxazoline ligands (Fig. 6): the SpinPHOX [71] (**L31**) developed by Ding, SIPHOX [72] (**L32**) reported by Zhou, HMSI-PHOX [73] (**L33**) developed by Lin and SMIPHOX [74] (**L34**) by Teng. The SMIPHOX was developed having in mind some distinct features compared with the other three, such as an spiro indane-based P,N ligand with non-C_2-symmetric skeleton and higher rigidity and only one chiral center avoiding the complex sterochemistry. Among them, we can highlight the work of Zhou and coworkers with the spiro phosphine-oxazoline (SIPHOX) Ir-catalysts. SIPHOX ligands were prepared from enantiopure 1,1′-spirobiindane-7,7′-diol (SPINOL), which are prepared from 3-methoxybenzaldehyde followed by resolution with *N*-benzylcinchonidinium chloride [75]. SPINOL was then transformed to the corresponding phosphine-triflate compounds by ditriflation of the diol, monophosphinylation with the desired diarylphosphine oxide in the presence of Pd(OAc)$_2$ followed by reduction with trichlorosilane. Phosphine-triflates were then transformed to the phosphine-acids by Pd-catalyzed carbonylation followed by hydrolysis of the formed esters. Amide formation with the desired 1,2-aminoalcohol in the presence of DCC (*N*,*N*′-dicyclohexylcarbodiimide) and HOBT (1-hydroxylbenzotriazole) followed by treatment with mesyl chloride and base led to spirocyclic phosphine-oxazolines **L32** (Scheme 17). They could efficiently reduce imines and represented the first Ir-catalyst precursors [Ir(cod)(SIPHOX)]BAr$_F$ (Fig. 15) able to reduce under basic reaction conditions a broad range of unsaturated carboxylic acids [72b,c], getting over the constraints of Rh- and Ru-catalysts, which are mainly restricted to acrylic and cinnamic acids (Fig. 15) [76]. The base is required to form the carboxylate anion that coordinates to iridium. Thus, Ir/**L32**, containing a bulky phosphine-aryl group (R^1 = 3,5-^{t}Bu$_2$Ph), proved to be highly active (TONs up to 10.000) and enantioselective (ee's >99%) with a group of α-aryloxy and α-alkyloxy substituted α,β-unsaturated acids (Fig. 15). Nevertheless, Ir/SIPHOX catalysts do not perform well for α,β-unsaturated esters [77]. The same authors demonstrated the potential of Ir/**L32** catalyst with the synthesis of a crucial intermediate in the preparation of rupintrivir (a rhinovirus protease inhibitor, see Section 6) [72c]. It should be noted that the key in the high activity of this catalyst can be found in the ligand's steric constraints which prevents the formation of inactive trimeric species, which are formed for most of the Ir/P-N catalyst [78].

Over the years, Zhou's group have extensively studied the hydrogenation of several different classes of α,β-unsaturated carboxyxlic acids [77,79]. Thus, for example, excellent ee's have been

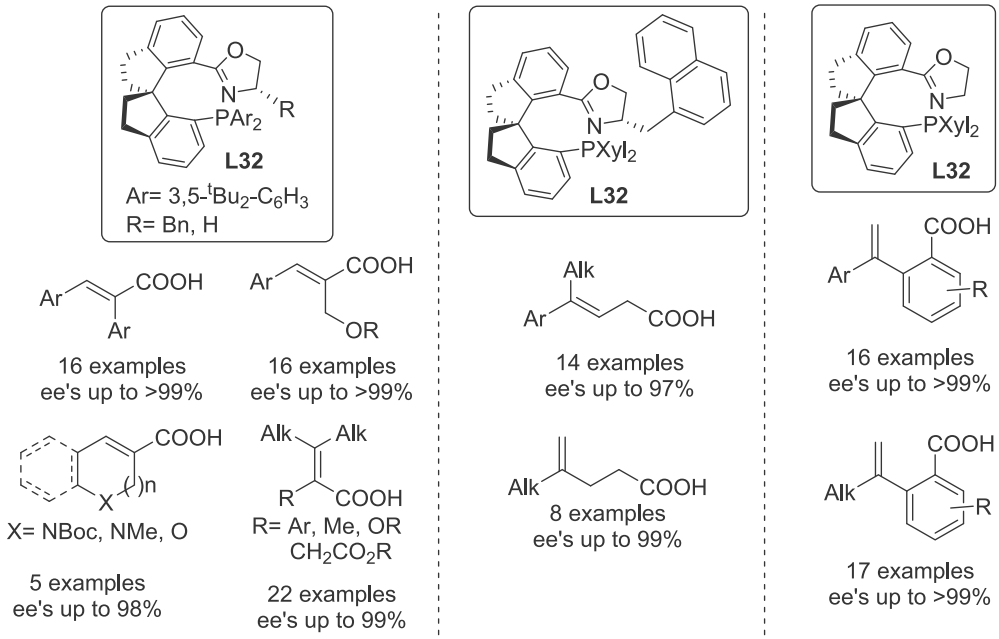


Fig. 16. Application of Ir/SIPHOX in the hydrogenation of α-aryloxy-, α-alkyl, and α-alkyloxy-substituted α,β-unsaturated carboxylic acids, and β,γ-unsaturated acids and γ,δ-unsaturated acids and acrylic acids.

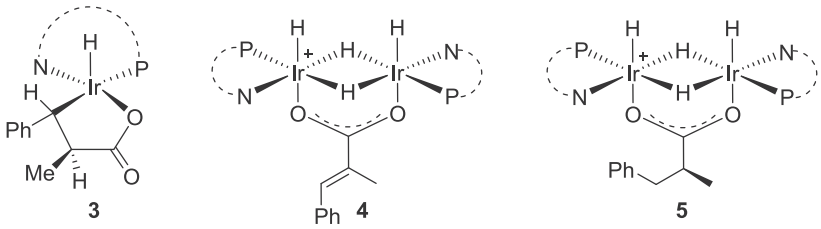
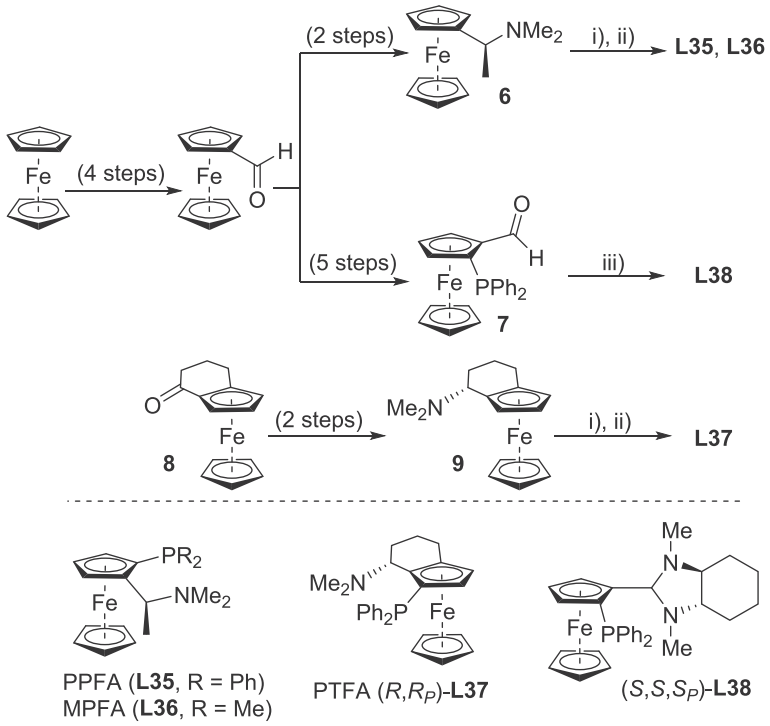


Fig. 17. Isolated intermediates **3**–**5** in the benchmark reaction of sodium (*E*)-2-methyl-3-phenyl acrylate using the Ir/**L32** catalyst (Ar = 3,5-^{t}Bu$_2$-C$_6$H$_3$, R = H).



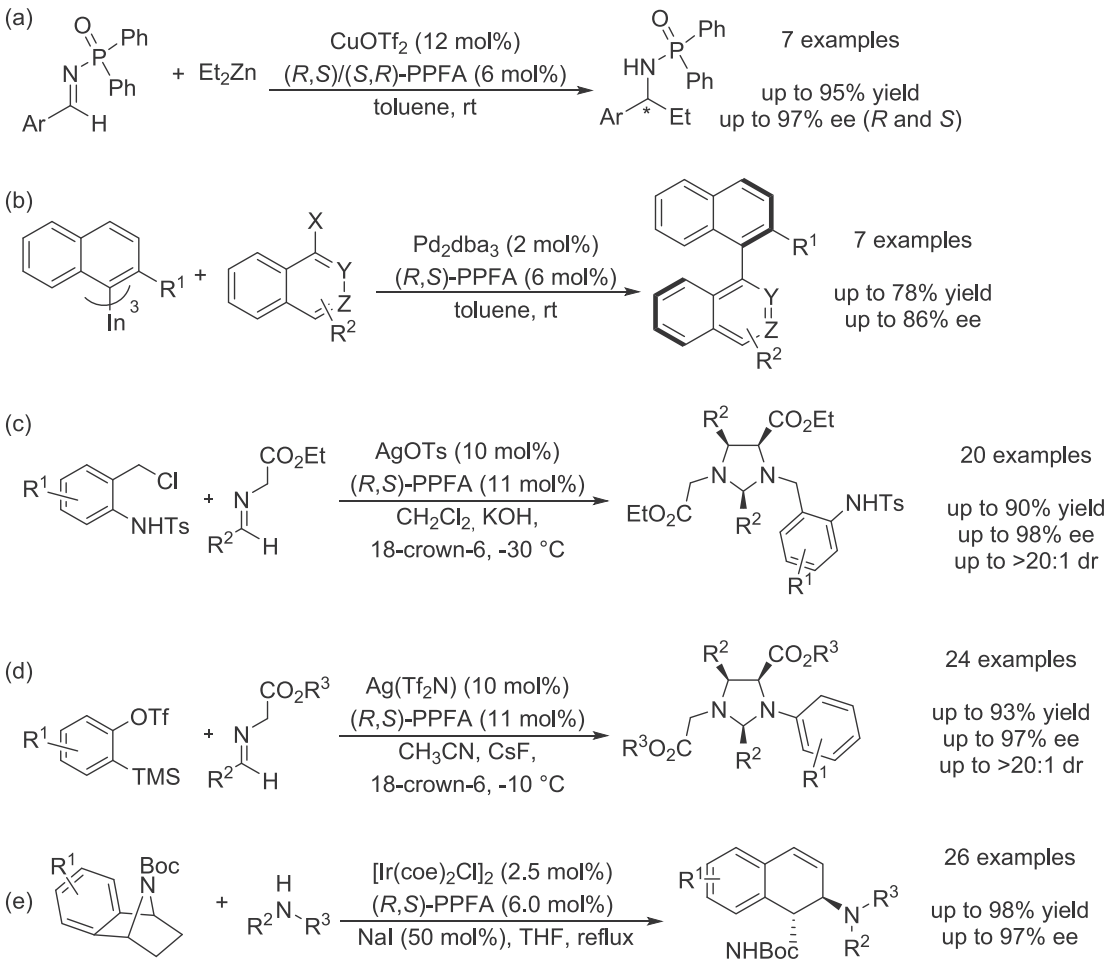
Scheme 18. Synthesis of phosphinoferrocenyl ligands **L35**–**L38**. i) BuLi-hexane (1.4 equiv.), diethyl ether, rt, 2 h; ii) ClPPh$_2$ (2 equiv.), reflux, 3 h; iii) (1*S*,2*S*)-*N*,*N*'-dimethylcyclohexane-1,2-diamine (1.1 equiv.), 75 °C, 12 h.

attained in the asymmetric hydrogenation of α-aryl- and α-oxymethyl-substituted cinnamic acids using Ir-SIPHOX catalysts (Fig. 16). This transformation were used in the preparation of (*S*)-(+)-homoisoflavone, a natural product with antibacterial activity (see Section 6) [80]. Latter, several heterocyclic olefins containing a carboxylic acid group were also successfully hydrogenated (ee's up to 99% ee, Fig. 16). Again Zhou's group made use of this finding for the synthesis of the GABA uptake inhibitors (*R*)-tiagabine and (*R*)-nipecotic acid (see Section 6) [72e]. Interestingly, Ir/SIPHOX is also able to efficiently reduced a large number of tetrasubstituted acrylic acids (ee's up to 99%; Fig. 16), which have subsequently be used in the synthesis of the pyrethroid insecticide Fenvalerate and the antihypertensive drug Mibefradil (see Section 6) [81]. Interestingly, Ir/SIPHOX catalyst maintained its efficient when the carboxylic is moved away from the olefin. Thus, a range of β,γ-unsaturated acids [72d] and terminal γ,δ-unsaturated acids [72f,82] were successfully hydrogenated (ee's up to 99%; Fig. 16) using Ir/SIPHOX (Ar = Xyl and R = 2-naphthylmethyl) catalyst. Again, the total synthesis of several natural products (e.g. (*R*)-xanthorrhizol, (*R*)-aristelegone-A . . .) were attained (see Section 6). Finally, Ir/SIPHOX (Ar = Xyl and R = H) demonstrated its usefulness in the hydrogenation of terminal olefins containing a benzoic acid group (ee's up to >99%; Fig. 16), leading compounds with a benzyl-methyl stereocenter like those found in the natural sesquiterpene phenols (*S*)-curcudiol and (*S*)-curcumene (see Section 6) [82]. Very recently, Zhang's group have accounted an oxa-spirocyclic version of **L32** that has demonstrated their usefulness in the hydrogenation of terminal methylene-tetrahydro-benzo[d]azepin-2-ones [83].

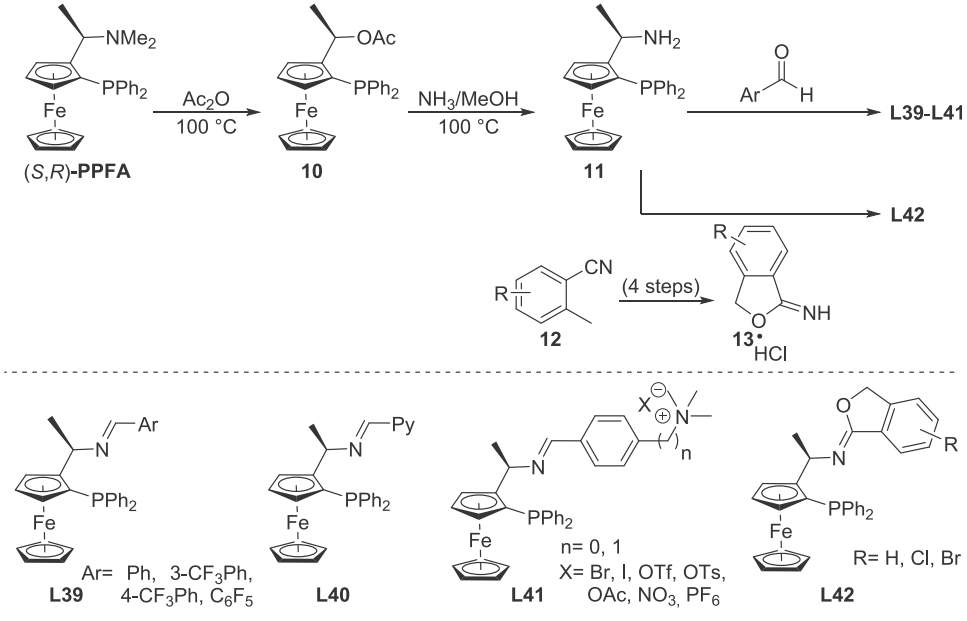
The mechanistic study, including DFT calculations, agrees with an Ir(III)/Ir(V) catalytic pathway [84]. More important, using sodium 2-methyl-3-phenylacrylate as a benchmark substrate they were able to isolate migratory insertion Ir(III) intermediate **3**, with the carboxylate coordinated to iridium (Fig. 17). They also managed to characterize by X-Ray diffraction dimeric hydrido complexes **4** and **5** (Fig. 16), which further support the coordination of the carboxylate to iridium.

3. Heterodonor P,N-other ligands in asymmetric catalysis

In this section, a collection of the developed heterodonor P,N-ligands with a N-donor group other than an oxazoline ring is presented. Besides the common tuneable properties of chiral ligands, e.g phosphorus group, backbone and source of chirality, P,N-other ligands allow variation on the hybridization of the N-atom. The tuning on the N-donor group leads to a wide array of P,N-other ligands. Ligands with amino *N*-donors (N-sp^3), imino *N*-donors (N-sp^2), cyclic imino *N*-donors (N-sp^2) and pyridino



Scheme 19. Applications of PPFA ligand in asymmetric catalysis.



Scheme 20. Synthesis of ferrocenylphosphino-imine ligands **L39–L42.**

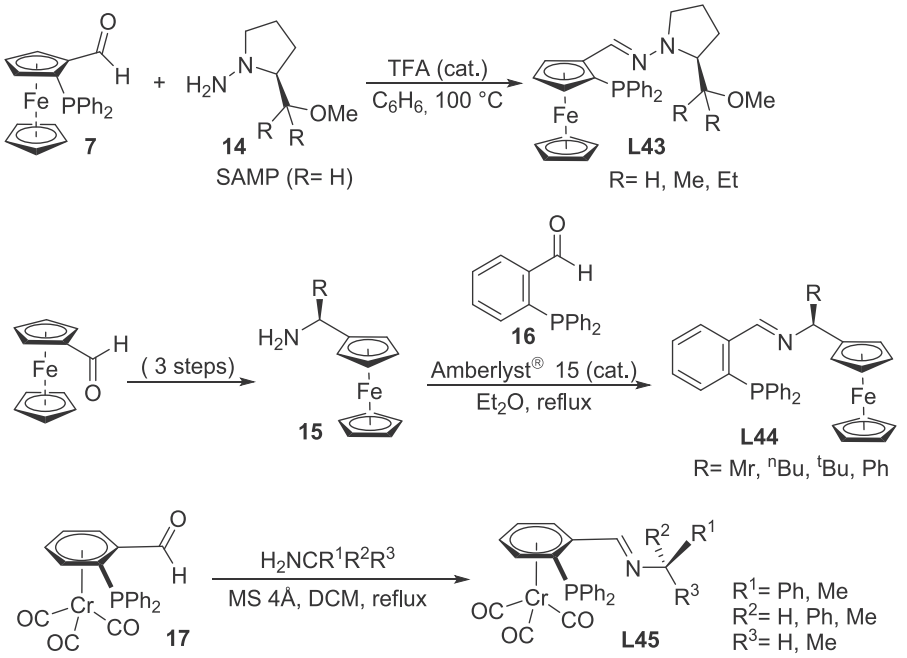
N-donors (N-sp^2) have been synthesized and used in several metal-catalyzed asymmetric reactions [3d,85].

3.1. P,N-ligands with planar chirality

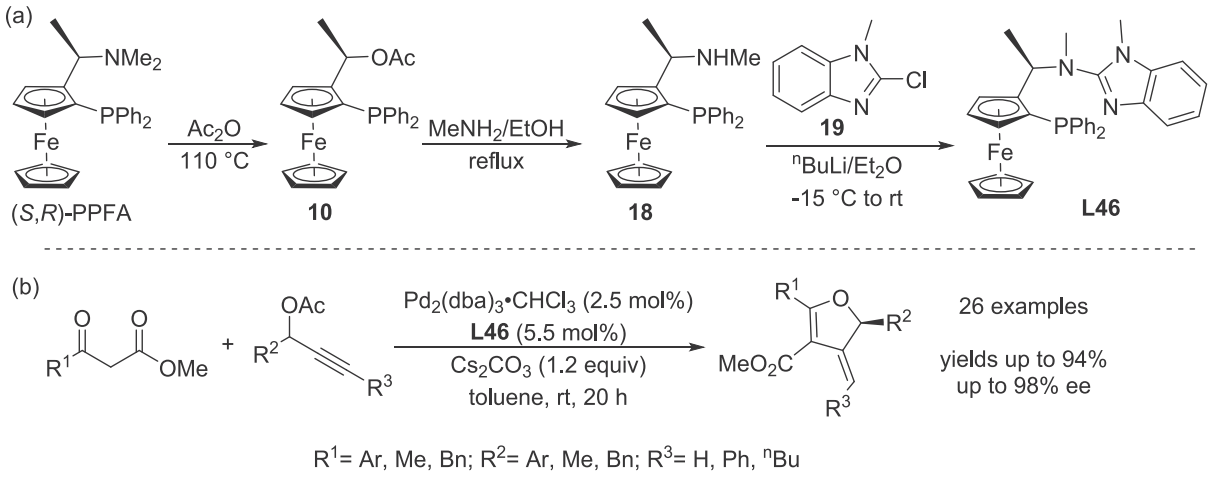
The first reports on chiral P,N-ligands came out back in the 70′s with the work of Hayashi and Kumada, where they showed that chiral aminophosphines were promising ligands for asymmetric catalysis [86]. In their early reports they developed the first P,N-ligands bearing planar chirality, the (aminoalkylferrocenyl)phos phines PPFA and MPFA (**L35** and **L36**, respectively, Scheme 18). PPFA and MPFA were synthesized by introducing a phosphino group into α-dimethylaminoethylferrocene (**6**) through stereoselective lithiation [86a]. The overall synthesis starts with the transformation of ferrocene to intermediate **6** in 6 steps, via the formation of formylferrocene (Scheme 18) [87]. Both ligands were initially applied to the Rh-catalyzed hydrosilylation of ketones with high yields (up to 89%) albeit with 49% ee [86a]. PPFA was also used in the Ni-catalyzed asymmetric Grignard cross-coupling with (1-phenylethyl)magnesium bromide and vinyl bromide providing an enantioselectivity of 63% ee [86b]. Later, the same synthetic strategy was used to prepare the more constrained PTFA ligand **L37** reported by Weissensteiner, but ligand **L37** was prepared from intermediate **8** through formation of the corresponding imine (Scheme 18) [88]. The decrease flexibility on ligand **L37** was beneficial for the enantioselectivity in the Ni-catalyzed asymmetric Grignard cross-coupling, affording an ee of 79% [89]. In 2006, Jin's group synthesized **L38** with a cyclic amine as nitrogen donor. **L38** was synthesized from formylferrocene *via* diphenylphosphinoferrocenecarboxaldehyde obtained through Kagan's method (Scheme 18) [90]. This modification was found to be beneficial for the asymmetric induction, which was illustrated with the excellent enantioselectivities obtained in the Pd-catalyzed allylic substitution with dimethylmalonate (99.6% ee) [91], which were comparable to the obtained with its P,N-oxazoline analogue [92].

Ferrocenes with planar chirality attracted considerable attention in asymmetric catalysis, especially PPFA, which has been widely used for other researchers in many asymmetric transformations (Scheme 19). For example, Wang accounted the use of PPFA to the Cu-catalyzed addition of diethylzinc to imines, affording high enantioselectivities (up to 97% ee; Scheme 19a) [93]. Later, Sestelo and Sarandeses employed PPFA as the chiral ligand for obtaining 1,1′-binaphthyls by Pd-catalyzed cross coupling reactions of triorganoindium reagents, with ee's up to 86% (Scheme 19b) [94]. Very recently, Guo has shown the use of PPFA in the Ag(I)-catalyzed tandem [3 + 2] cycloaddition/1,4-addition between aza-o-quinone methides (ao-QMs) and azomethine ylides, yielding imidazolidine derivatives with excellent diastereo- and enantioselectivities (up to 20:1 dr and 98% ee; Scheme 19c) [95]. The strategy has been extended to the addition of arynes, generated *in situ* from *o*-silylaryl triflates (Scheme 19d) [96]. Finally, PPFA has also showed utility in the Ir-catalyzed ring-opening of low-activity azabenzonorbornadiene with various aliphatic and aromatic amines, providing the corresponding chiral vicinal 1,2-diamine scaffolds in high yields and enantioselectivities (up to 97% ee; Scheme 19e) [97].

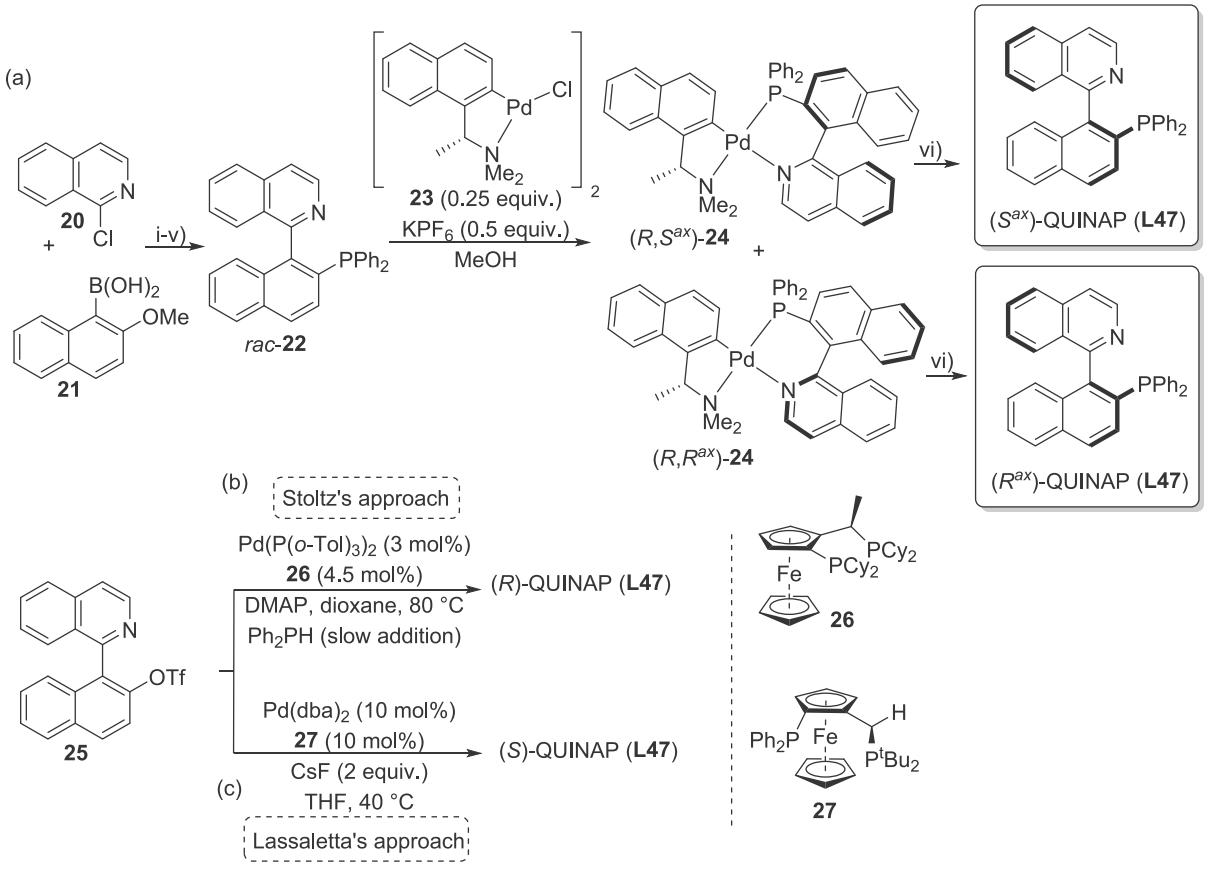
Hayashi described the transformation of (*S*,*R*)-PPFA (**L35**; Scheme 18) to P-imine ligands **L39** in three steps (Scheme 20). To achieve new ligands **L39** the dimethylamino group on (*S*,*R*)-**L35** was replaced by an amino moiety via acetate intermediate **10**. Next, condensation of amino intermediate **11** with benzaldehyde furnished P-imine ligands (*S*,*R*)-**L39** [98]. Ligands with electron-withdrawing groups at the aryl moiety provided higher enantioselectivities than its N-sp^3 counterpart PFFA (**L35**) (up to 90% ee *vs* 16% ee) in the Rh-catalyzed asymmetric hydrosilylation of acetophenones [98]. Ligands **L39** were also screened in the Pd-catalyzed allylic alkylations and again, the best selectivities were offered with a ligand having an electrodeficient aryl group. Using dimethylmalonate as nucleophile, the substitution of diphenylallyl acetate and pivalate and some cyclic substrates furnished promising enantioselectivities (up to 96% ee and 91% ee, respectively) [99]. Since then, other ferrocenylphosphino-imine ligands have been prepared from ferrocenylphosphino-amine compound **11** and the corresponding aldehyde (ligands **L40**–**L41**; Scheme 20) [100]. In contrast, ligand **L42** was prepared by mixing **11** with imidate **13**, which was prepared from the desired 2-methylbenzonitrile (**12**) in 4 steps (Scheme 20) [101].



Scheme 21. Synthesis of α-phosphino-β-imine ligands **L43**–**L45.**



Scheme 22. Synthesis of ferrocene-based phosphine-benzimidazole ligands **L46** and its use in the Pd-catalyzed [3 + 2] cycloaddition of propargylic esters with β-ketoesters.



Scheme 23. a) Original synthesis and resolution of QUINAP ligand **L47.** b) and c) Posterior improved methodologies by Stoltz and Lassaletta, respectively. i) $Pd(PPh)_4$, Na_2CO_3, DME, reflux; ii) BBr_3, CH_2Cl_2; iii) Tf_2O, DMAP, DCM; iv) $Ph_2P(O)H$, $Pd(OAc)_2$, dppp; v) $HSiCl_3$, NEt_3; vi) dppe, DCM.

In general, ligands **L40**–**L42** attained also high enantioselectivities in the benchmark Pd-allylic alkylation [100,101]. In addition, ligands **L41** containing quaternary ammonium salts were also tested in the substitution of the benchmark substrate with different carbon nucleophiles and benzyl amine, providing enantioselectivities up to 94% ee (**L41**, X = I, n = 0) [100b]. This ligand was also employed in allylic etherification reactions with a range of benzyl alcohols, providing enantioselectivities up to 91% ee, but moderate yields (up to 74%) [102]. Ligands **L42** (R = 5-Cl) bearing an imidate moiety showed even higher enantioselectivities in the allylic substitution of 1,3-diphenylallyl acetate using different malonate nucleophiles (up to 99% yield and >99% ee) [101]. In addition, the alkylation of cyclic substrates and the unhindered substrate *rac*-1,3-dimethyl-3-acetoxyprop-1-ene also resulted in good enantioselectivities (ee's ranging from 75 to 90%). Phosphino-imidate ligands **L42** were also applied in the Ir-catalyzed hydrogenation of di-, tri- and tetrasubstituted olefins, providing moderate to good enantioselectivities (45–91% ee) [103].

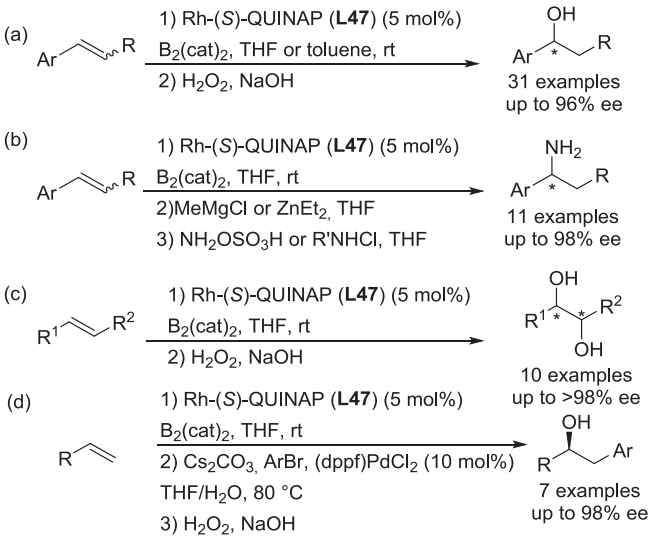
Similarly, α-phosphino-β-imine ligands **L43**–**L45** were prepared from the corresponding aldehyde and amine.

Phosphine-hydrazone ligands **L43** were obtained through condensation of intermediate **7** (also used for the synthesis of **L38**; Scheme 18) and the corresponding pyrrolidine **14** (Scheme 21). These ligands were screened in the Pd-catalyzed allylic substitution of the benchmark linear substrate with dimethyl malonate (**L43**, R = H; 96% ee) and benzylamine (**L43**, R = Me; 96% ee) [104]. Ligands **L44**, derived from condensation of 1-ferrocenylalkylamine **15** and 2-(diphenylphosphino)benzaldehyde **16** (Scheme 21), provided a better enantioselectivity of 97% ee in the benchmark reaction [105]. Ligands **L45**, having a phenylchromium tricarbonyl motif as planar chirality source (Scheme 21), gave even a higher enantioselectivity (>98% ee) than **L43** and **L44** when tested in the benchmark allylic substitution reaction [106]. Studies showed that for these ligands the enantioinduction is predominantly controlled by the planar chiral element and increases with the bulkiness of the *N*-substituents of the imine.

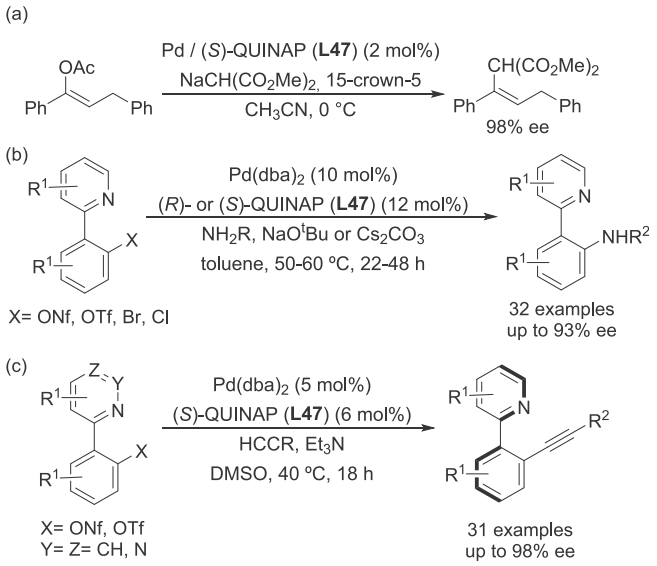
Recently, (*S,R*)-PPFA ligand (Scheme 18) has been modified to provide ferrocene ligands **L46** with a benzimidazole moiety (Scheme 22a). As for ligands **L39**–**L41**, their synthesis proceeds through acetate intermediate **10** but in this case, amine **18** was subjected to reaction with benzimidazole **19** to yield the corresponding ligand [107]. Ligand **L46** was key to achieve the highly enantioselective Pd-catalyzed [3 + 2] cycloaddition of propargylic esters with β-ketoesters, providing high yields and enantioselectivities (up to 98% ee). The reaction gave access to a range of chiral 2,3-dihydrofurans with an exocyclic double bond that remain unavailable with the known synthetic methods (Scheme 22b).

3.2. P,N-ligands with axial chirality

P,N-ligands with axial chirality have found place in a broad range of applications in asymmetric catalysis [85e,g]. The advances of BINAP ligand in Ru-catalyzed asymmetric hydrogenations [108] together with the contemporary success of ferrocene-based P,N-ligands by Hayashi and Kumada [86a-b,d], led to the development of QUINAP (**L47**), which can be considered as the first highly efficient axially chiral P,N-ligand [109]. The crucial step in the synthesis of the racemic ligand was achieved via Pd-catalyzed cross-coupling of aryl chloride **20** and boronic acid **21** (Scheme 23a). After cleavage of the methyl ether group, the phosphine group was introduced through conventional chemistry. At this point, it was required a final diastereomeric resolution of the corresponding palladium salts obtained through reaction of *rac*-**22** and palladium complex **23**. Diastereomers **24** could then be decomplexed by reaction with a 1,2-bis-(diphenylphosphino)ethane (dppe) to furnish the enantiomerically pure (*R*)- and (*S*)-**L47** [109,110]. However, this methodology implied two main drawbacks. First, stoichiometric amounts of chiral palladium complex **23** were required, and second, the introduction of the phosphine group had to be done prior to the resolution step. This implied a resolution for every single ligand and thus, limiting the access to ligand diversity. These limitations have prompted to the search of more straightforward synthetic routes for the synthesis of enantiopure QUINAP and related ligands, by many research groups [111]. A novel way for the synthesis of QUINAP came in 2013 by Stoltz et al [111f]. The method consisted in the Pd-catalyzed asymmetric phosphination of aryl triflate **25** via dynamic kinetic resolution using Pd/**26** catalytic system (Scheme 23b). Recrystallization further increased the ee from 90% to up to >99.5%. In 2016, Lassaletta reported a new methodology for the synthesis of QUINAP via Pd-catalyzed dynamic kinetic C–P cross-coupling between triflate **25** and a trimethylsilylphosphine, with the use of a Josiphos-type ligand **27** (Scheme 23c) [111g]. This method gave access to QUINAP with 91.5% ee as well as several other potential P,N-ligands with axial chirality.



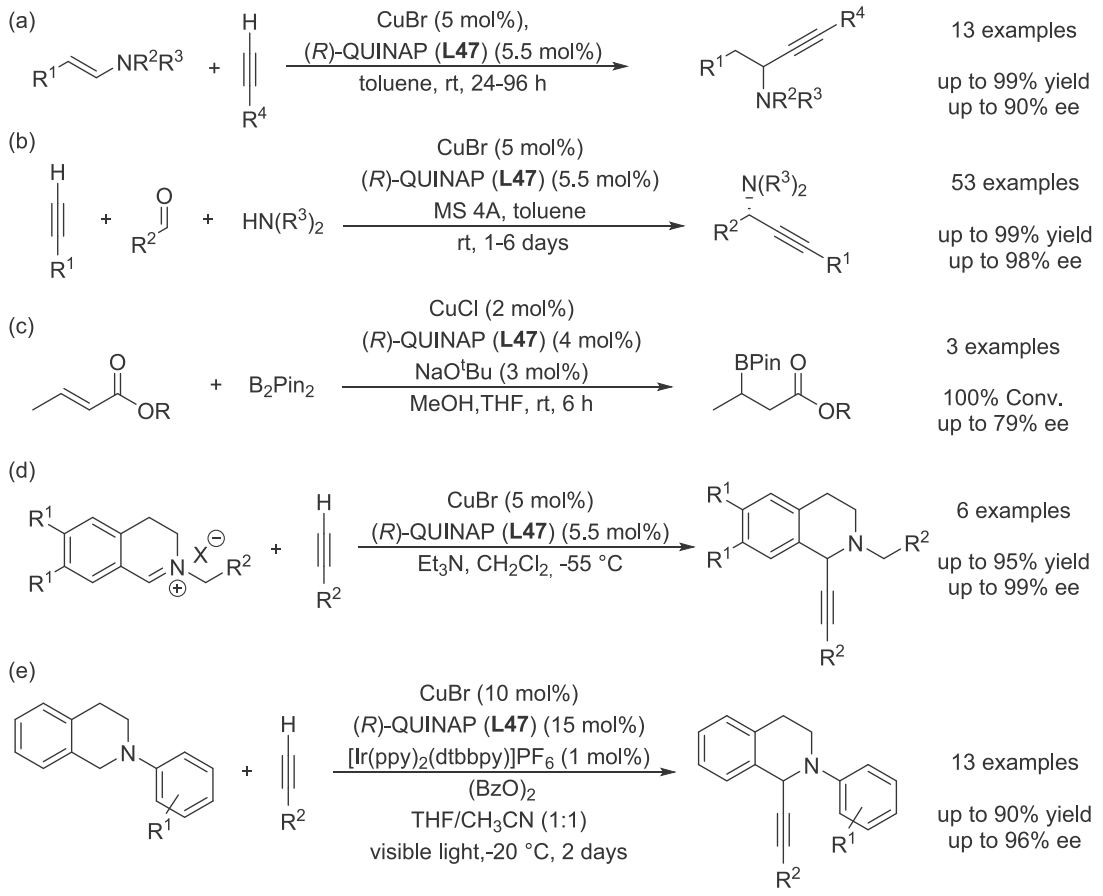
Scheme 24. Application of (*S*)-QUINAP ligand (**L47**) to Rh-catalyzed hydroboration and diboration of alkenes to produce; a) chiral alcohols, b) amines, c) and diols. d) The tandem diboration/Suzuki/oxidation reactions.



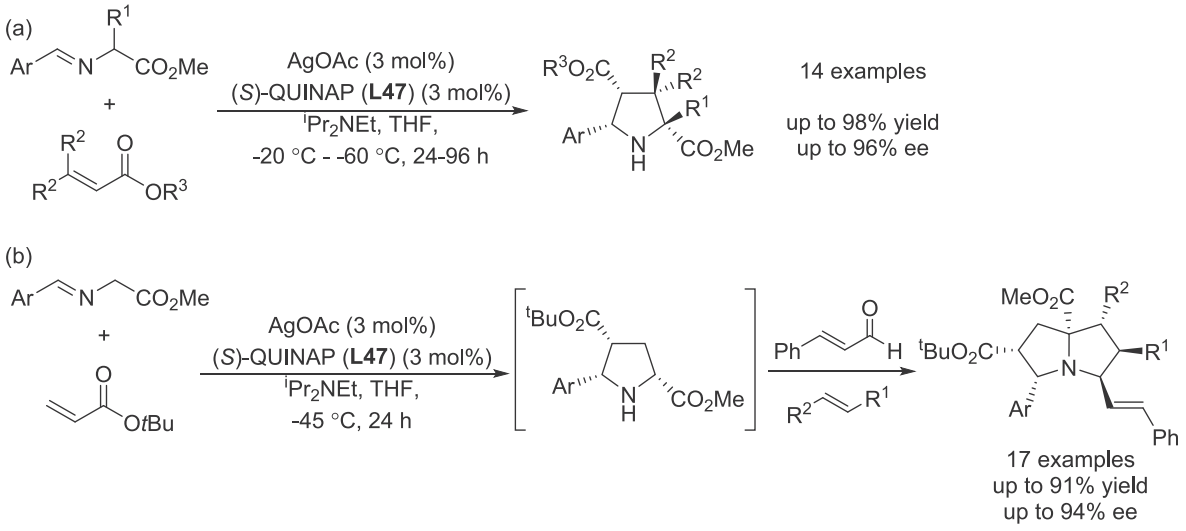
Scheme 25. Pd-catalyzed reactions with QUINAP (**L47**) in the a) allylic substitution, b) dynamic kinetic asymmetric Buchwald-Hartwig amination and c) alkynylation.

Over the years it has been demonstrated that QUINAP is among the most outstanding axially chiral P,N-ligands with applications in many enantioselective transformations [85e,g]. The initial work with QUINAP was focused on Rh-catalyzed hydroboration of aryl alkenes and Pd-catalyzed allylic alkylation. Later it has also showed its utility in several other asymmetric transformations. Brown et al. early demonstrated the value of QUINAP in the Rh-catalyzed hydroboration of vinylarenes, which after oxidation led to variety of secondary alcohols with ee's up to 96% (Scheme 24a) [112]. This methodology was also used in the synthesis of primary and secondary chiral amines with good to high enantioselectivities (77–98% ee, Scheme 24b) [113]. In this case, the obtained chiral catecholboronate esters were transformed to the desired amines through alkylation with MeMgCl or $ZnEt_2$, followed by conventional electrophilic amination with NH_2OSO_3H (for primary amines) or R′NHCl (for secondary amines).

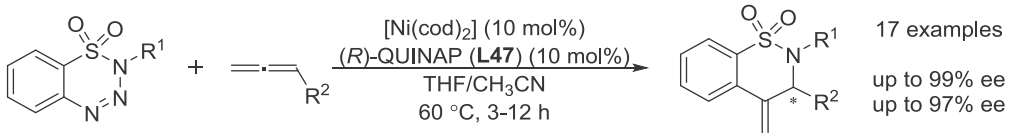
Morken and co-workers found that QUINAP was an excellent ligand also for the enantioselective Rh-catalyzed diboration of alkenes with dicathecol diboron [114]. It efficiently catalyzed the



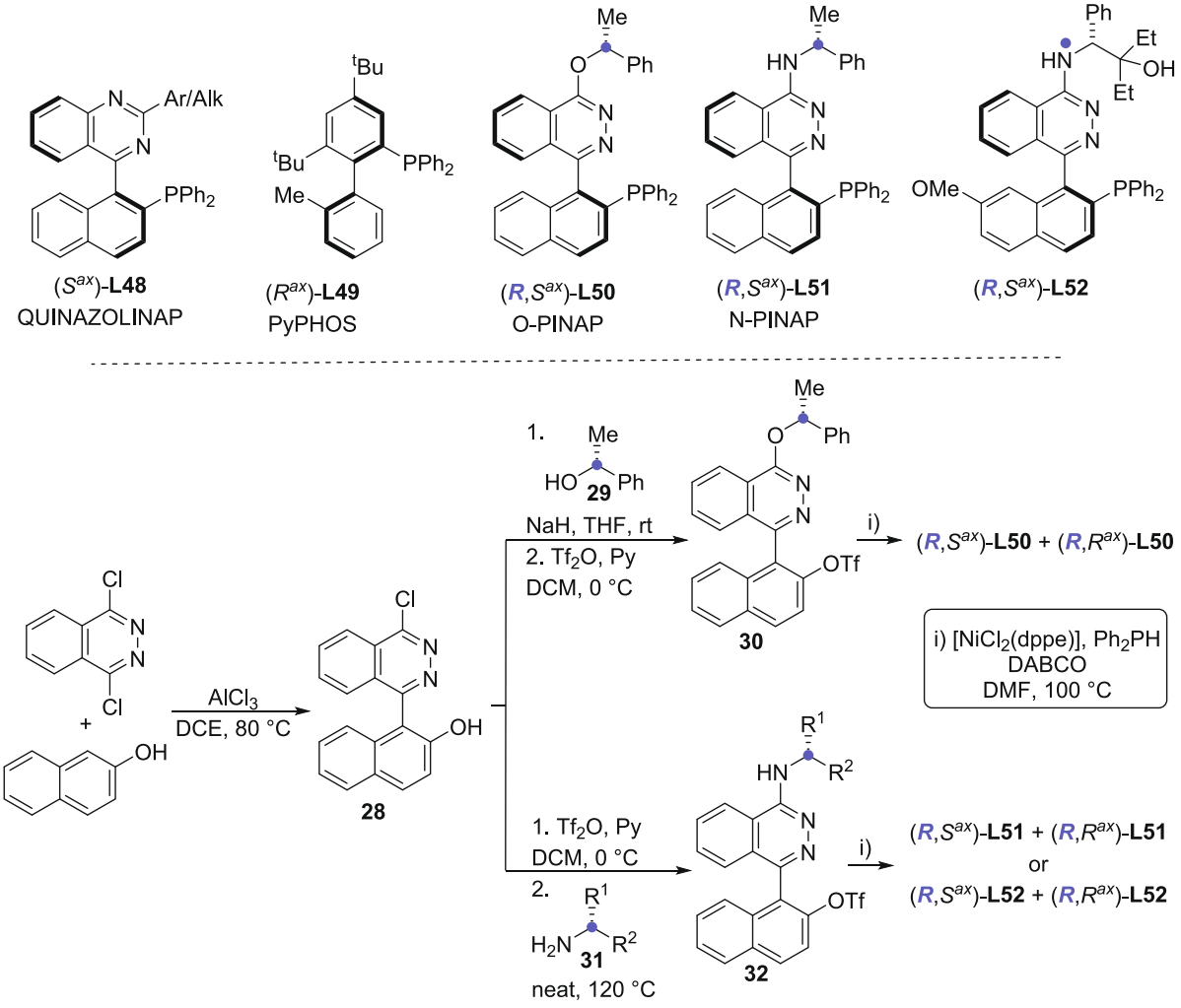
Scheme 26. Application of QUINAP (**L47**) in asymmetric Cu-catalyzed reactions.



Scheme 27. Ag-catalyzed [3 + 2] cycloaddition reactions with (*S*)-QUINAP (**L47**).



Scheme 28. Ni-catalyzed allene cycloaddition with (*R*)-QUINAP (**L47**).



Scheme 29. Axially chiral ligands **L48**–**L52** and the synthetic route for PINAP type ligands **L50**–**L52**.

reaction of alkenes with dicatechol–diborane, to yield the *syn*-addition products. Subsequent oxidation yielded the corresponding enantiopure diols (Scheme 24c). The system showed a big scope for *trans*-disubstituted olefins, and unlike the Rh/Quinap-catalyzed hydroboration, the reaction occurred also with purely aliphatic alkenes. For trisubstituted alkenes, the enantioselectivities were also very high although yields were somewhat lower, while monosubstituted and *cis*-substituted alkenes reacted with lower enantioselection. Finally, Morken's system also allowed the Rh-catalyzed tandem diboration/Suzuki/oxidation reaction to provide several chiral 1-aryl-2-ols in one-pot and in an operationally simple way (Scheme 24d) [114b].

As stated above, the early work with QUINAP showed that it was also useful in the Pd-catalyzed alkylation of *rac*-1,3-diphenylallyl acetate and dimethyl malonate (98% ee, Scheme 25a) [115]. Recently, Lassaletta and co-workers accounted the use of Pd/QUINAP catalyst in the dynamic kinetic asymmetric Buchwald-Hartwig amination and alkynylation reactions (Scheme 25b,c) [116]. Thus, a variety of enantiopure amino- and alkynyl-heterobiaryls were attained in high yields and ee 's up to 93% and 98%, respectively. Both processes were used to access to different axially chiral ligands, such as the IAN-type N,N-ligands [116b]

Knochel and co-workers were the first in showing the utility of QUINAP in Cu-catalyzed coupling reactions. Initially, the Cu(I)/QUINAP catalyst was applied to a range of enamines with terminal alkynes providing the corresponding propargylamines in up to 90% ee (Scheme 26a) [117]. Later, it was found that the same system allowed the three-component reaction between aldehydes, amines, and alkynes (A^3 coupling). A wide range of propargylic amines could be afforded with good yields and enantioselectivities without the need to preform sensitive enamines (Scheme 26b) [118]. QUINAP was also screened in the Cu-catalyzed β-borylation of α,β-unsaturated esters, but while excellent conversions were achieved, the enantioselectivities didn't surpass 79% ee (Scheme 26c) [119]. Schreiber applied the Cu/QUINAP system to the alkynylation of different isoquinoline iminium salts providing chiral 1-alkynyl tetrahydroisoquinoline derivatives (ee's up to 99%; Scheme 26d) [120]. More recently, the Cu/QUINAP has been combined with a photo redox catalytic system for the cross-dehydrogenative-coupling of alkynes to *N*-aryl tetrahydroquinolines (Scheme 26e) [121]. This strategy allows the direct use of tetrahydroquinolines without preformation of the iminium salt maintaining the high ee's (up to 96%), albeit with moderate to high yields (up to 90%).

The QUINAP ligand was found to be an excellent candidate for the Ag-catalyzed [3 + 2] cycloaddition reaction of *tert*-butyl acrylate with azomethine ylides. The reaction gives access to pyrrolidines with multiple stereocentres, with an *endo*:*exo* ratio of >20:1 and up to 96% ee (Scheme 27a) [122]. In 2013, Reisman expanded this methodology to the preparation of pyrrolizidines with up to 6 stereogenic centers in one flask with up to 94% ee (Scheme 27b) [123].

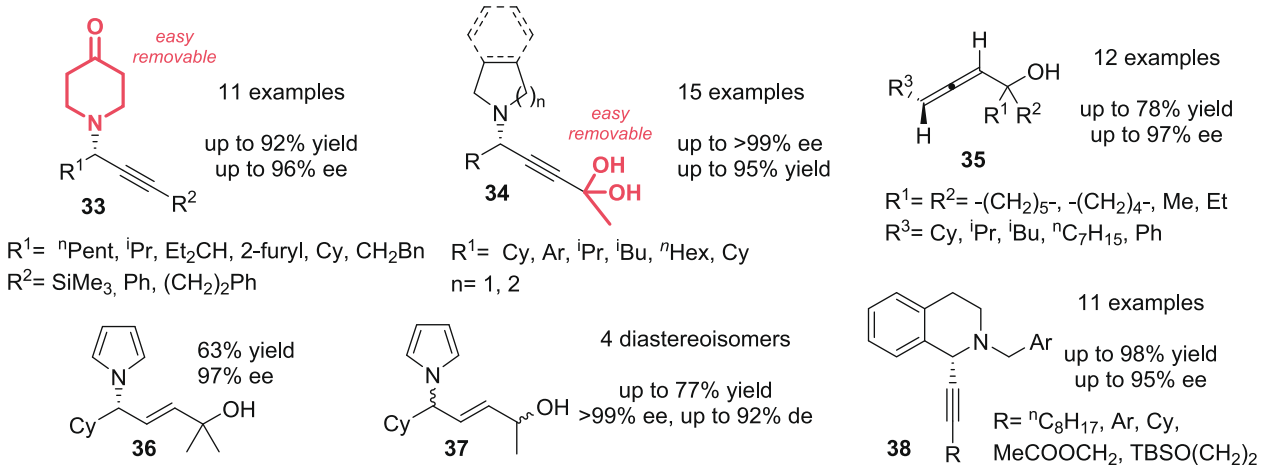


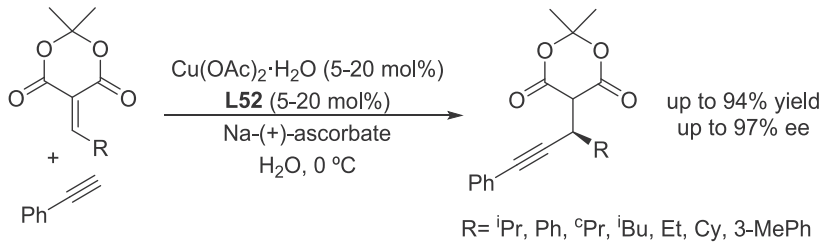
Fig. 18. Selected results of the scope of N-PINAP (**L51**) in Cu-catalyzed A^3 coupling reactions.

In 2010, Murakami reported the Ni-catalyzed allene cycloaddition reaction of 1,2,3,4-benzothiatriazine-1,1(2H)-dioxides and allenes using QUINAP (Scheme 28) [124]. The reaction showed a broad scope with enantioselectivities up to 97% ee.

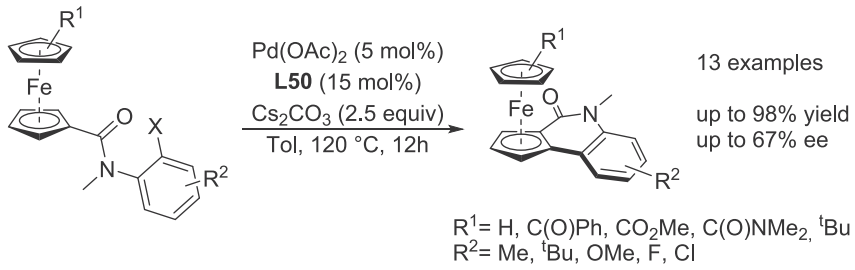
The success with QUINAP pushed other researcher to explore other related atropisomeric P,N-ligands **L48**–**L52** (Scheme 29) in asymmetric catalysis. QUINAZOLINAP (**L48**) [125] and PyPHOS (**L49**) [126] were prepared following a similar route than the used originally for QUINAP. These ligands also required to be resolved for which stoichiometric amounts of the chiral Pd complex **23** were needed. In addition, in the case of QUINAZOLINAP, the resolution procedure had to be further modified depending on the steric bulk of the substituent at the 2-position. This was not the case for PINAP ligands (**L50**–**L52**), which were designed to overcome these drawbacks. For these ligands, the diastereoisomers can therefore be separated by crystallization or column chromatography (Scheme 29) [127]. Thus, the racemic backbone was first easily prepared by selective oxidative Friedel–Crafts coupling of the dichlorophthalazine with 2-naphthol. Then, heteroaryl chloride **28** could react with (*R*)-phenylethanol (**29**) followed by triflation to provide **30**, or being first subjected to triflation and then react with the desired chiral amine **31** to provide **32**. Finally, using the same methodology as in the synthesis of QUINAZOLINAP, **30** and **32** were phosphinated to furnish PINAP type ligands **L50**–**L52** [128]. Separation of diastereomeric (R,S^{ax})- and (R,R^{ax})-mixtures were then easily done by column chromatography [128].

The application of ligands **L48**–**L52**, showed in some cases better results and even broader applicability than QUINAP. For instance QUINAZOLINAP ligands exhibited even slightly higher enantioselectivities in the Rh-hydroboration of a broad selection of vinylarenes, thanks to the tunability of the substituent at the 2-position of the atropoisomeric backbone [125b,h]. Concretely, the use of 2-methyl QUINAZOLINAP (**L48**; R = Me) provided excellent enantioselectivities (up to 99.5% ee). Note that the high ee's are maintained when using tri- and tetrasubstituted vinyl arenes (e.g. indene, stilbene and 1,2-dihydronaphthalene), which usually proceeded with low enantioselectivities. **L48** were also applied to Pd-catalyzed allylic alkylations. The enantioselectivity was dependent on the 2-position of the quinazoline backbone, being ligands with a 2-^{i}Pr substituent the most enantioselective (up to 94% ee) [125b,f,g]. PyPHOS (**L49**) ligands also proved to be useful in the Rh-catalyzed hydroboration of vinylarenes.

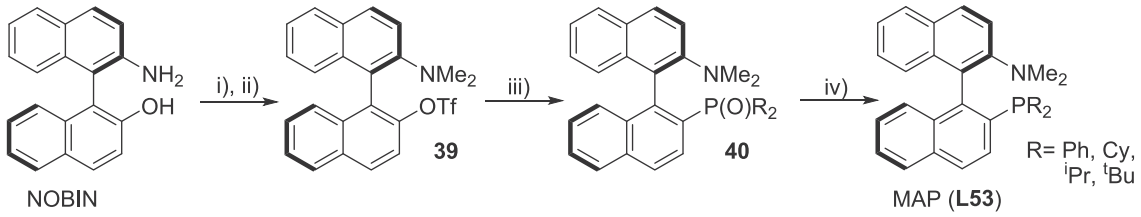
As previously commented, PINAP (**L50**–**L52**) ligands have the advantage over QUINAP and related ligands of not requiring chiral Pd salts for their resolution, and therefore they are easily accessed. Moreover, Carreira showed that O-PINAP ligand (**L50**) gave comparable ee's than QUINAP in the hydroboration of styrenes (up to 94% ee) and the cycloaddition of azomethine ylides and acrylates (up to 95% ee) [127a]. More important is the excellent performance achieved in Cu-catalysis by the PINAP ligand family. N-PINAP (**L51**) exhibited even higher enantioselectivities in the Cu-catalyzed A^3 coupling for the preparation of propargyl amines (90–99% ee) [127a]. Later, the scope of the reaction has been further extended by Carreira and Ma. For instance, Carreira reported the preparation of propargylic amines bearing the more labile group 4-piperidone, which allowed easy deprotection to afford propargylic primary amines **33** in high yields (up to 92%) and up to 96% ee (Fig. 18) [129]. Ma developed a highly enantioselective A^3 coupling of pyrrolidine, 2-methylbut-3-yn-2-ol and several aromatic aldehydes, which previously had shown lower enantioselectivities than aliphatic aldehydes (Fig. 18, compounds **34**). A range of propargylic amines were obtained in 91–>99% ee [130]. The Cu/PINAP three-component coupling of propargylic alcohols, aldehydes and pyrrolidine was also used for the synthesis of chiral allenols **35** (Fig. 18) [131]. The reaction proceeds through formation of the corresponding propargylic amine and posterior Zn-mediated deamination. More recently, Ma has disclosed the A^3 coupling of terminal alkynes, aldehydes and 3-pyrroline or isoindoline and subsequent [1,5]-hydride transfer catalyzed by CuBr to provide the (*E*)-N-allyl pyrroles with high yields. By using N-PINAP ligands **(L51)** it



Scheme 30. Copper-catalyzed alkynylation of Meldrum's acid derivatives with **L52**.



Scheme 31. Pd/**L50**-catalyzed asymmetric intramolecular Cp – H bond functionalization/cyclization reaction to construct planar chiral quinilinoferrocenes.



Scheme 32. Synthesis of ligands **L53**. i) CH_2O, $NaBH_4$, H_2SO_4, THF, rt; ii) Tf_2O, Py, DCM, 0 °C; iii) $R_2P(O)H$, $(AcO)_2Pd$, dppb, $^iPr_2NEt$, DMSO, 120 °C; iv) Cl_3SiH, Et_3N, xylene, 120 °C.

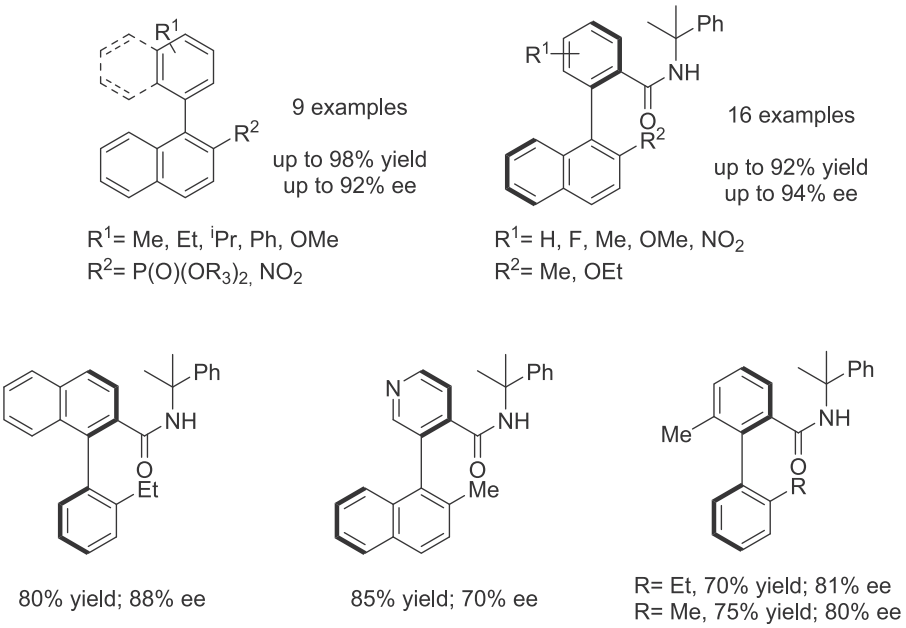


Fig. 19. Scope of axially chiral biaryls obtained through Pd-catalyzed Suzuki-Miyaura coupling of boronic acids and aryl halides with **L53** ligand (R = Cy).

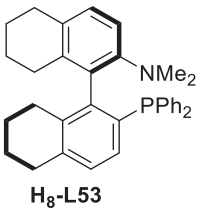
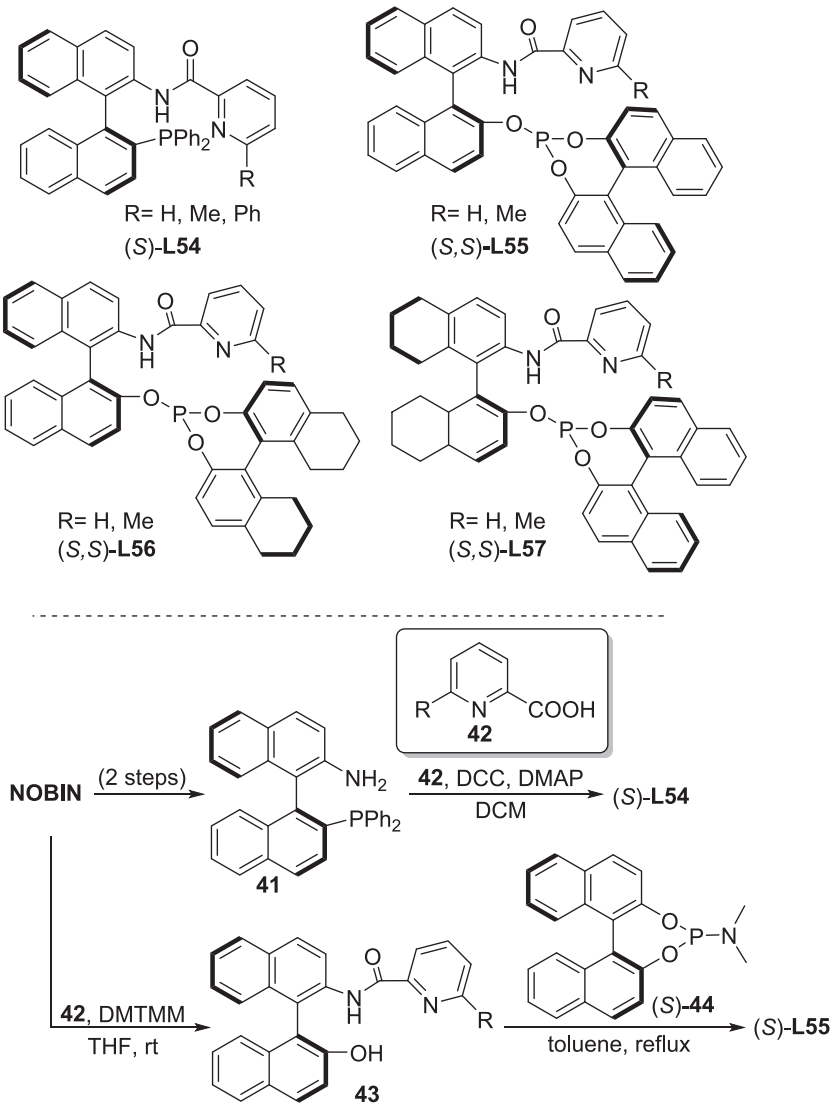


Fig. 20. Axially chiral ligand **H_8-L53.**

was possible to achieve the chiral (*E*)-N-allyl pyrroles in 97% ee and the four possible diastereoisomers of **37** in >99% ee (Fig. 18) [132]. The synthetic applicability of the A^3 coupling using the Cu/N-PINAP system has been recently shown by Oguri, who used this methodology to prepare anti-malarial 6-aza-artemisinins in only four steps [133]. It has been also found that the use of tetrahydroisoquinoline as an amine source in A^3 couplings affording tetrahydroisoquinoline-alkaloid derivatives (**38**, Fig. 18) [134]. The corresponding products were furnished with excellent yields and high enantioselectivities (up to 95% ee). This strategy has been fruitfully applied in the total synthesis of several natural products, such as (+)-crispine A and (+)-dysoxyline with an excellent ee of 98% [134], and various naturally occurring alkaloids (see Section 6) [135].

Another important application of Cu/PINAP catalytic systems is the alkyne conjugate addition to Meldrum's acid derivatives. The initial catalyst screening showed that while phosphine ligands (e.g. Josiphos, BINAP and Monophos) and N,N-ligands gave low ee's (up to 25%), the first generation of PINAP ligands



Scheme 33. NOBIN-derived P-pyridine ligands **L54**–**L57**.

(**L50**–**L52**) gave moderate yields (up to 58%) and enantioselectivities (up to 80% ee). The incorporation of amino alcohols derived from amino acids in the 2-position of the PINAP scaffold, lead to more enantioselective ligands for this transformation (Scheme 30, ligand **L52**). In addition, methoxy-substituted ligands (**L52**) catalyzed the reaction faster. With the optimized ligand, the addition of phenylacetetylene to various Meldrum's acids in aqueous media proceeded smoothly and with enantioselectivities of 82–97% ee [136].

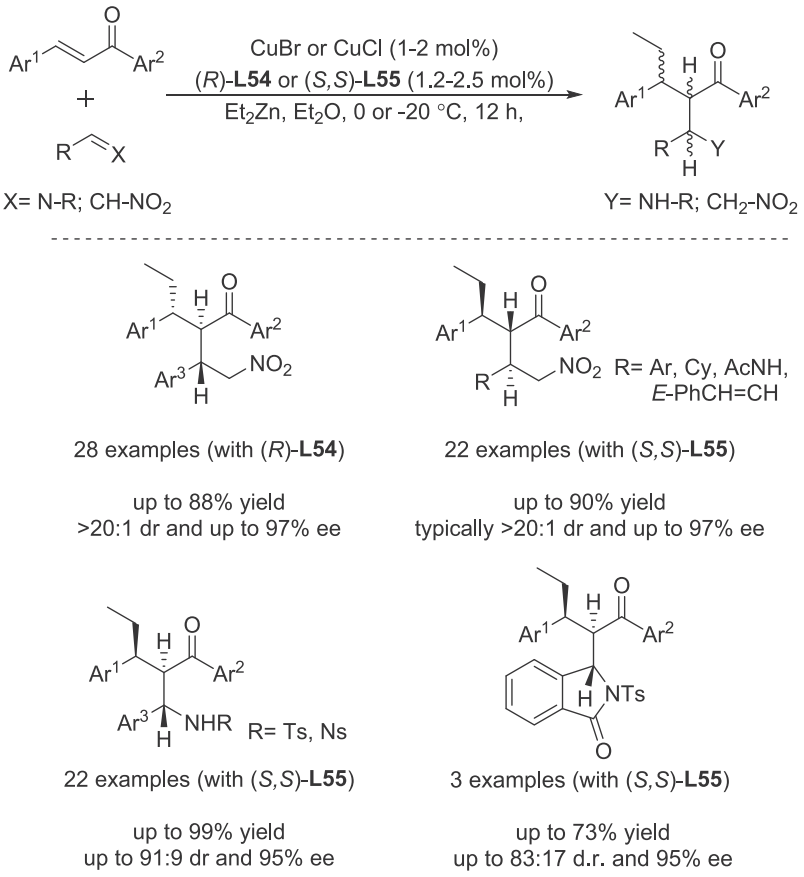
Finally, Gu et al. showed a different application for O-PINAP (**L50**) ligands. Thus, a range of quinilinoferrocenes with a planar chirality were attained via Pd-catalyzed asymmetric intramolecular Cp—H bond functionalization/cyclization reaction of 2-halophenyl ferrocenecarboxylic amides [137]. However, only moderate enantioselectivities were achieved (up to 67% ee, Scheme 31).

Another important family of axially chiral ligands are the nitrogen analogues of Hayashi's MOP ligands [138], the MAP ligand family **L53** (Scheme 32) [139]. Kočovský and co-workers synthesized for the first time the MAP ligands from the known biaryl amino alcohol NOBIN. First, alkylation of the amine group takes place, followed by the introduction of the diphenylphosphine group on triflate intermediate **39** trough Pd-catalyzed coupling with $R_2P(O)H$. Successive reduction of intermediate **40** affords the desired MAP ligand. Although designed to act as bidentate P, N-donor ligands, NMR studies of the $PdCl_2$/MAP complex showed a mixture of three species, where the major one was a cyclometallated complex [140].

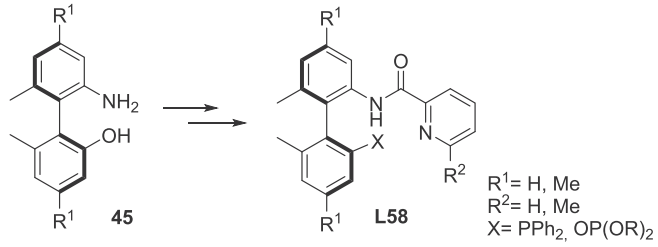
MAP ligand (R = Ph) was applied to various Pd-catalyzed asymmetric transformations, namely asymmetric allylic alkylation, Hartwig-Buchwald aminations and Suzuki cross-couplings (ee's up to 73%) [141]. Next, related **L53** with R = Cy allowed for the first time the preparation of enantiopure chiral biaryls with up to 92% enantiomeric excess through asymmetric Suzuki-Miyaura (Fig. 19 [142]). Later, the substrate scope of boronic acids and aryl halides was expanded, including also axially chiral heteroaromatic and biphenyl compounds (Fig. 19) [143].

Following the same synthetic strategy than for MAP-ligands, Ding prepared the octahydro analogues H_8-MAP (**H_8-L53**, Fig. 20) which gave higher enantioselectivities than **L53** in the Pd-catalyzed alkylation of (*E*)-1,3-diphenylallyl acetate (83% ee *vs.* 73% ee) [144]. The higher enantioselectivity obtained was attributed to the larger bite angle of the **H_8-L53** ligands [145].

Axially chiral P,N-ligands **L54**–**L57** with a rigid amide linker are also derived from NOBIN (Scheme 33). To synthesize **L54**, NOBIN is first transformed to amino-phosphine compound **41** in 3 steps, which then reacts with 2-picolinic acid **42**. Ligands **L54** were screened in the Cu-catalyzed 1,4-addition of diethylzinc to



Scheme 34. Scope of the Cu-catalyzed tandem conjugate addition-Mannich reaction using ligands (*R*)-**L54** and (*S,S*)-**L55** (R = Me).



Scheme 35. Ligands **L58** derived from chiral biphenyl backbone **45**.

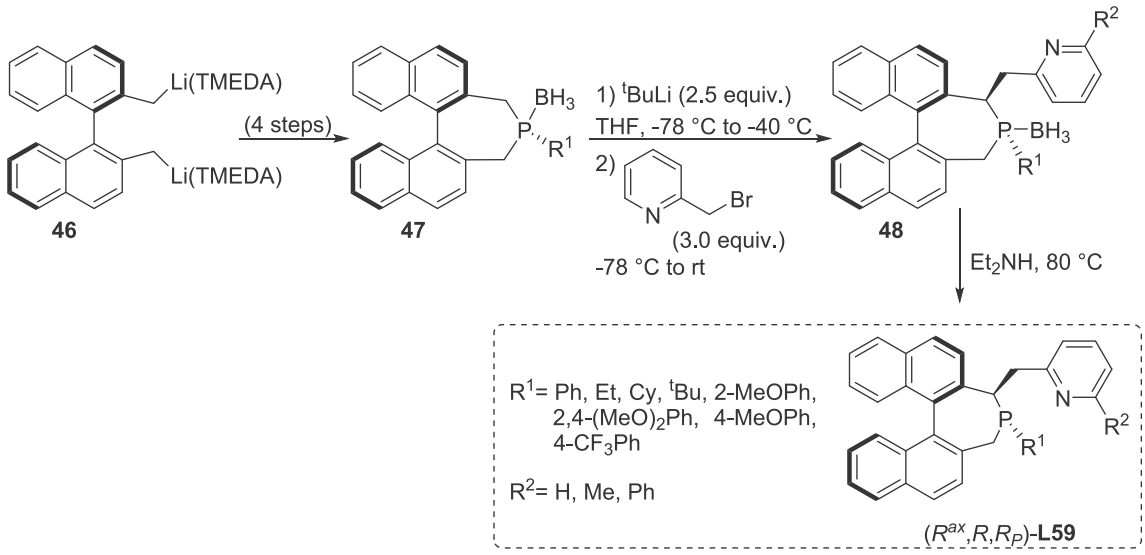
different linear enones. A ligand with a 2-Me-pyridine moiety (**L54**, R = Me) provided the highest enantioselectivities (up to 98% ee). A promising enantioselectivity (up to 98 ee) was obtained also for the purely aliphatic enone (*E*)-5-methylhex-3-en-2-one [146]. More recently, the presence of a phenyl group in the *ortho*-position of the pyridyl moiety (**L54**, R = Ph) allowed the conjugate addition of various aldehydes with good yields (78–90%) and good to high enantioselectivities (75–98% ee) [147].

Later, Hu and co-workers described the analogues phosphinite ligands **L55**–**L57** (Scheme 33). The synthesis of (*S*)-**L55** is shown is Scheme 33. In this case the pyridine-carboxylate moiety was installed prior to the insertion of the phosphorus group. Next, intermediate **43** was mixed with (*S*)-Feringa's phosphoroamidite (*S*)-**44** to afford the desired ligand. (*S*)-**L55** (R = Me) afforded enantioselectivities up to 97% ee in the Cu-catalyzed conjugate addition of diethylzinc to linear enones (uo to 97% ee) [148]. H_8-NOBIN-derivatives **L56** and **L57**, which were obtained in a similar manner than **L55**, showed also an excellent catalytic performance [149]. However, ligands **L55** as well as **L54** failed for cyclic enones, with ee's not higher than 53% ee.

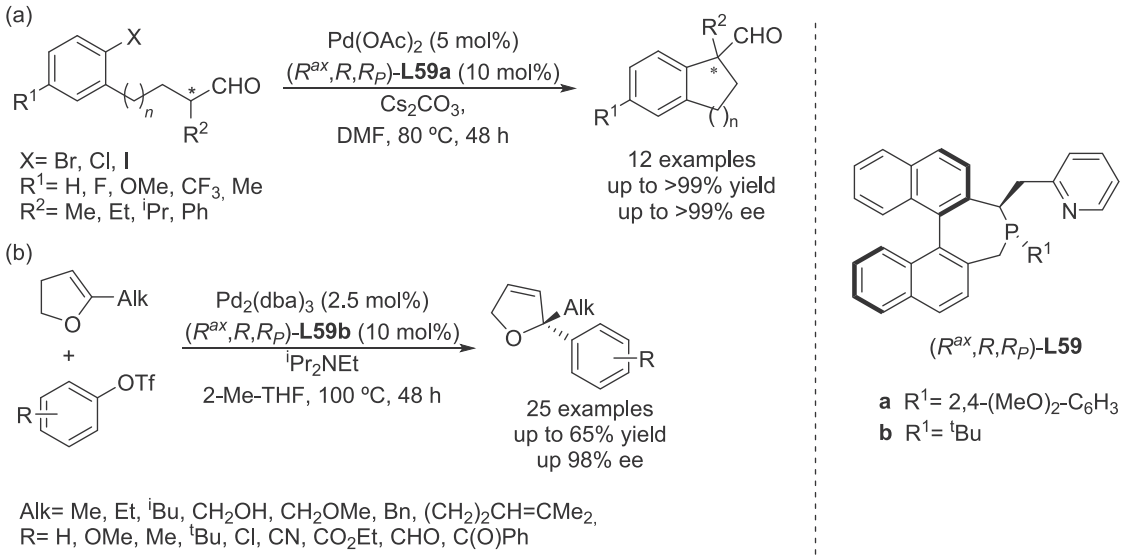
Ligands (*R*)-**L54** and (*S,S*)-**L55** (R = Me) have been efficiently used in different asymmetric tandem Cu-catalyzed Michael/Mannich reactions, furnishing excellent enantioselectivities (Scheme 34). The procedure allowed the synthesis of a broad range of chiral functionalized products with multiple stereocenters, which could be used to prepare valuable compounds, such as pyrrolidines, isoindolinones and azetidines [150].

The more electron-rich chiral biphenyl backbone **45** has been also used to prepare atropoisomeric P,N-ligands (Scheme 35). Phosphine- and phosphite-pyridyl ligands **L58** gave excellent enantioselectivities in the Cu-catalyzed conjugate addition of diethylzinc to linear enones (ee's up to 96%) [151].

Atroposiomeric ligands **L59** with a 2-pyridyl moiety to a binepine scaffold have shown excellent results in asymmetric Pd-catalysis. Besides axial chirality, these ligands contain two elements of central chirality, one in the benzylic position and the other at the phosphorus atom (Scheme 36). The synthesis of ligands **L59** starts from dilithiated binaphthyl compound **46**, which is transformed to borane-protected binepine **47** in 4 steps. Then, the benzylpyridine moiety is incorporated in the presence of BuLi, providing **48** as a single diastereoisomers except in the cases where the phosphorus center was a phenyl group [152]. Finally, borane-protected compounds **48** were deprotected by refluxing them in an excess of diethylamine for 4 days, yielding ligands **L59** as off-white crystalline with good to excellent yields.. Ligands **L59** were first tested in the Pd-catalyzed intramolecular α-arylation of α-branched aldehydes, surpassing the results achieved with QUINAP, PINAP or PHOX. The ligand screening revealed that a ligand with a



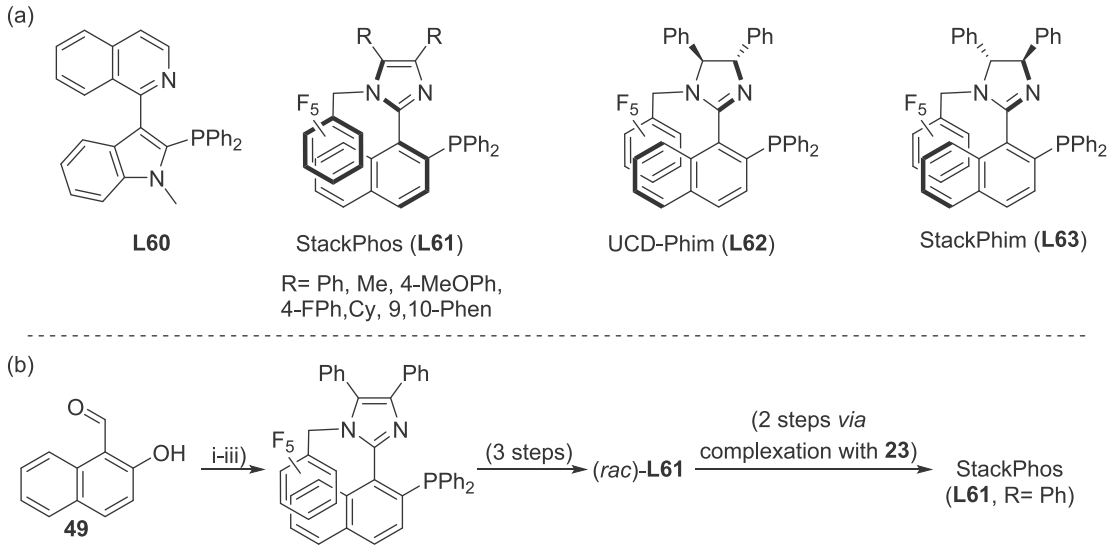
Scheme 36. Synthesis of binepine ligands **L59**.



Scheme 37. Application of (R^{ax},*R*,R_P)-L59 ligands in Pd-catalyzed reactions. (a) α-Arylation of aldehydes with L59a and (b) Heck reaction with L59b.

more electronrich aromatic substituent in the P-group and a non-substituted pyridyl moiety (**L59a**) showed the best catalytic performance (Scheme 37a). A selection of aldehydes could be used furnishing the corresponding cyclic products with excellent enantioselectivities (up to >99% ee) and good yields [152] It was also successfully used in the Pd-catalyzed Heck reaction between 2-substituted furans and aryl triflates to yield functionalized 2,5-dihydrofurans with fully saturated C_2 stereocenters. In this case the optimal ligand contained a *tert*-butyl moiety at the phosphorus group (**L59b**), showing moderate yields but enantioselectivities up to 94% ee for a range of substrates (Scheme 37b) [153]. To gain information about the catalytic species formed during catalysis, the authors performed the complexation of ligands **L59** to $[PdCl_2(CH_3CN)_2]$, leading to air-stable complexes $[(\mathbf{L59})PdCl_2]$. NMR and IR spectroscopy proved the bidentate coordination of the ligand, which was also corroborated with the molecular geometry obtained by single-crystal X-ray analysis. It was also found that the ligand adopts a nearly ideal square-planar geometry and that the P-donor has a stronger *trans* effect than the N-donor atom [152].

The first developed generation of axially chiral ligands were based on 6-membered heterocyclic motifs. All of them were built on a binaphthalene or a biphenyl backbones with an element in the *ortho*-position that hinders the rotation about the biaryl bond [108c-e]. The replacement of one of the naphthalene rings by a 5-membered ring was already attempted by Brown et al., with the synthesis of the indole-based ligand **L60** (Scheme 38). However, the new ligand turned to be not configurationally stable. In 2003, Aponick designed the StackPhos ligand bearing an imidazole group (**L61**, R = Ph, Scheme 38), in which the π – π interaction between the electron-rich naphthalene ring and the electron-poor pentafluorophenyl group on the non-coordinating nitrogen is crucial to prevent tropoisomerism [154]. The synthesis of racemic **L61** was achieved in 6 straightforward steps starting from 2-hydroxy-1-naphthaldehyde **49**, in which the imidazole ring and the diphenylphosphino group were readily introduced



Scheme 38. (a) Ligands **L60**–**L63** bearing a five membered-N-containing ring. (b) Synthesis of **L61**: i) $(PhCO)_2$, NH_4OAc, AcOH, 140 °C; ii) TBSCl, Et_3N, DCM, rt; iii) NaH, THF, $C_6F_6CH_2Br$, −78 °C.

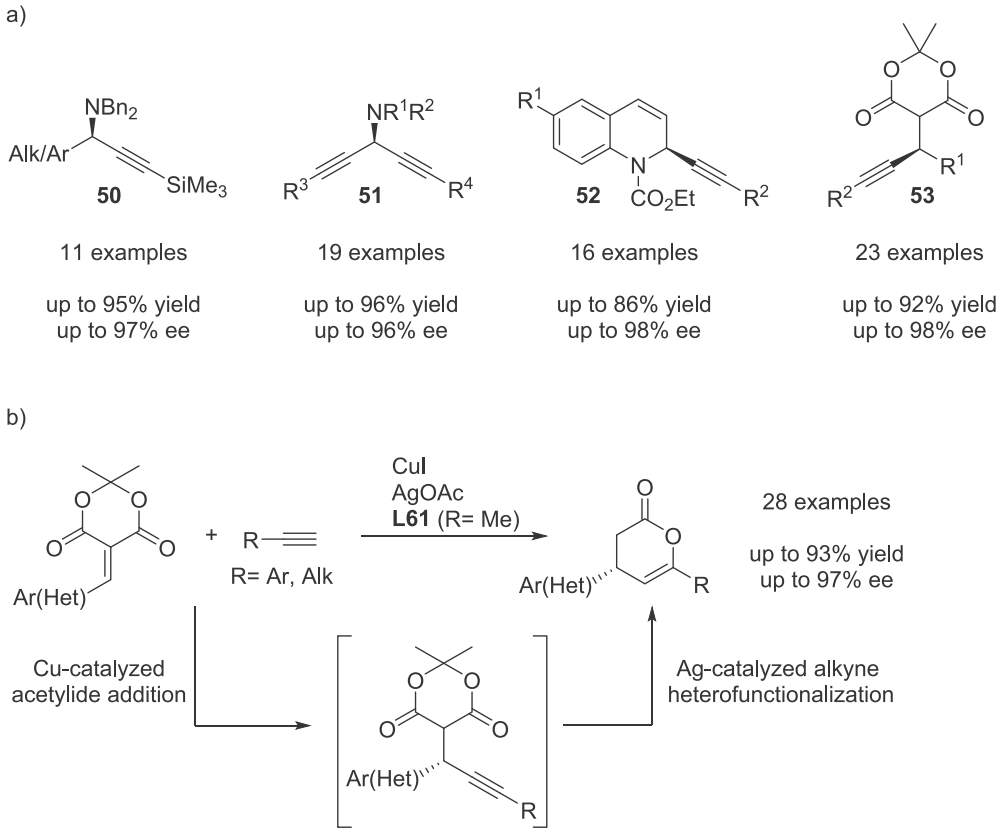
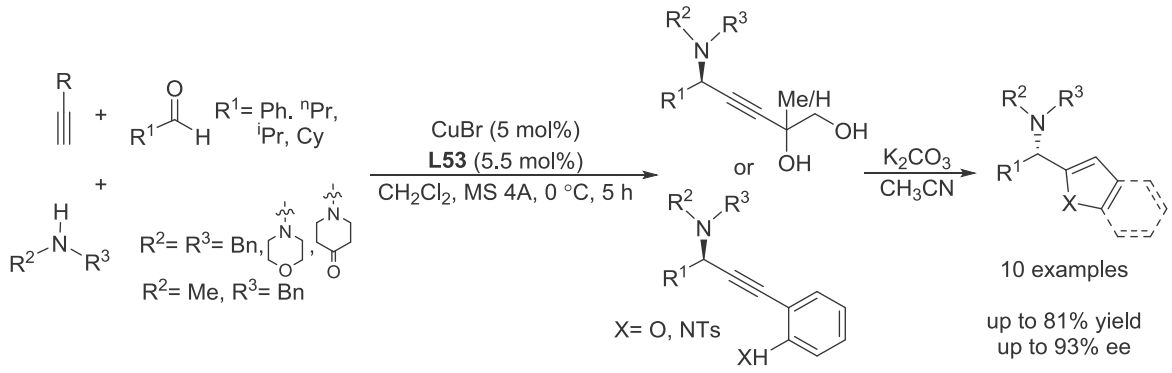


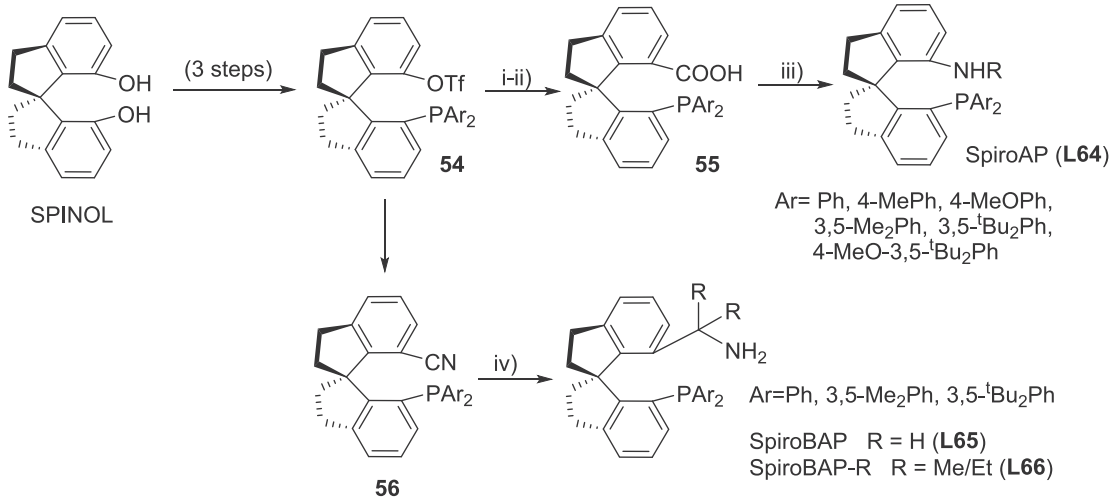
Fig. 21. Scope of StackPhos ligand in Cu-catalyzed coupling reactions (**L61**, R = Ph; compounds **50**–**52**) and in the Cu-catalyzed alkyne conjugate addition to Meldrum's acid derivatives (**L61**, R = Me; compounds **53**).

(Scheme 38). In contrast to QUINAP and its derivatives, the resolution of **L61** was achieved through deracemization instead of resolution. Reaction of racemic ligand with chiral Pd-salt **23** resulted in a single diastereoisomer, which was then treated with dppe to release ligand **L61** in high yield and 98% ee. Later, related phosphinoimidazoline ligands **L62**–**L63** (Scheme 38) were independently developed by Guiry (UCD-Phim) [155] and Aponick (StackPhim) [156]. The idea behind them was to circumvent the use of stoichiometric amounts of expensive chiral Pd-amine complex **23** to access the enantiopure ligands. Similarly to Carreira's PINAP, these ligands bear an element with central chirality that allows the separation of the diastereomeric mixture through recrystallization or column chromatography. Note that StackPhim (**L62**) and UCD-Phim (**L62**) are diastereomers.

The first application of the StackPhos ligand (**L61**, R = Ph) was in the Cu-catalyzed A^3-coupling between dibenzylamine,



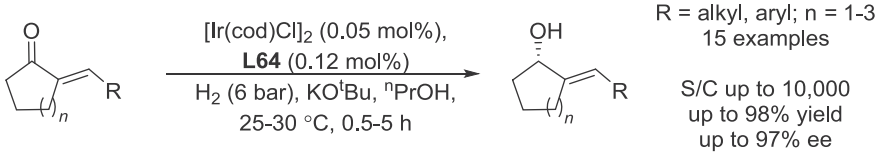
Scheme 39. Cu-catalyzed A^3-coupling/cyclization sequence with StackPhim (**L63**).



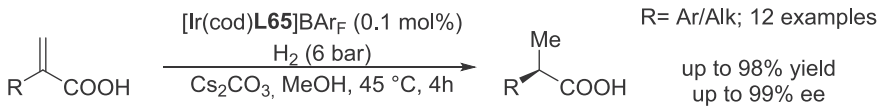
Scheme 40. Synthesis of spiro ligands **L64**–**L66** derived from SPINOL. i) 15 mol % $Pd(OAc)_2$, 15 mol % dppp, CO (1 atm), Et_3N, DMSO, MeOH, 70 °C; ii) 40–60% KOH, methanol, reflux; iii) NaN_3, H_2SO_4, iv) 10 mol % $Pd(PPh_3)_4$, $Zn(CN)_2$, dimethylformamide, 130 °C.

trimethylsilylacetylene and a range of aldehydes, including the more challenging aromatic ones. The corresponding propargylamines **50** were yielded in high yields and ee's up to 97% (Fig. 21a) [154]. The protocol was extended to the synthesis of amino skipped diynes **51** (up to 96% ee), a class of chiral molecules with minimal differences in two of the substituents rendering them chiral (Fig. 21a) [157]. The Cu/StackPhos system has also allowed the enantioselective copper-catalyzed alkynylation of quinolinium salts and chromanones, delivering the desired products **52** in high yields and enantioselectivities (up to 98% ee; Fig. 21a) [158]. The potential of the reaction was demonstrated in the syntheses of the tetrahydroquinoline alkaloids [158a] (+)-galipinine, (+)-cuspareine, and (−)-angustureinem, as well as (−)-martinellic acid (see Section 6) [159]. More recently, a set of StackPhos ligands bearing different substituents in the imidazole ring have been applied to the alkyne conjugate addition to Meldrum's acid derivatives. A ligand with a methyl group (**L61**, R = Me) in combination with $Cu(OAc)_2$ exhibited the best catalytic performance (up to 92% yield and 98% ee) [160]. The transformation gives β-alkynyl Meldrum's acid building blocks (compounds **53**, Fig. 21a), which could be used in the asymmetric synthesis of the vasopressin V2-receptor agonist OPC 51,803 (see Section 6). More recently, Aponick's group used **L61** for the synthesis of chiral δ-lactones via a tandem acetylide addition/alkyne heterofuntionalization process catalyzed by Cu and Ag, respectively (Fig. 21b) [161].

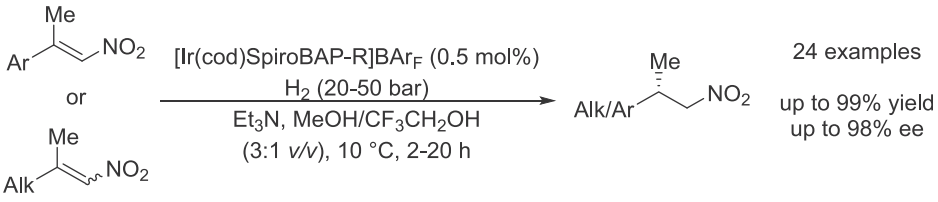
The newer UCD-Phim ligands **L62**, developed by Guiry and coworkers, showed excellent results in the Cu-catalyzed A^3-coupling reaction of aliphatic aldehydes, showing in some of the cases greater enantioselectivities than StackPhos ligands (up to 98% ee) [155]. In 2019, the scope was extended to aromatic, alkenylic and alkynylic aldehydes, as well as secondary cyclic amines, achieving up to 99% ee [162]. The StackPhim ligand **L63**, developed by Aponick, has been used to prepare C2-aminoalkyl five-membered heterocycle motifs (up to 94% ee, Scheme 39). The strategy used consists in a convergent alkynylation/cyclization sequence [156].



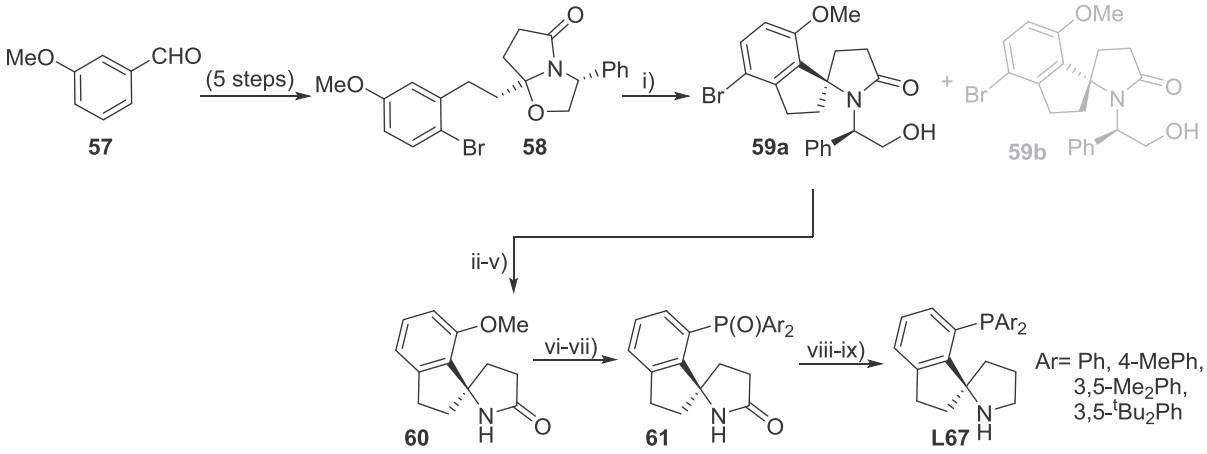
Scheme 41. Ir-catalyzed hydrogenation of *exo*-cyclic α,β-unsaturated ketones with SpiroAP ligand (**L64**, Ar = 3,5-^{t}Bu$_2$-C_6H_3) .



Scheme 42. The hydrogenation of α-aryl- and α-alkyl acrylic acids with SpiroBAP based complex [Ir(cod)(**L65**)]BAr$_F$ (**L65**, Ar = 3,5-^{t}Bu$_2$-C$_6$H$_3$).



Scheme 43. Hydrogenation of pure and diastereomeric mixtures of nitroalkenes with SpiroBAP-R complex [Ir(cod)(**L66**)]BAr$_F$ (**L66**, Ar = 3,5-^{t}Bu$_2$Ph, R = Me).



Scheme 44. Synthesis of spiro ligands **L67**. i) AlCl$_3$, DCE, −10 °C; ii) LiOH·H$_2$O, DMSO, 170 °C; iii) HCl (4 N), THF, 70 °C; iv) H$_2$, Pd/C, MeOH; v) BBr$_3$, CH$_2$Cl$_2$, −20 °C; vi) PhNTf$_2$, Cs$_2$CO$_3$, DMF; (vii) Ar$_2$P(O)H, Pd(OAc)$_2$, dppb, ^{i}Pr$_2$NEt, DMSO; viii) Cl$_3$SiH, toluene, 85 °C; ix) LiAlH$_4$, THF, 60 °C.

3.3. Spiro P,N-ligands

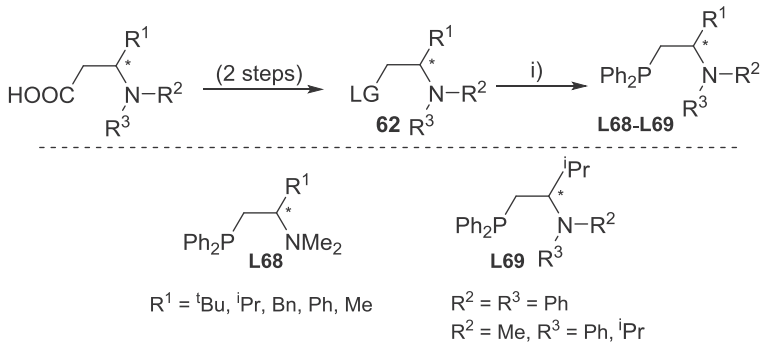
Amino-phosphine ligands with a spiro center (**L64**–**L66**, Scheme 40) have proved to be highly effective in the hydrogenation of α,β-unsaturated ketones as well as alkenes bearing nitro or carboxylic acid groups when using Ir-catalysts. The first ligands of this class were the SpiroAP ligands (**L64**) developed by Zhou et al. [163]. The introduction of a CH$_2$-group before the primary amino moiety, and later a CMe$_2$-group, afforded chiral spiro benzylamino-phosphine SpiroBAP [164] and SpiroBAP-R [165] ligands (**L65**–**L66**). The synthesis of amino-phosphine spiro ligands **L64**–**L66** starts with the transformation of commercially available SPINOL into diarylphosphine/triflate intermediate **54** (Scheme 40). To obtain SPiroAP ligands (**L64**), **54** is converted to the dimethyl ester derivative by Pd-catalyzed carbonylation, followed by subsequent basic hydrolysis to provide carboxylic acid derivative **55**. In the case of SpiroBAP and SpiroBAP-R ligands (**L65**–**L66**), the synthesis proceeds through Pd-catalyzed cyanation of **54**. Next, reduction of cyanate intermediate **56** with LiAlH$_4$ or with MeLi afforded SpiroBAP and SpiroBAP-R ligands, respectively.

SpiroAP ligands (**L64**) were screened in the Ir-hydrogenation of exocyclic α,β-unsaturated enones to afford *exo*-cyclic allylic alcohols and β-arylmethyl cyclic alcohols [163]. The corresponding Ir-complexes were formed *in situ* during catalysis. The best ligand contained a bulky phosphine group (Ar = 3,5-di-*tert*-butylphenyl), giving excellent enantioselectivities and yields (Scheme 41). The potential of this methodology was demonstrated with the synthesis of a crucial intermediate in the preparation loxoprofen, a nonsteroidal anti-inflammatory drug (see Section 6).

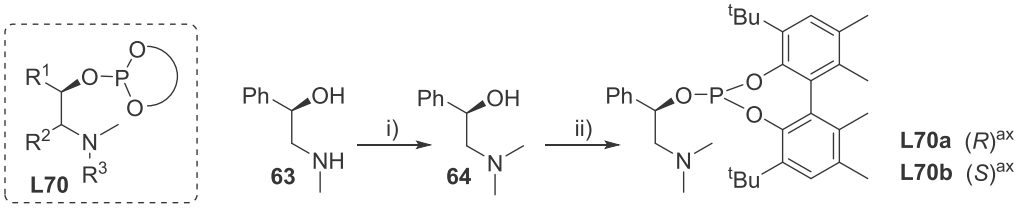
Prompted by the excellent results obtained in the hydrogenation of ketones, Zhou and co-workers prepared spiro benzylamino-phosphine SpiroBAP (**L65**) [164]. In this case, Ir-complexes were synthesized prior to catalysis, following the same procedure used for preparing [Ir(cod)(**L8**)]BAr$_F$. The new complexes were stable to air and and could be stored without degradation for a few months. X-ray diffraction analysis showed that **L65** (Ar = Ph) acts as a chelating P,N ligand and creates a rigid chiral pocket around the iridium center. Again, the presence of a bulky aryl phosphine (**L65**, Ar = 3,5-^{t}Bu$_2$-C$_6$H$_3$) exhibited the best catalytic results in the hydrogenation of α-aryl- and α-alkyl acrylic acids (Scheme 42). A range of chiral carboxylic acids, including naproxen and related anti-inflammatory drugs, were attained in excellent enantioselectivities (up to 98%) and TOFs (up to 6000 h^{-1}).

The presence of a dimethyl group at the benzylic position of the amine group on SpiroBAP-R ligands allowed the enantioconvergent hydrogenation of β-aryl-β-methyl-nitroalkenes (91–98% ee values) and β-alkyl-β-methyl-nitroalkenes (77–95% ee values; Scheme 43) [165]. [Ir(cod)(**L66**)]BAr$_F$ was able to hydrogenate diastereomeric mixtures of *E*- and *Z*-nitroalkenes, thus avoiding tedious isolation of the substrate isomers.

Very recently, Jiao and co-workers have published the air-stable ligands **L67** bearing a rigid spiro[indane-1,2′-pyrrolidine] backbone (Scheme 44) [166]. In contrast to SPINOL-derived ligands **L64**–**L66**,



Scheme 45. Synthesis of β-aminophosphine ligands **L68**–**L69**. i) PPh_2, KO^{t}Bu, THF.



Scheme 46. General structure of phosphite-amino ligands **L70** and synthesis of **L70a**–**b**. i) Formic acid/paraformaldehyde/H_2O; ii) $ClP(OR)_2$, R = **a** and **b**, Py, toluene, rt.

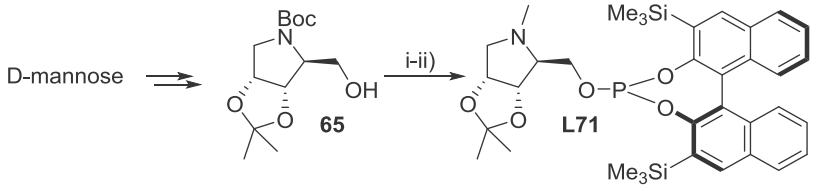
the spiral center must be created during the synthesis of ligands **L67** (Scheme 44). Thus, the key step to build the spiral center is accomplished through $AlCl_3$-mediated intramolecular Friedel–Crafts-type reaction of **58**, which is obtained first from **57** after 5 steps. After three recrystallizations of the diastereomeric mixture of **59a**–**b,** pure diastereoisomer **59a** was afforded. Next, compound **60** is obtained via multiple steps. Demethylation of **60** followed by triflation of the phenolic hydroxy group, coupling with diphenylphosphine oxide and two subsequent reduction steps gave ligand **L67**. Ligands **L67** were applied in the Pd-catalyzed asymmetric allylic substitution of benchmark substrate with dimethylmalonate but also with several alcohols and amines as nucleophiles with moderate to high yields and enantioselectivities (60–99% yield and 61–97% ee). The authors were able to obtain a crystal structure of [Pd(II)(η^3-1,3-diphenylallyl)(**L67**, Ar = 3,5-^{t}Bu$_2$Ph)]PF_6, which gave information about the transition states of the substitution reactions.

3.4. P,N-Ligands with central chirality

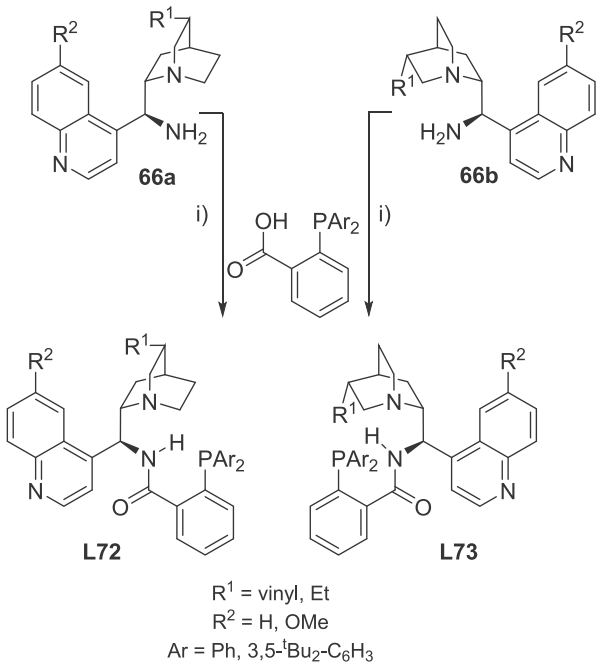
3.4.1. P-amino ligands

Many new P,N-ligands bearing central chirality has also been developed. Few years later of the discovery of PPFA ligands (**L35**), Hayashi and Kumada designed a new library of ligands **L68** from natural α-amino acids (Scheme 45). Phosphine-amino ligands **L68** catalyzed the Ni- Grignard cross-coupling of (1-phenylethyl) magnesium bromide and vinyl bromide, for which the bulkiest *tert*-Leuphos ligand **L68** (R^1 = ^{t}Bu) provided the highest ee value (up to 94% ee) [86c]. The asymmetric induction was thought to result from the hemilability of these ligands. Several analogues of these chiral β-aminophosphine, have been developed throughout the years, because of their stability, low toxicity and ease handling. These ligands can be readily synthesized through nucleophilic phosphide substitution of derivatized amino alcohols **62** containing a leaving group (LG) (Scheme 45). Besides, this scaffold has been also used in the design of other P,N-ligands containing an imine, amide or pyridine as N-donor group. A review about β-aminophosphine derivative has been recently reported [85e]. Another example of β-aminophosphine ligands are compounds **L69** derived from L-valine (Scheme 45), which were applied in the palladium catalyzed allylic substitution of (*E*)-1,3-diphenylallyl acetate with dimethyl malonate. The nitrogen substitution constituted a key factor in the stereochemical outcome of the reaction, with enantioselectivities that ranged from 56% ee (*R*) to 92% ee (*S*) [167].

Air-stable phosphite-amino ligands **L70** (Scheme 46) were prepared in two steps also from commercial 1,2-amino alcohols. These ligands were tested in enantioselective Pd-catalyzed allylic substitution reactions. A mechanistic study allowed the optimization of the ligand parameters from a full ligand library, identifying ligands **L70a**–**b** as the best. High enantioselectivities were achieved for a linear and cyclic substrate with several C-, N-, and O-nucleophiles (32 examples, ee values up to 99%) [168]. Ligands **L70a**–**b** were easily obtained by methylation of intermediates **63** with formic acid and formaldehyde resulted in dimethylated amino alcohols **64**. Subsequent reaction with the desired phosphorochloridite led to ligands **L70a**–**b**. Studies on the Pd-π-allyl intermediates provided insights about the effect of the ligand parameters on the origin of the enantioselectivity. It was found that the higher enantioselectivities obtained with ligands



Scheme 47. Synthesis of phosphite-amino ligand **L71**. i) $LiAlH_4$, THF, reflux; ii) $ClP(OR)_2$, Py, toluene, rt.



Scheme 48. Synthesis of chinchone-derived ligands **L72–L73**. i) DCC, DMAP, DCM, rt.

containing a hydrogen as the R^2 substituent (**L70**), compared with ligands with a R^2 = Me, were mainly due to a higher electronic differentiation between the more electrophilic allylic terminal C atoms, making the major Pd-η^3 allyl isomer more reactive [168].

β-Aminophosphine ligands derived from starting material other than amino acids have been also found to be efficient in Pd-allylic substitutions. For instance, phosphite-amino ligand **L71** with a protected pyrrolidine-3,4-diol moiety has been recently prepared from cheap D-mannose (Scheme 47) [169]. *N*-Boc protected aminoalcohol **65**, which was obtained from D-mannose [170], was subjected to Boc deprotection followed by reaction with the appropriate phosphorochloridite. The optimized ligand **L71** was employed in the Pd-catalyzed enantioselective allylic substitution of linear and cyclic substrates. Enantioselectivities ranging from 80 to 91% ee were obtained using various C- and N-nucleophiles. In the case of cyclic substrates both enantiomers of the final products could be attained by switching the chirality of the biaryl phosphite group. A study of the Pd–π-allyl intermediates showed that to achieve high enantioselectivities in the substitution of cyclic substrates, the ligand components need to be appropriately chosen to either enhance the difference in the ratio of the Pd–allyl isomers formed or to enhance the reactivity of the nucleophile towards each Pd–allyl isomer. In contrast, the key of success when using linear substrates is to avoid the formation of Pd–allyl complexes with monodentate coordinated ligands. The study also indicated that the sugar backbone is able to control the configuration of the amino group upon coordination [169]. Note that **L71** contains an amino group that is part of a cyclic backbone. Most of the P-amino ligands that exhibited remarkable results in asymmetric catalysis contain a non-cyclic amino group [85b,d]. Only few P,N-ligands bearing a cyclic amine have provided high enantioselectivities, mostly achieved only in the benchmark substrate [97,171].

In 2011, a new family of cinchona-derived phosphino-amine ligands (**L72**–**L73**) was developed by Dixon and co-workers [172]. These ligands consist on a cinchona backbone bearing three different sites that allow a cooperative catalysis: a Brønsted (—N) and a Lewis base (—P) and a H-bond-donor group (—NH). Ligands **L72** and **L73** were readily prepared from commercially available *ortho*-diphenylphosphino benzoic acids and the desired 9-amino(9-deoxy)*epi*cinchona alkaloids (**66a**–**b**; Scheme 48).

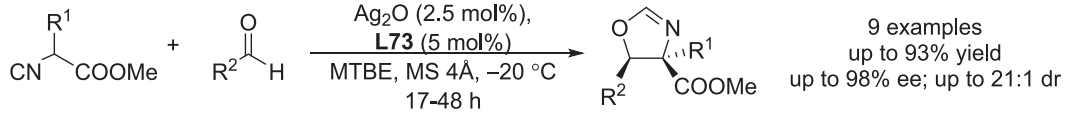
Phosphine-amino ligands **L72** and **L73** (R^1 = Et; R^2 = H; Ar = Ph) were mixed with Ag_2O to yield cooperative Ag(I)-based Brønsted base/Lewis acid catalysts that effectively promoted the asymmetric aldol reaction of isocyanoacetate nucleophiles and aldehydes (Scheme 49) [172]. Both aromatic and branched aliphatic aldehydes could be used to provide oxazolines with high diastereo- and enantioselectivities (up to 98%) by using ligand **L73** (R^1 = Et; R^2 = H; Ar = Ph). However, linear aliphatic aldehydes showed lower enantioselectivities.

After its first application, Ag(I)/**L72** catalyst has been efficiently used in the enantioselective catalytic addition of isocyanides to many other electrophilic compound such as aldehydes [173], aldimines [174], ketones [175] ketimines [176], allenoates [177], alkynyl ketones [178], other carbon–carbon double bond containing electron withdrawing groups (EWG) [179], and *p*-quinone methides (p-QMs) [180]. Besides isocyanide chemistry, quinine-derived ligands **L72** have recently showed impressive results in asymmetric Cu-catalyzed cross-coupling reactions (Scheme 50) [181]. Ligand **L72a** (R^1 = vinyl; R^2 = OMe; Ar = 3,5-^{t}Bu$_2$-C$_6$H$_3$) allowed the largely unexplored asymmetric Cu-catalyzed Sonogashira Csp^3-Csp cross-coupling between a range ofalkyl halides and alkynes (>120 examples, up to 99% ee; Scheme 50a). To show the utility of this transformation, they performed the asymmetric Sonogashira C(sp^3)—C(sp) cross-coupling reaction of a mesogenic compound with the core structures of several bioactive molecules, such as estrone, biotin etc (see Section 6). **L72b** (R^1 = vinyl; R^2 = OMe; Ar = Ph) has also allowed the radical asymmetric oxidative C(sp^3)—C(sp) cross-coupling of unactivated C(sp^3)—H bonds on *N*-fluorocarboxamides with terminal alkynes (Scheme 50b) [182]. A range of chiral alkynyl amides were afforded in a highly regio-, chemo-, and enantioselective manner (up to 97% ee).

Very recently, chinchona-derived ligands **L72c**–**d** (R^1 = vinyl; R^2 = OMe; Ar = 2,6-Me$_2$-C$_6$H$_3$ or 9-phenanthryl) have been used in the Cu-catalyzed enantioconvergent radical Suzuki – Miyaura C(sp^3) – C(sp^2) cross-coupling of racemic alkyl halides with B(mac)-derived boronate esters (Scheme 50c) [183]. The reaction showed a broad scope regarding both coupling partners, including aryl- and heteroarylboronate esters, as well as benzyl-, heterobenzyl-, and propargyl bromides and chlorides furnishing high enantioselectivities.

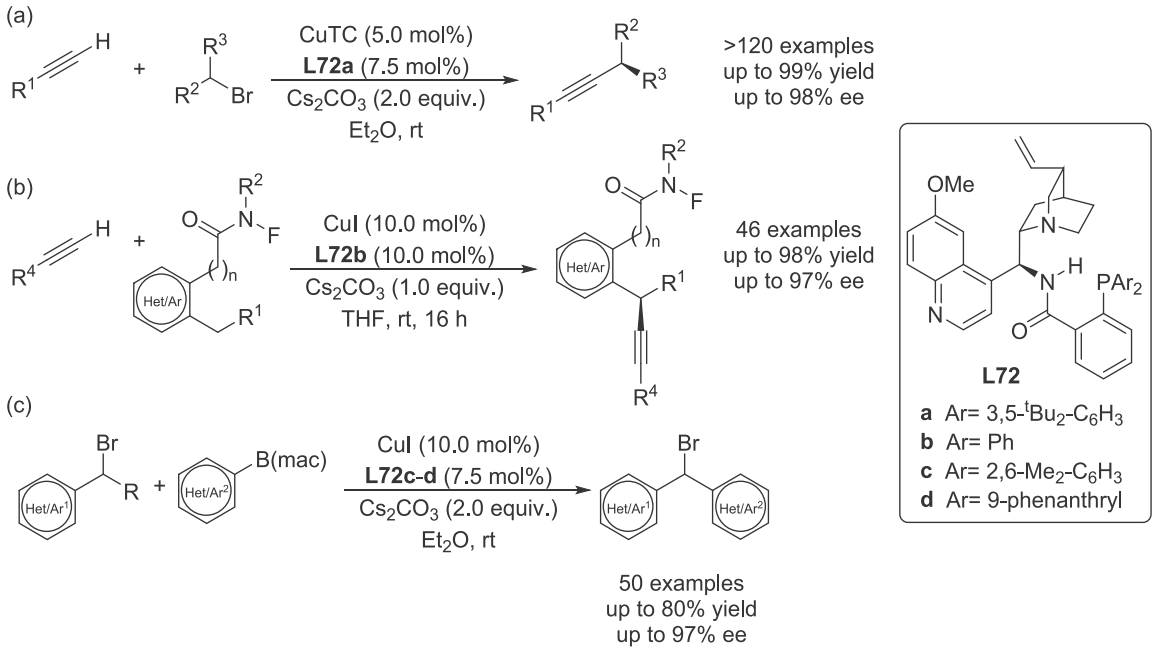
3.4.2. P-imine ligands

As ferrocene-based P-imine ligands **L43**–**L45** (Scheme 21), the phosphine-imino ligands **L74**–**L77** bearing central chirality (Scheme 51) were initially applied in Pd-allylic substitutions. All

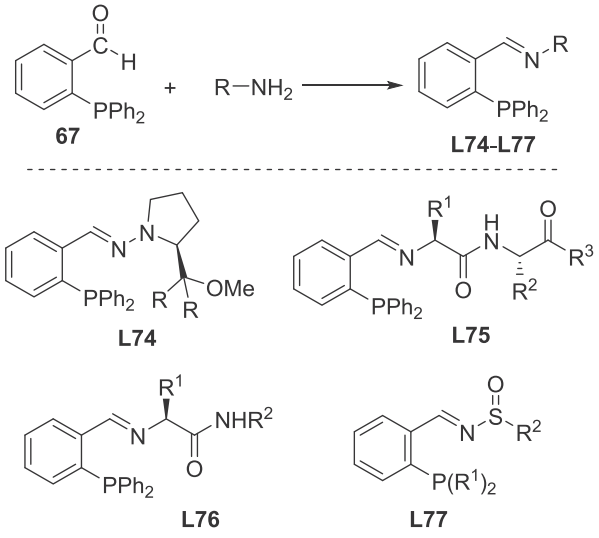


R^1= Ph, Bn; R^2= 3-BrPh, 4-FPh, 3-FPh, 4-BrPh, 4-MeOPh, 4-ClPh, 4-CO_2MePh

Scheme 49. Ag-catalyzed isocyanoacetate aldol reaction using Dixon's ligand **L73** (R^1 = Et; R^2 = H; Ar = Ph).



Scheme 50. Cu-catalyzed asymmetric Sonogashira Csp^3-Csp cross-coupling reactions and asymmetric Suzuki – Miyaura Csp^3-Csp^2 cross-coupling with chinchona P,N-ligands **L72a–d.**



Scheme 51. General synthesis of phosphino-imine ligands **L74–L77** bearing central chirality.

ligands could be easily prepared by mixing (diphenylphosphino)b enzaldehyde **67** with a desired chiral amino scaffold (for ligands **L74–L76**) or a sulfinamide (for ligand **L77**).

Thus, ligands **L74**, prepared from commercially available SAMP as the chiral amine, provided somewhat lower enantioselectivity (up to 92% ee) than related ligand **L43** (up to 96% ee) [104] in the Pd-allylic substitution reactions [184]. Using available peptides as chiral amines, Hoveyda et al. prepared a large library of peptide-based ligands **L75** and **L76**. Over the years, its modular nature has allowed to achieve excellent enantioselectivities in the Cu-catalyzed conjugate addition of a broad range of α,β-unsaturated substrates (Fig. 22) [185] For example, **L75a** (R^1 = ^{i}Pr, R^2 = Bn, R^3- = NH^nBu) exhibited excellent enantioselectivities (up to 98% ee) in the conjugate addition of different alkylzincs to cyclic enones [185a,h], while **L75b** (R^1 = ^{i}Pr, R^2 = *p*-O^{t}Bu-Bn, R^3 = NH^nBu) was preferred for the linear ones (Fig. 22) [185b,e]. Both ligands have been very useful also with unsaturated furanones, with ee's up to >98% (**L75a**) and up to 97% ee (**L75b**) (Fig. 22) [185f]. When nitroalkenes were used as Michael acceptors, the best ligands were found to be **L75c** (R^1 = ^{t}Bu, R^2 = *p*-OBn-Bn, R^3 = NH^nBu) for cyclic nitroalkenes (up to 96% ee) [185c], and **L75d** (R^1 = ^{t}Bu, R^2 = *p*-OBn-Bn, R^3 = NEt_2) for trisubstituted linear nitroalkenes (up to 98% ee; Fig. 22) [185g,186]. The Cu/**L75d** was used by Carreira in the total synthesis of (+)-Daphmanidin E (see Section 6) [187]. The same ligand also allowed the tandem conjugate addition–nitro-Mannich reaction for the preparation of *anti*- and *syn*-β-nitroamines with three contiguous stereocenters (up to 96% ee; Fig. 22) [188].

A ligand bearing only a peptidic fragment has been also efficiently used in the Cu-catalyzed conjugate addition of cyclic enones (up to >98% ee) [185d] and lactones (up to 96% ee) [185f]. Ligands **L76** have been found to induce high enantioselection in a wide range of asymmetric C—N bond forming transformations such as the aza-Diels-Alder [189] and Mannich type reactions [189b,190].

P,N-sulfinyl imine ligands **L77**, in which the chirality is found in the sulphur atom, were obtained via Ti-mediated condensation of the corresponding sulfinamide with compound **67** (Scheme 51). With a *tert*-butyl substituent attached to the imine an enantioselectivity up to 96% ee in the allylic alkylation of the benchmark substrate was attained [191]. Ligands **L77** were also used to the Ir-catalyzed hydrogenation of trisubstituted olefins, but with only moderate enantioselectivities [192].

Other ligands bearing the chirality at the sulphur centre are the P-sulfoximine ligands **L78–L81** (Scheme 52), which have been efficiently used in Ir-catalyzed hydrogenation reactions. Bolm et al. developed phosphinosulfoximine ligands **L78** and **L79** in few steps. The key step consists in the Cu-mediated coupling *N*-arylation of sulfoximines with bromo-aryl phosphine oxide **68**. Reductive deoxygenation of **69** with trichlorosilane gave the corresponding ligands as solid, air-stable products in good yields Scheme 52 [193].

Ligands **L78** were screened to the enantioselective Ir-catalyzed hydrogenation of *N*-aryl imines, using iodine as a promoter. A

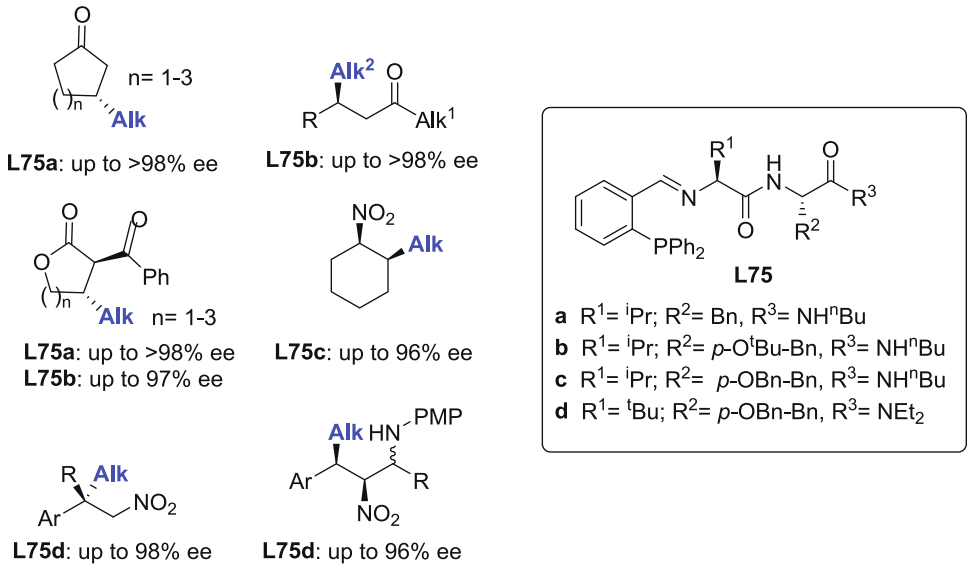
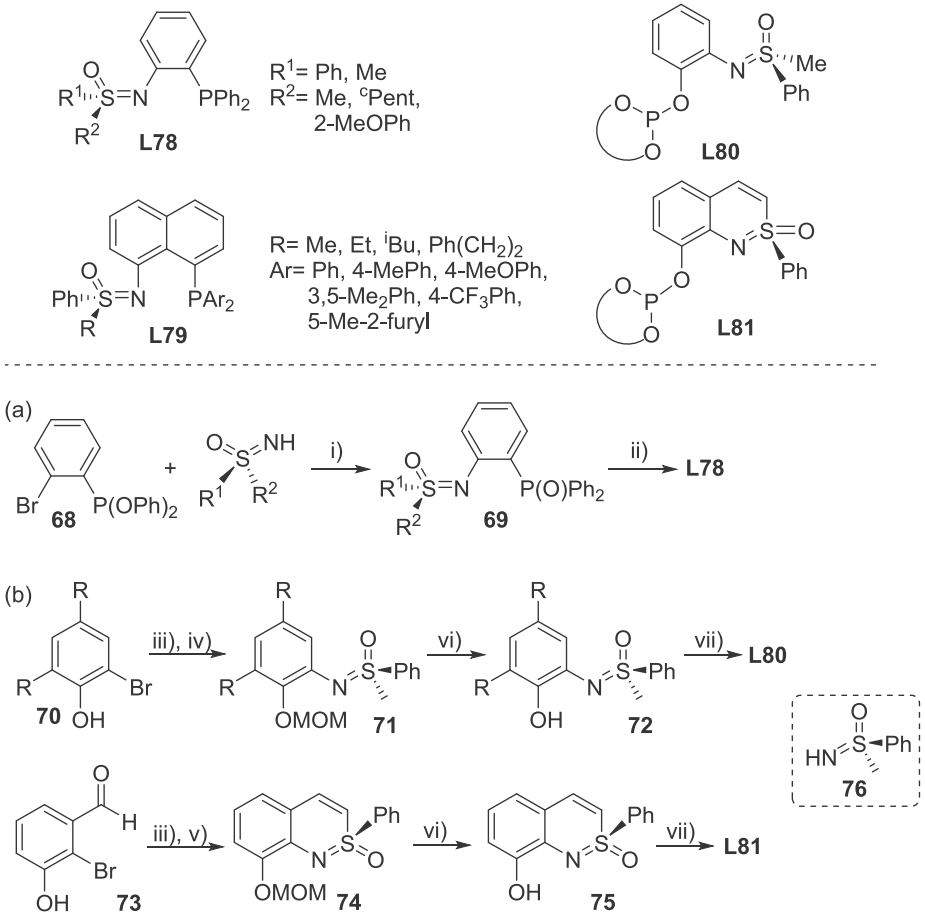
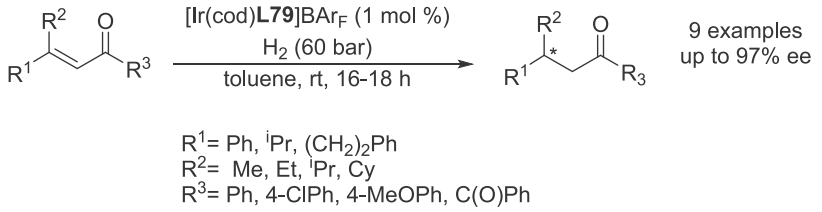


Fig. 22. Scope of the ligand family **L75** in Cu-catalyzed conjugate additions.



Scheme 52. P-sulfoximine ligands **L78**–**L81.** a) Synthesis of **L78:** i) CuI, CsOAc, DMSO, 90 °C; ii) Cl_3SiH, NEt_3, toluene, 90 °C. b) Synthesis of **L80** and **L81**: iii) MOMCl, NEt_3, THF, rt; iv) **76**, CuI, DMEDA, NaI, Cs_2CO_3, toluene, 110 °C; v) **76**, $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, toluene, reflux; vi) ^iPrOH/HCl/THF (2:1:1), rt; vii) $ClP(OR)_2$, Py, toluene, rt.

ligand containing an isobutyl and a phenyl *N*-substituent provided the best catalytic performance. With the optimal ligand it was possible to reduce a range of imines with ee's over 90% ee for most of the substrates [193]. Later, analogous bicyclic ligands **L79** were prepared following a similar synthetic strategy starting from 1,8-diiodonaphthalene. These ligands showed 92% ee in the hydrogenation of 2-methylquinoline, albeit moderate enantioselectivities were obtained for other quinolone derivatives (55–87% ee) [194]. More important are the results attained in the olefin hydrogenation of β,β'-disubstituted enones [195]. Prior to this,



Scheme 53. Ir-catalyzed hydrogenation of α,β-unsaturated enones with ligands **L79**.

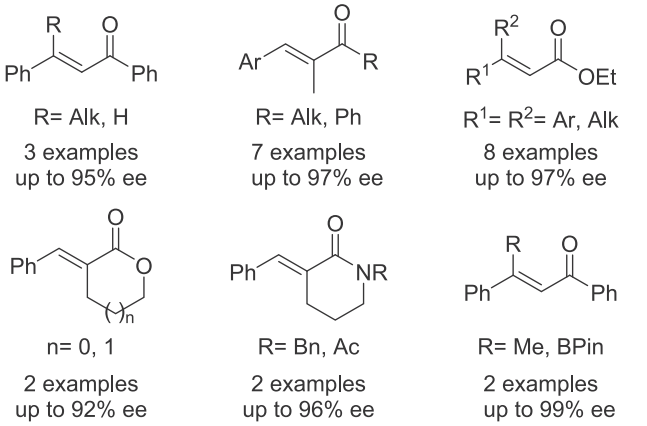


Fig. 23. Scope of **L80**–**L81** in the Ir-catalyzed hydrogenation of olefins with poorly coordinating groups.

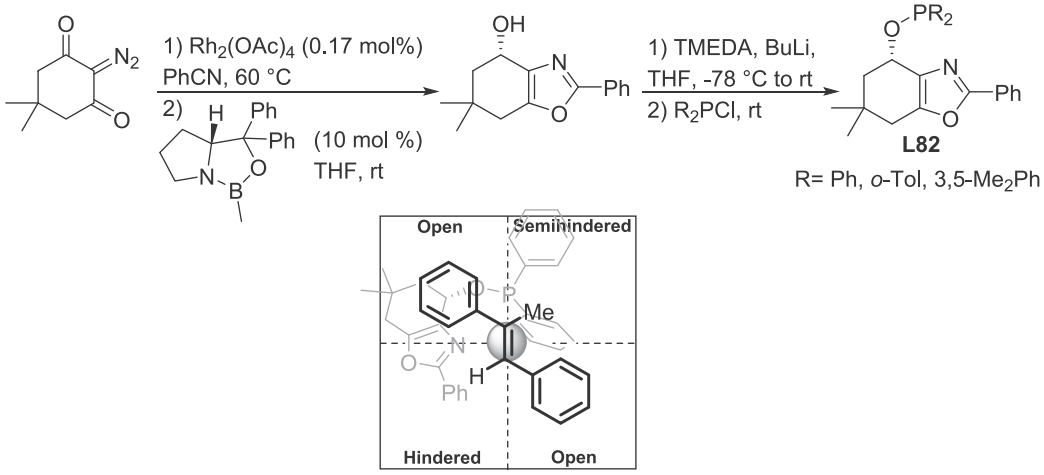
the existing methods for preparing valuable optically pure ketones were mainly non-catalytic and with a limited substrate scope [196]. A range of enones could be reduced with enantioselectivities up to 97% ee (Scheme 53). However, the effectiveness of the catalyst is affected by the substitution pattern of the enone and the steric constraints of the olefin substituents. For instance, a low enantioselectivity was observed for α,β-disubstituted enones (55% ee for (*E*)-3-methyl-4-phenyl-3-buten-2-one) [197].

To increase the scope of P-sulfoximine ligands in Ir-hydrogenation reactions, the phosphine group on **L78** has been recently substituted by biaryl phosphite moieties, leading to ligands **L80**. The more rigid benzothiazine derivative **L81** was also synthesized [198]. In contrast to **L78**–**L79**, the sulfoximine group was inserted prior to the P-group. The synthesis of **L80**–**L81** starts with alcohol protection of the corresponding 1-Br-phenols **70** and **73** with methoxymethyl chloride. Then, MOM-protected intermediates were coupled with (*S*)-S-methyl-S-phenylsulfoximine (**76**), which upon deprotection of the MOM group in acid media, reacted with the desired phosphorochloridite. Finally, Ir-complexes [Ir(cod)(**L80**-**L81**)]BAr_F were prepared using the same methodology than for [Ir(cod)(**L8**)]BAr_F [198]. The authors found that Ir-complexes containing ligands **L80** were obtained as a mixture of isomers. In contrast, complexes containing ligands **L81** with a more rigid backbone were present as a single isomer, suggesting that in the case of ligands **L80** two different stable conformations for the six-membered chelate ring are possible. One more time, having a biaryl phosphite moiety on the ligand scaffold improved the substrate versatility of the hydrogenation reaction. Thus, [Ir(cod)(**L80**–**L81**)]BAr_F complexes increased the scope attained in the reduction of α,β-unsaturated enones (95–97% ee), including α,β-disubstituted enones and with an exocyclic double bond. Furthermore, other olefins bearing poorly coordinative groups, such as lactones, diphenyl alkenylboronic esters among others, were also hydrogenated with ee's up to 99% (Fig. 23).

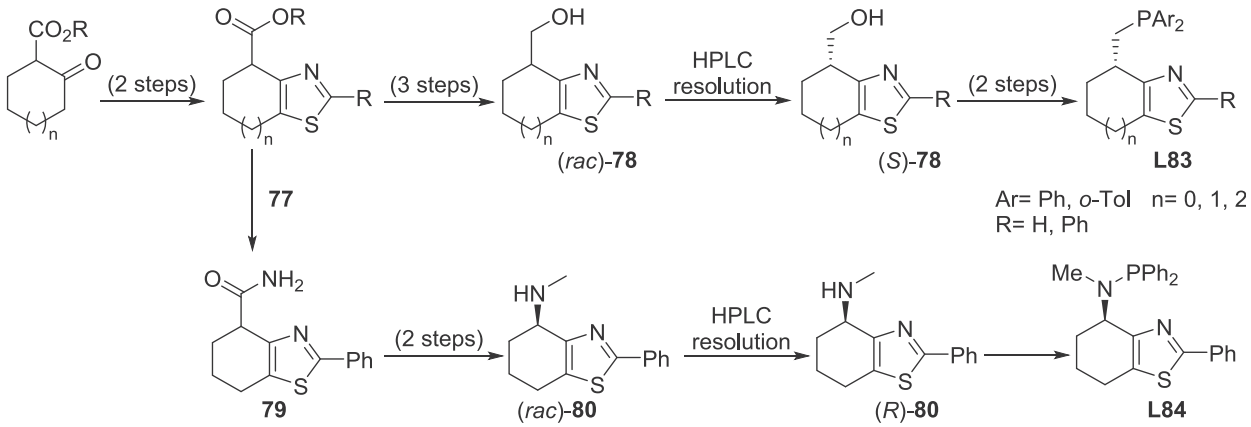
3.4.3. P-cyclic imino ligands

As mentioned previously (see Section 2) the phosphino-oxazoline ligands (PHOX) made a breakthrough in asymmetric catalysis due to their synthetic versatility and broad catalytic applicability [85c,199]. With the aim of exploring other five-membered nitrogen heterocycles, P,N-ligands bearing aromatic heterocycles such as oxazoles, thiazoles and imidazoles, as well as other non-aromatic rings (e.g. thiazolines and imidazolines) have been developed. The resulting P,N ligands have shown excellent results in asymmetric catalysis, especially in Ir-catalyzed hydrogenations and in Pd-catalyzed reactions.

This field has been pioneered by Andersson's group with the aim to enlarge the substrate versatility in the challenging hydrogenation of unfunctionalized olefins. They started by rational design of the bicyclic oxazole-based *P,N*-ligands **L82** (Scheme 54)



Scheme 54. Synthesis of phosphinite-ozaxole ligands **L82** and enantioselectivity quadrant model.



Scheme 55. Synthesis of P-thiazole ligands **L83** and **L84.**

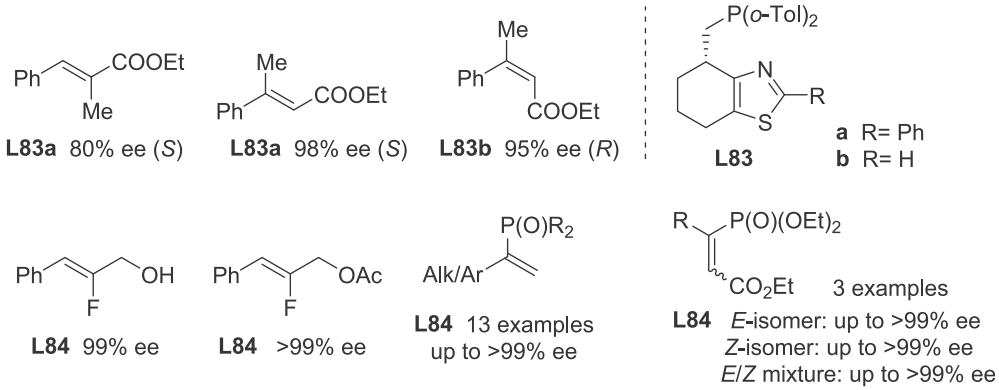


Fig. 24. Selected results for the asymmetric hydrogenation with [Ir(cod)(**L83-L84**)]BAr_F catalysts.

[200]. Their synthesis starts with the transformation of diazodimedone in presence of a catalyst and benzonitrile. Catalytic enantioselective reduction of the obtained keto oxazole with (*R*)-Me-CBS-borane provided (*S*)-alcohol derivative, in which the desired phosphinite group was installed through conventional chemistry. These ligands met the criteria established from a computational study made by the same authors about the hydrogenation of (*E*)-1,2-diphenyl-1-propene with the Pfaltz Ir/PHOX-catalyst [201]. Thus, ligands **L82** combines the presence of a P- and a N-donor atom, to achieve a significant *trans* effect, with a rigid bicycle to reduce conformational flexibility, and a six-membered chelate ring is generated upon complexation to Ir. All this resulted in Ir/**L82** complexes that generate an appropriate chiral environment for asymmetric induction to the substrate (Scheme 54). The outstanding enantioselectivities (93–99% ee) achieved by the Ir/**L82** complexes in the hydrogenation of 1,2-disubstituted styrenes corroborated the computationally derived selectivity model.

Then, by systematic modification of **L82** by replacing either the oxazole by a thiazole group or the phosphinite group by a *N*-phosphine moiety, phosphine-thiazole **L83** [202] and *N*-phosphine-thiazole ligands **L84** [64e] were obtained (Scheme 55). In the case of **L83**, 5- and 6- and 7- fused-rings were studied. Both ligand families are derived from ketoesters¸ which were transformed into thiazole esters **77** through condensation with benzothioamide. Next, for the preparation of phosphine ligands **L83**, the corresponding thiazole ester **77** was converted to alcohol (*rac*)-**78**. In contrast, when the target was the aminophosphine ligand **L84**, ester **77** was first converted to the amide **79** and then it was reduced to amine (*rac*)-**80**. Both, alcohol and amine derivatives were obtained as racemates and resolved by preparative chiral HPLC. Finally, they were converted to the corresponding phosphine or aminophosphine ligands through already reported chemistry.

The catalyst precursors [Ir(cod)(**L83-L84**)]BAr_F were prepared using the same methodology than for [Ir(cod)(**L8**)]BAr_F, and were tested in asymmetric hydrogenation reactions. By selecting the appropriate ligand **L82**–**L84** it was possible to increase the substrate scope considerable. For instance, phosphine-thiazole ligands **L83** showed to be more suitable than the oxazole counterpart **L82** in the Ir-hydrogenation of α,β-unsaturated esters. To note that the six-membered ring backbone showed the best catalytic performance. With a di-*o*-tolyl phosphine moiety and the appropriated substituent on the thiazole ring, derivatives of α- and β-methyl cinnamic acid ethyl esters were reduced with high enantioselectivities (80–98% ee for (*E*)-olefins and 95% ee for a (*Z*)-olefin) (Fig. 24) [202].

Instead, for the reduction of vinyl fluorides the best enantioselectivities was achieved with [Ir(cod)(**L84**)]BAr_F [64e]. At this time, the hydrogenation of fluorine-containing olefins was little explored, probably, due to the ability of vinylic fluorine to be cleaved off [203]. In contrast, the Ir/**L84** catalyst showed little defluorination. Although the substrate scope was limited, it was possible to hydrogenate a trisubstituted fluoroolefin bearing a hydroxy and an acetate group in 99% and >99% ee, respectively (Fig. 24). Ir-catalyst bearing ligand **L84** was also very useful in the hydrogenation of 1,1′-disubstituted vinylphosphonates and carboxyethylvinylphosphonates (Fig. 24) [204]. It should be noted that for this last type of substrates, *E*- and *Z*-isomers as well as their mixtures could be hydrogenated in excellent enantioselectivities (up to >99% ee). Finally, with the use of both thiazole ligands

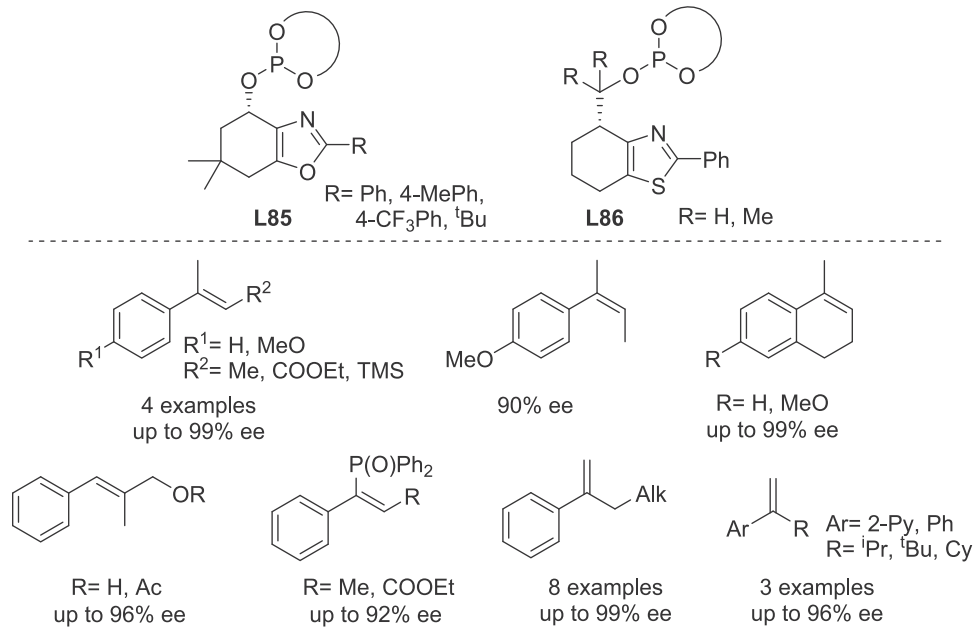


Fig. 25. Phosphite-thiazole ligands igands **L85**–**L86** and the scope of hydrogenated olefins with [Ir(cod)(**L86**)]BAr_F.

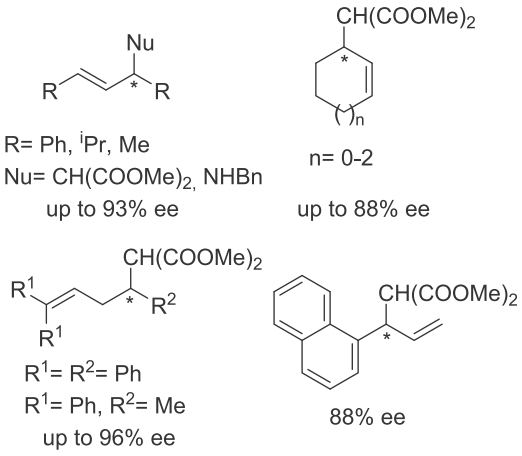


Fig. 26. Products obtained from the Pd-catalyzed allylic substitution reactions with **L85**.

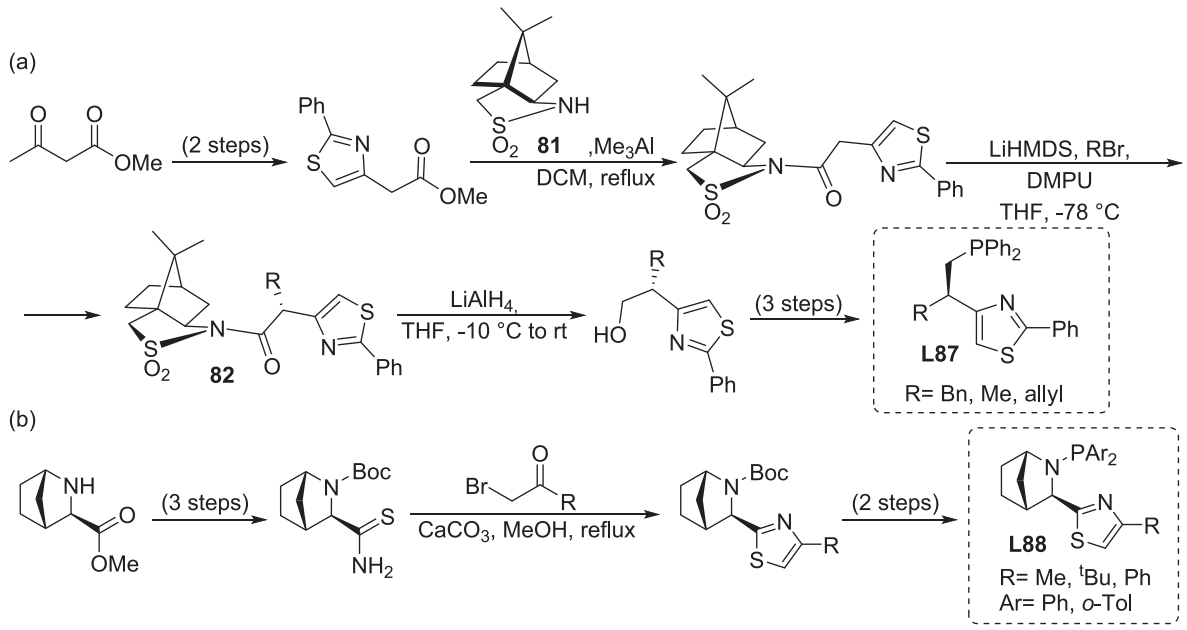
L83 (R = Ar = Ph, n = 1) and **L84**, it was possible to hydrogenate a range of 1,1′-diaryl substituted olefins in excellent enantioselectivities (up to >99% ee) [205].

The corresponding phosphite-oxazole and thiazole-based ligands **L85**–**L86** were also prepared and applied in Ir-catalyzed hydrogenation of unfunctionalized olefins or with poorly coordinative groups (Fig. 25). Thiazole-based ligands **L86** provided the highest enantioselectivities. The introduction of the phosphite moiety allows to extend the substrate scope. Ir/**L86** catalytic system allowed the hydrogenation of both *E*- and *Z*-trisubstituted olefins along with 1,1′-disubstituted terminal alkenes, furnishing excellent enantioselectivities (ee's up to 99%) [206]. The catalytic system also tolerated the presence in the olefin of some neighboring polar groups (e.g. esters, alcohols, phosphinates ...) for which ee values up to 99% has been also attained.

Useful, ligands **L85** and **L86** were also screened in the Pd-allylic substitution reaction [207]. After ligand screening and in contrast to the hydrogenation, it was found that oxazole ligands (**L85**) exhibited in general higher enantioselectivities than **L86**. With the proper selection of each ligand parameter it was possible to achieve high enantio- and regioselectivities (ee up to 96%) for a variety of cyclic and tri-, di- and monosubstituted linear substrates (Fig. 26). The study of Pd-allyl intermediates by NMR and DFT aided to understand the influence of the ligands parameters on the ratio of the Pd-allyl species and the electrophilicity of the allylic terminal carbon atoms. Ligands **L85** provided also high enantio- and regioselectivities in Pd-catalyzed intermolecular Heck reactions of 2,3-dihydrofuran with several aryl triflates [208].

To study the effect of the backbone in the catalytic activity, Andersson's group developed the other two ligand families **L87** [209] and **L88** [210] (Scheme 56), in which the backbone was modified while keeping the thiazole unit. Ligands **L87**, which feature an open-chain-backbone, were synthesized from inexpensive methyl 3-oxobutanoate (Scheme 56a). The synthesis starts with the introduction of the thiazole ring. Next, Oppolzer sultam (**81**) was introduced in order to incorporate a chiral alkyl chain by using diverse alkyl halides in the presence of lithium hexamethyldisilazide (LHMDS). Each chiral ligand precursor **82** was obtained with high diastereomeric purities. After reduction with $LiAlH_4$, the corresponding alcohols were transformed to the final phosphinothiazole ligands **L87**. Unfortunately, the new ligands **L87** were slightly less successful than the their more rigid counterparts **L83** in the Ir-catalyzed hydrogenation of unfunctionalized trisubstituted olefins, allylic alcohols and imines [209].

In contrast, the introduction of a bicyclic amine into the ligand resulted beneficial in terms of scope for the Ir-hydrogenation of poorly coordinative olefins [64f,h,210,211]. In addition, their synthesis was achieved in fewer steps than **L87** (Scheme 56b). Ligands **L88** were synthesized from (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-car-boxylic acid [212]. This intermediate was transformed to *N*-Boc-protected thioamide in 3 steps, which was then cyclized with an α-bromoketone to provide the N-protected thiazole. After removal of the protecting group, the phosphorus fragment was incorporated to ligands **L88**. The resulting Ir-complexes [Ir(cod)(**L88**)]BAr_F were efficiently used in the hydrogenation of olefins bearing a variety of poorly coordinating groups, showing comparable results to those obtained with phosphine-thiazole **L84** [210]. Moreover, the use of Ir/**L88** was beneficial, widening the scope of the hydrogenated olefins (Fig. 27a). Excellent enantioselectivities were obtained for vinyl boronates (up to 98% ee) [64f], vinylic,



Scheme 56. Synthesis of: a) phosphine-thiazole ligands **L87** and b) *N*-phosphine-thiazole ligands **L88**.

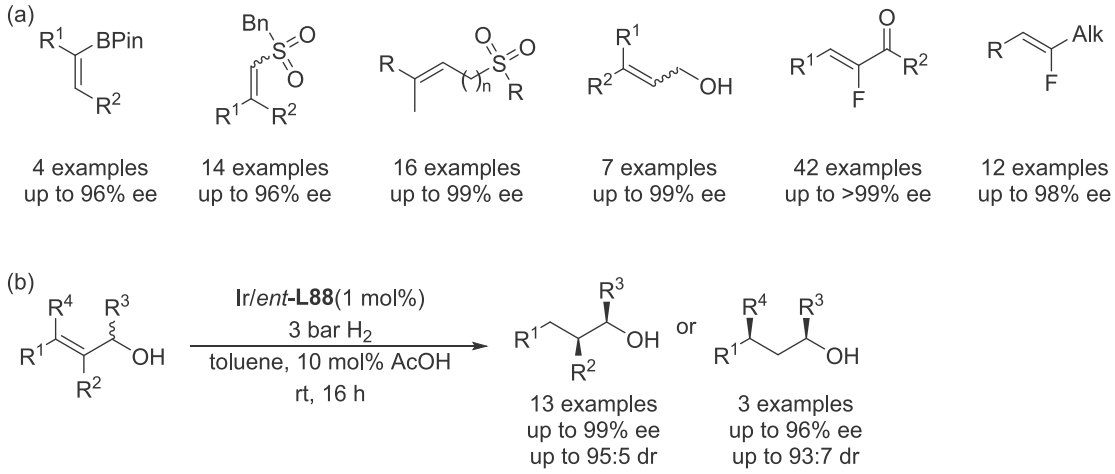


Fig. 27. Relevant results for the Ir-catalyzed hydrogenation a) of olefins with **L88** (R = Ph, Ar = *o*-Tol) and b) of allylic alcohol via dynamic kinetic resolution with *ent*-**L88** (R = Ph, Ar = *o*-Tol).

allylic and homoallylic sulfones (up to 99% ee) [211a], γ-substituted cinnamyl alcohols (up to 99% ee) [64h] and very recently to α,β-unsaturated α-fluoro aryl and alkyl ketones (up to >99% ee) [211c]. Importantly, the use of an Ir-complex containing the enantiomer of **L88** (R = Ph, Ar = *o*-Tol) allowed the cooperative dynamic kinetic asymmetric hydrogenation of allylic alcohols (Fig. 27b), to produce a broad range of chiral alcohols containing two stereogenic centres with excellent diastereoselectivities (up to 95:5) and enantioselectivities (up to 99%) [211b]. Mechanistic studies supported that racemization of the substrate is achieved by cleavage and reforming of the oxygen–carbon bond.

The combination of a biaryl phosphite and the nitrogenated bicyclic backbone of **L88**, lead to the family of ligands **L89** (Fig. 28) [66]. [Ir(cod)(**L89**)]BAr_F were synthesized following the same methodology than for [Ir(cod)(**L8**)]BAr_F. Ir-complexes with a ligand bearing an $(S)^{ax}$-binaphthol moiety helped to expand the substrate scope of the previous successful *N*-phosphane ligands **L88** on the Ir-hydrogenation of unfunctionalized olefins. For example, *E*- and *Z*-tri- and 1,1′-disubstituted substrates, α,β-unsaturated enones, alkenylboronic esters and disubstituted olefins were reduced with excellent enantioselectivities (up to 99% ee) [66]

From the results obtained with the oxazole- and thiazole-based ligands developed by Andersson's group it can been concluded that they showed a different substrate scope in the hydrogenation of olefins. Having this in mind, the group developed a new set of ligands with an imidazole ring (**L90**; Scheme 57), to investigate even further the substrate scope [213]. The imidazole moiety was formed through condensation of ester **83** (obtained from esterification of 2-aminonicotinic acid) with the corresponding α-bromoacetophenone. Regioselective hydrogenation of **84** with Pd/C in TFA and subsequent reduction of the ester moiety yielded the corresponding alcohol. After HPLC resolution, chiral alcohol was transformed to the phosphine-imidazole ligands **L90**.

Following the same methodology than for [Ir(cod)(**L8**)]BAr_F, ligands **L90** were complexed to $[IrCl(cod)]_2$ and mixed with $NaBAr_F$ to give the corresponding iridium/BAr_F complexes. Ir-complexes of

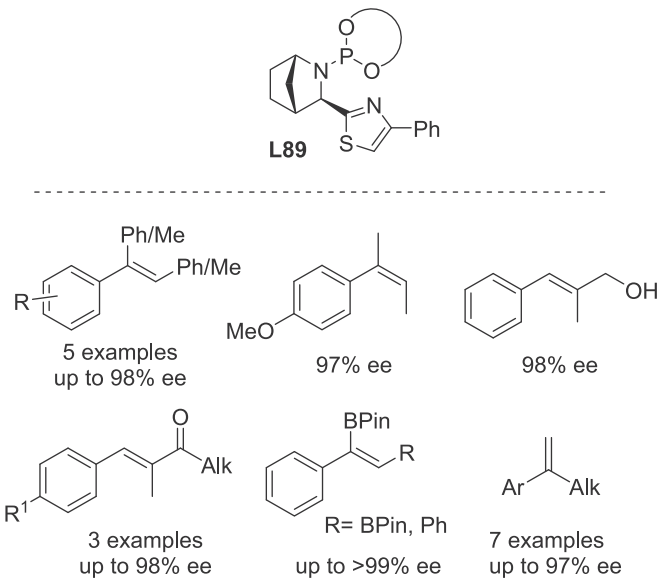


Fig. 28. Ligands **L89** and the scope of [Ir(cod)(**L89**)]BAr_F in the hydrogenation of olefins.

imidazole ligands **L90** showed a similar catalytic performance to its oxazole and thiazole analogues in the asymmetric hydrogenation of olefins with poorly-coordinative groups (up to 98% ee). In addition, imidazole ligands **L90** showed good results in the Ir-catalyzed hydrogenation of the demanding vinyl fluorides. It was proposed that the reason was the decreased basicity of the imidazole ring, resulting in less defluorination. The Ir/**L90** catalyst (R = Ph, Ar = Ph or 3,5-Me_2-C_6H_3) were able to reduce various vinyl fluorides with up to 86% ee, including unsaturated esters that the previously commented ligands **84** could not hydrogenate (Fig. 29) [213].

Interestingly, the tuning of the substituent on the imidazole ring of ligand **L90** led to excellent ligands for the highly regio- and enantioselective reduction of 1,4-cyclohexadienes (Scheme 58-a-d) [214]. They showed an impressive substrate scope, providing excellent results for substrates having little functionality, but also for others bearing strongly coordinating substituents and heterocycles fused rings (up to 99% ee). Finally, ligand **L90d** has been recently used in the asymmetric hydrogenation of allylsilanes (ee's up to 99%; Scheme 58e) [215]. The compounds were further subjected to the Hosomi-Sakurai allylation yielding the corresponding homoallylic alcohols with three stereogenic centers in excellent diastereoselectivities.

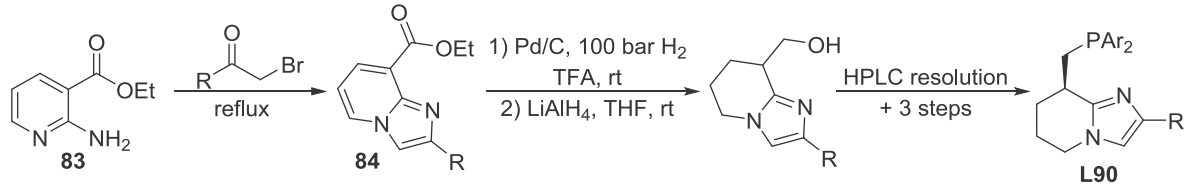
Recently, Riera, Verdaguer and co-workers presented the synthesis of a novel class of P-chirogenic aminophosphine-imidazole ligands **L91**–**L92** [216], (Scheme 59) which are analogues the MaxPHOX family of ligands [43]. The new ligands were prepared from *N*-Boc valine, as MaxPHOX ligands, but the imidazole moiety was introduced through condensation with *ortho*-phenylenediamine (ligand **L91**) or with phenacylbromide, followed by cyclization with ammonium acetate (ligands **L92**). Removal of the borane protecting group with neat pyrrolidine, followed by treatment with $[IrCl(cod)]_2$ and counterion exchange with $NaBAr_F$ yielded the corresponding MaxPHOX/Ir-complexes. A catalyst precursor based on benzoimidazole ligand (**L91**) was found to be superior than its imidazole counterpart in the hydrogenation of the model cyclic β-enamide (89% *vs* 72% ee). However, it showed a lower catalytic activity and enantioselectivity than its oxazoline analogue.

Phosphite-thiazoline ligands **L93** [18c] (Scheme 60) were designed to expand the substrate scope of successful phosphite-oxazoline ligand family **L23**, which despite their versatility there was still room for improvement in the Pd-catalyzed allylic substitution of cyclic substrates [48b]. To this aim, the oxazoline was replaced with a thiazoline (ligands **L93**), in order to reduce the chiral pocket created by the ligands and make it more appropriate for cyclic substrates. Ligands **L93** were synthesized from (*R*)-cysteine methyl ester hydrochloride in only 3 steps (Scheme 60) [18c]. Then, the thiazoline group was formed by coupling with ethyl benzimidate hydrochloride. Next, the formed thiazoline ester was reduced with MeMgBr to afford hydroxyl thiazoline in 40% ee. Semipreparative chiral HPLC was used to give access to both enantiomers of **86**. Finally, the phosphite group was introduced to provide ligands **L93**.

As predicted, phosphite–thiazoline ligands **L93** improved considerably the enantioselectivities of unhindered cyclic substrates (up to 94% ee; Fig. 30a), while oxazoline analogues **L23** worked better for the rest of substrates. The introduction of a thiazoline ring was also advantageous for the Ir-catalyzed hydrogenation of olefins [217]. Ir/BAr_F complexes bearing thiazoline ligands **L93** allowed to increase the number of substrates efficiently reduced, including *Z*-trisubstituted olefins, trifluoromethylated olefins and enones (Fig. 30b).

Busacca and co-workers patented the phosphine-imidazolines analogues of PHOX ligands, the so called BIPI (**L94**) (Boehringer-Ingelheim phosphinoimidazolines) [218]. The additional nitrogen atom provides an extra tuning site in the ligand scaffold by modifying the *N*-substituent group. Ligands **L94** were synthesized in a modular way as shown in Scheme 61 [219]. The imidazoline ring was built by condensation of *o*-haloimidates with the desired chiral diamine, furnishing the haloimidazolines. Then, the phosphine group was installed *via* the aromatic S_NAr reaction with phosphide nucleophiles. Finally, reaction of the resulting phosphine-imidazolines with the corresponding alkyl halides furnished BIPI ligands **L94** (Scheme 61). In the cases where R^2 was an electron-rich aryl group (e.g., R^2 = *p*-OMe-C_6H_4) or with electron-deficient aryl groups on the phosphine (e.g. Ar = 3,5-F_2-C_6H_3), the N-alkyl substituent was incorporated previous to the phosphine moiety.

BIPI ligands (**L94**) were screened in Pd-catalyzed intramolecular Heck reactions that involve the formation of a chiral quaternary centre [219,220]. It was shown that the enantioselectivity increased with the use of more electron deficient phosphines (e.g. Ar = 3,5-F_2-C_6H_3), which allowed to achieve the highest enantioselectivities reported at that time with BINAP and PHOX for challenging substrates (ee's up to 87%; Scheme 62). Over the years, BIPI ligands have also been used in the Rh- and Ir-catalyzed hydrogenation of imines [221], unsaturated ureas [222], urea esters, Boc-, Cbz-enecarbamates and enamides [223], and



Scheme 57. Synthesis of phosphine-imidazole ligands **L90**.

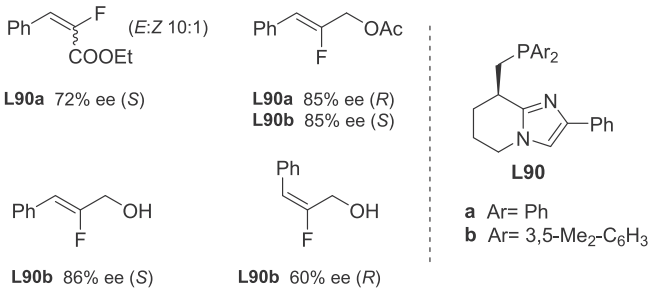


Fig. 29. Relevant results for the Ir-hydrogenation of vinyl fluorides with [Ir(cod)(**L90**)]BAr_F.

unfunctionalized olefins [56b]. The BIPI ligand was also used in the synthesis of a cathepsin S inhibitor (see Section 6) [224].

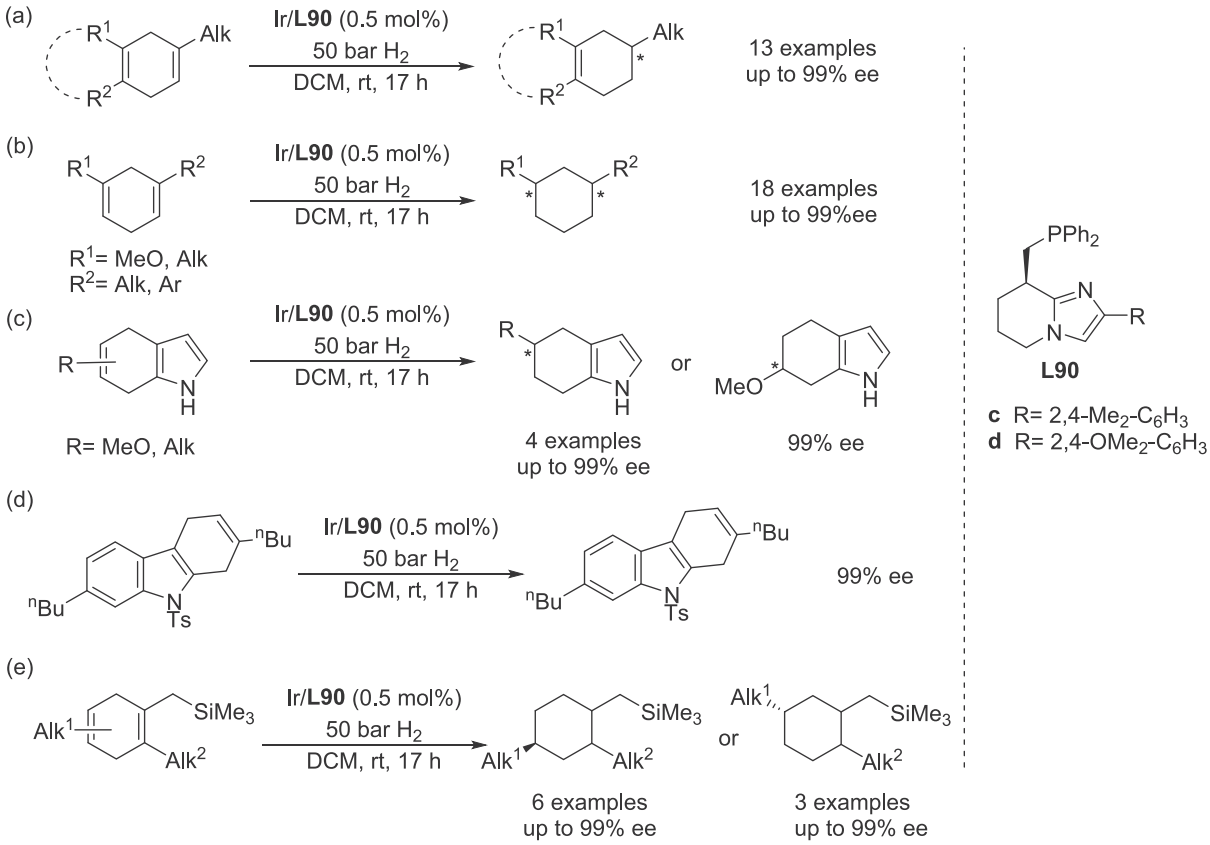
A year later of the development of BIPI ligands, Pfaltz and co-workers reported a similar ligand family called PHIM ligands (**L95**, Fig. 31). In this case, easily accessible α-hydroxyamides were used instead of diamines, so one of the alkyl substituents on the resulting imidazoline ring was exchanged by a hydrogen atom. The correpsonding Ir-complexes were prepared by using the same protocol used for [Ir(cod)(**L8**)]BAr_F complexes and tested in the hydrogenation of various unfunctionalized olefins, exhibiting in some cases higher enantioselectivities than its PHOX analogues [225]. Later, Ir-complexes containing PHIM ligands were efficiently applied in the asymmetric hydrogenation of the poorly studied vinylsilanes [226].

Then, Pfaltz also patented the SimplePHIM ligands (**L96**), which are a simplified version of PHIM ligands (Scheme 63) [227]. These ligands were obtained from oxalyl chloride, which was coupled with the corresponding aminoalcohols to yield intermediate **87**. After formation of the oxazoline ring using standard procedures, the phosphine group was installed to afford ligands **L96**. [Ir(cod)(**L96**)]BAr_F complexes were evaluated in the hydrogenation of acetophenone *N*-phenylimine [228] and vinylsilanes [226]. Although they provided high enantioselectivities (up to 95% and 88% ee, respectively), they didn't showed the best catalytic performance among all ligands tested. In contrast, they turned to be very efficient in the asymmetric hydrogenation of terminal boronic esters (up to 96% ee, Scheme 63) [52b].

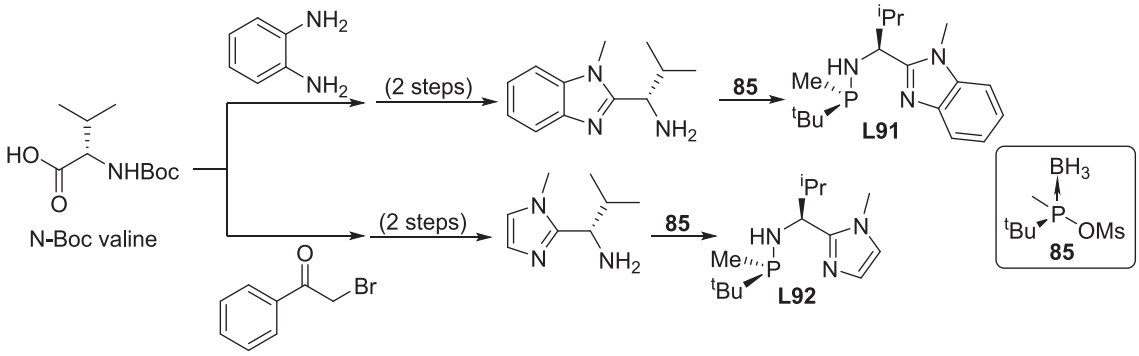
3.4.4. P-pyridino ligands

Heterodonor P,N-ligands containing a pyridine group have turn into popular alternatives to P-oxazoline ligands because of the pyridine robustness and their straightforward synthesis. However, few P-pyridine ligands have provided outstanding results in terms of reaction scope. The success of QUINAP and PHOX ligands pushed Katsuki and co-workers to develop phosphine-pyridine ligands **L97** and apply them in Pd-catalyzed asymmetric allylic substitutions [229,230]. Next, other similar bicyclic P-pyridine ligands have been synthesized and used in many asymmetric transformations (**L98**–**L104**; Scheme 64a). The synthesis of **L97** starts with chloropyrindine or chlorotetrahydroquinoline compounds, which were transformed into the corresponding chiral intermediates **88** in 5 steps, *via* epoxide formation and its subsequent opening [231]. Next, Suzuki cross-coupling of compounds **88** with 2-hydroxyphenylboronic acid gave the corresponding pyridylphenols, which can be then converted into the desired 2-(phosphinoaryl)pyridines in a conventional manner (Scheme 64b) [229].

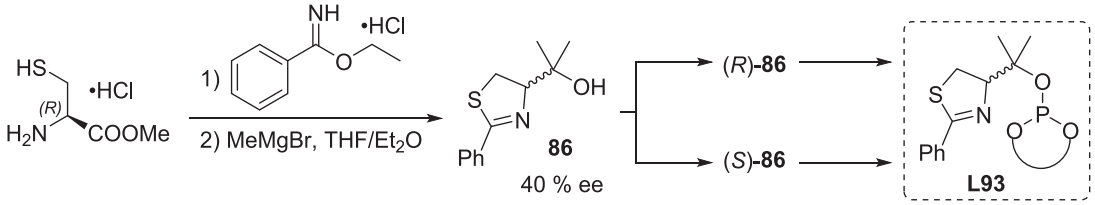
A ligand with a 5-membered fused ring and an isopropyl substituent (**L97**, n = 1, R = ^{i}Pr), provided the best enantioselectivities in the Pd-catalyzed allylic alkylation of linear substrates with



Scheme 58. Scope of ligands **L90c-d** in the asymmetric Ir-hydrogenation of dienes.



Scheme 59. Synthesis of P-chirogenic aminophosphine-imidazole ligands **L91–L92**.



Scheme 60. Synthesis of phosphite-thiazoline ligands **L93**.

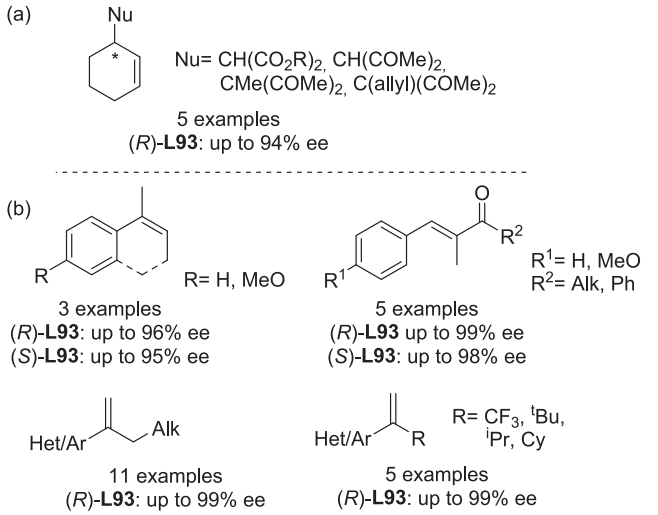
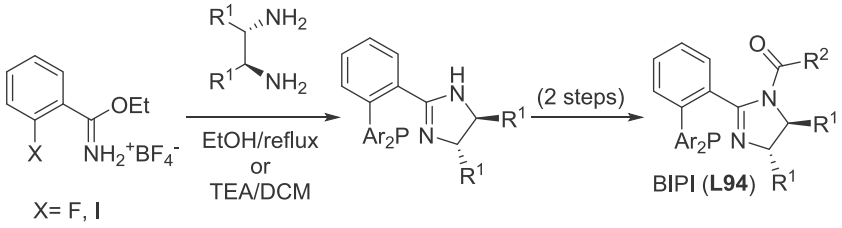


Fig. 30. Relevant results from the application of ligands **L93** in a) Pd-catalyzed allylic substitutions and b) Ir-catalyzed hydrogenation of olefins.

dimethyl malonate (up to 98% ee) [229,230]. This ligand was also used in Pd-catalyzed intramolecular allylic amination [232], Baeyer-Villiger reactions [233] and tandem allylic substitution reactions for the formation of heterocycles [234], providing moderate to good enantioselectivities.

A similar ligand bearing a pinene moiety was developed by Chelucci's and Malkov-Kočovský's groups, simultaneously (**L98**, Scheme 64). This ligand could be synthesized in fewer steps than **L97** since it is derived from chiral and inexpensive (−)-β-pinene [235]. Ligands **L98** were used in the Pd-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate (50% ee) [235a] and in the Pd-catalyzed Heck reaction of dihydrofuran and phenyl triflate (88% ee) [235b]. The use of *ent*-**L98** with an isopropyl substituent on the pinene moiety increased the scope and enantioselectivity provided by **L97** in the Pd-catalyzed Baeyer-Villiger reaction of cyclobutanones [236]

Following the same synthetic methodology, Andersson reported phosphine and phosphinite ligands **L99** and **L100** with the phosphorous donor atom attached to the pinene chiral motif. The *cis* phosphine ligand **L99** gave the highest enantioselectivities (up to 97%; Fig. 32) in the Ir-catalyzed hydrogenation of different trisubstituted olefins (e.g. methylstilbene derivatives, α,β-unsaturated

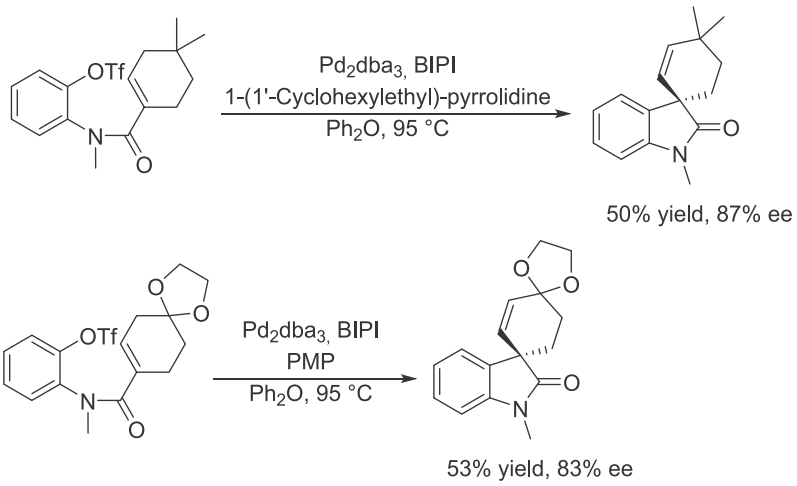


R^1= ^{t}Bu, Ph, 4-MeOPh, 3,5-Me_2Ph, 4-FPh, 4-ClPh, 4-CF_3Ph, 3,5-F_2Ph, 4-OMsPh, 4-CO_2MePh

Ar= Ph, 3,5-F_2Ph

R^2= 2-Naph, 1-Naph, 4-MeOBz, Bz, 4-CNBz, Me, Bn

Scheme 61. Synthesis of phosphine-imidazoline BIPI ligands (**L94**).



Scheme 62. Pd-catalyzed intramolecular asymmetric Heck reaction with BIPI ligand **L94** (Ar = R^1 = 3,5-F_2-C_6H_3, R^3 = 2-Naph).

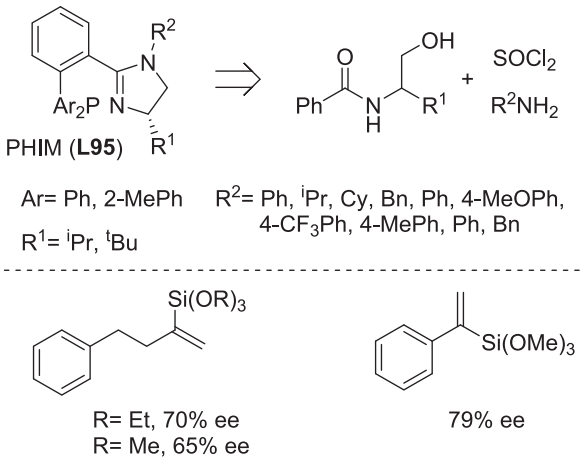
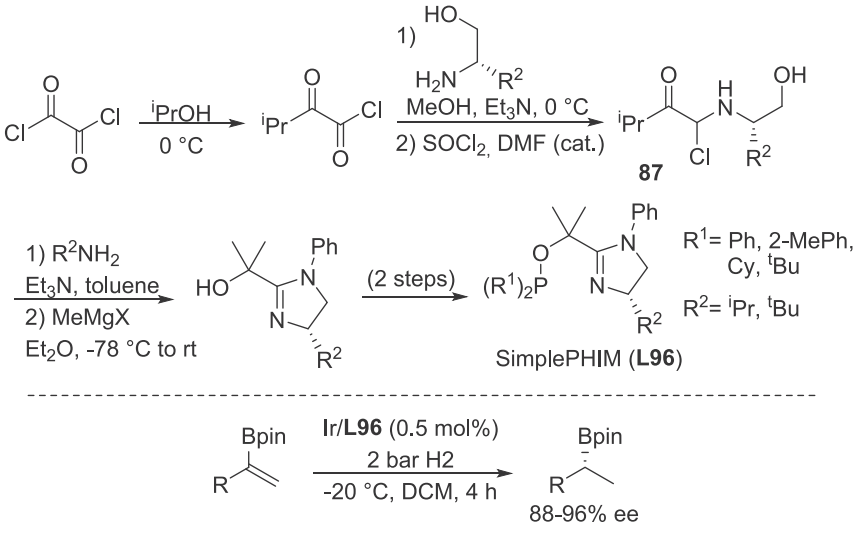


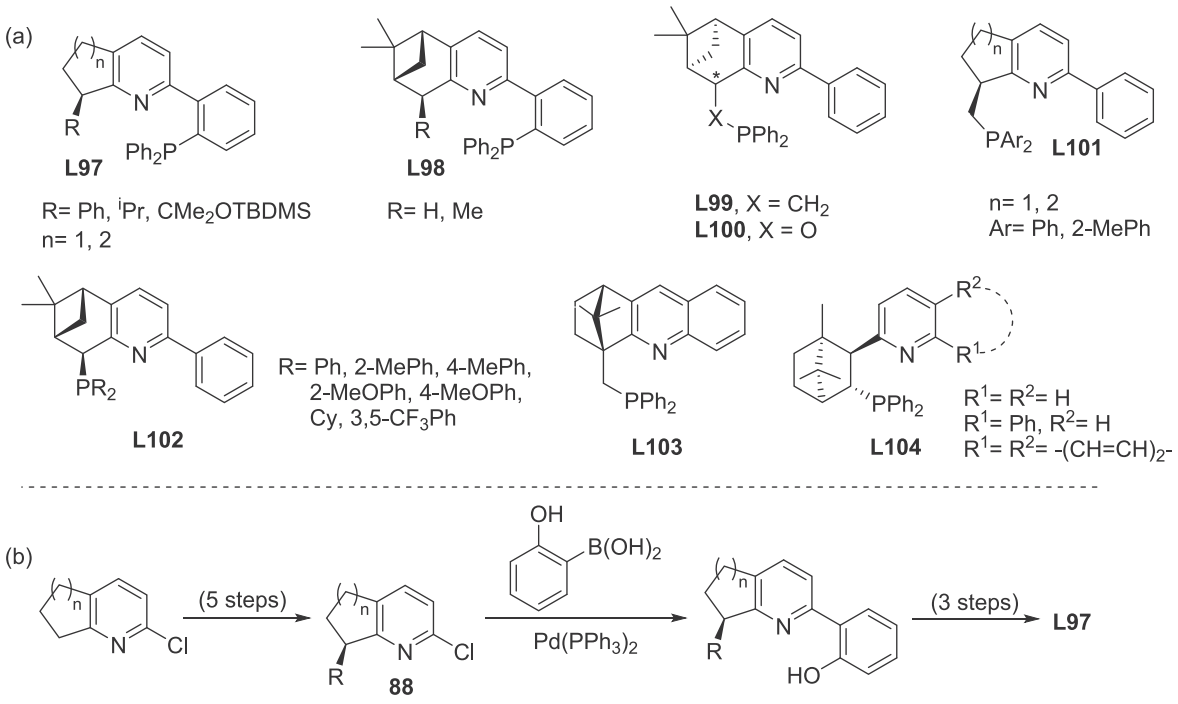
Fig. 31. Phosphine-imidazoline PHIM ligands (**L95**) and their use in the Ir-hydrogenation of poorly studied vinylsilanes.

esters ...) [237]. However, activities were poor even at 100 bar of hydrogen pressure. Later, the same group developed ligands **L101**, in which the pinene element has been removed. The resulting ligands have indeed the same backbone than oxazole, thiazole and imidazole ligands **L83**, **L84** and **L90**, but with a pyridine *N*-donor group. The correpsonding Ir-complexes were obtained using the same protocol described for [Ir(cod)(**L8**)]BAr_F. The new Ir-catalysts showed better activities and enantioselectivities than the ones with pinene-containing ligands **L99** in the hydrogenation of several trisubstituted olefins (up to 99% ee; Fig. 32) [238]. In most of the cases, complexes bearing five-membered-ring ligands (n = 1) were better catalysts than six membered-ring, which is the opposite trend observed in the case of their oxazole, thiazole and imidazole counterparts.

Ligands **L102** are also analogues of **L98** but with the phosphine group directly attached to the pinene ring instead of being at the phenyl scaffold. [Ir(cod)(**L102**)]BAr_F were applied to the reduction of different olefins although they only proved to be successful for some 1,1′-disubstituted enol phosphonates, providing 70–90% ee (**L102**, R = *p*-MeO-C_6H_4; Fig. 32) [239].



Scheme 63. Synthesis of SimplePHIM ligands **L96** and the hydrogenation of terminal boronic esters with [Ir(cod)(**L96**)]BAr_F (R^1 = Cy, R^2 = ^{t}Bu).



Scheme 64. (a) Bicyclic P-pyridine ligands **L97–L104**. (b) Synthesis of **L97**.

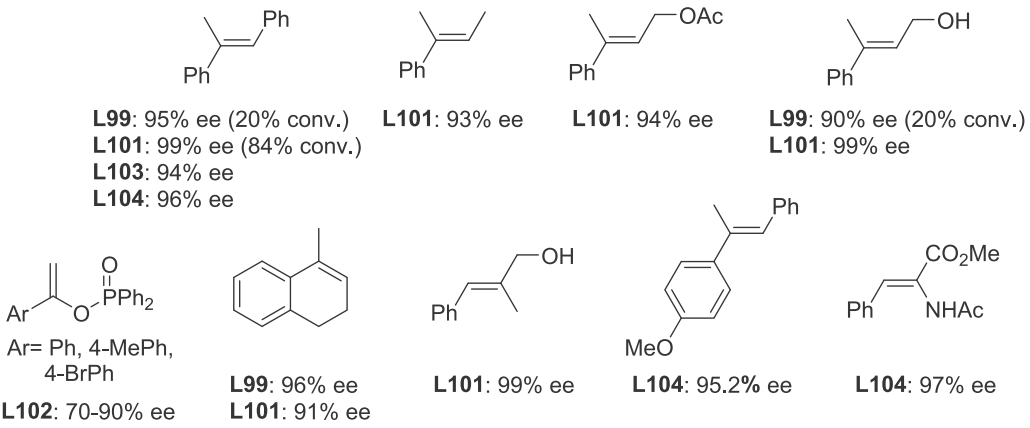
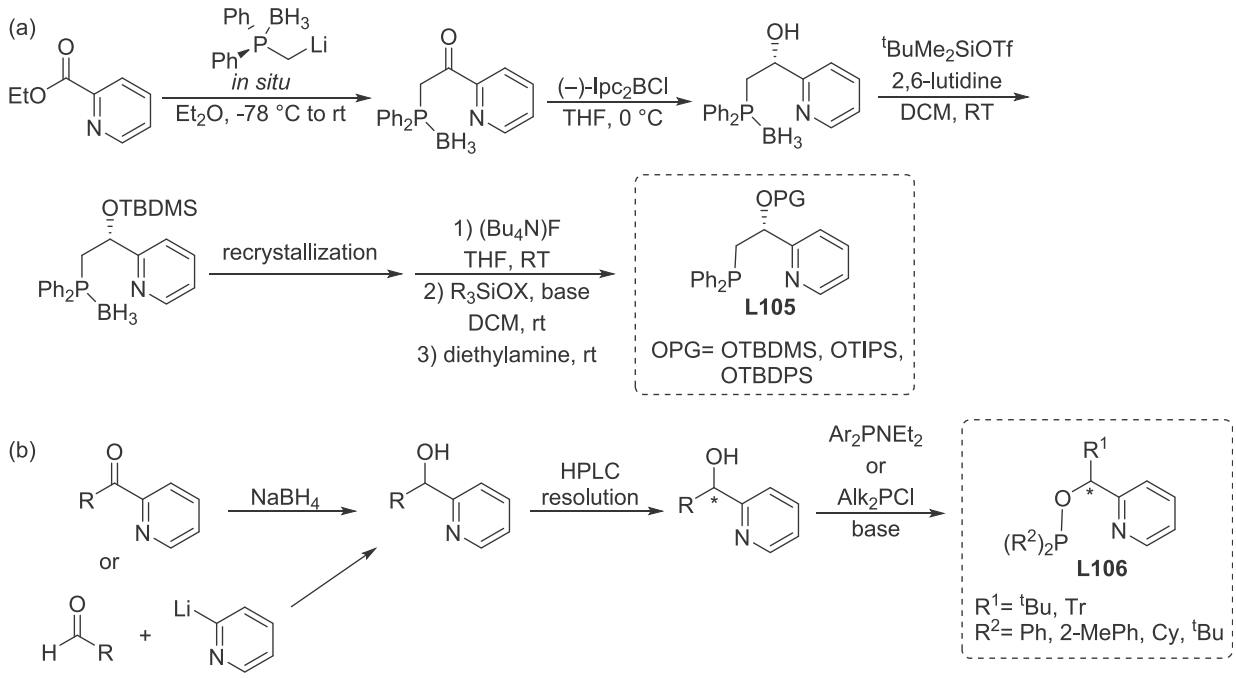


Fig. 32. Representative results for the Ir-catalyzed hydrogenation of olefins with ligands **L99–L104.** Unless otherwise specified, conversion was higher than 90%.

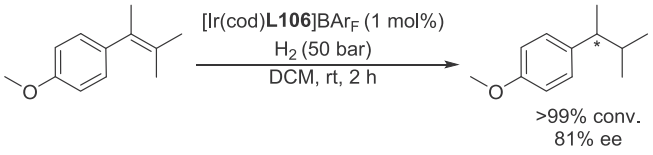
Later, the pinene moiety was replaced by a (+)-camphor moiety to give ligands **L103** and **L104**. [Ir(cod)(**L103**)]BAr_F was screened in the asymmetric hydrogenation of various substrates, although it only gave a high enantioselectivity in the reduction of *trans*-α-methylstilbene (94% ee, Fig. 32) [240]. [Ir(cod)(**L104**)]BAr_F were also applied in the Ir-catalyzed hydrogenation of *trans*-α-methylstilbenes. A complex containing a ligand without any substituent on the pyridyl moiety (**L104**, $R^1 = R^2 = H$) provided the best enantioselectivities (up to 96% ee, Fig. 32) [241]. However, the hydrogenation of trisubstituted alkenes functionalized with alcohol, acetate and ester groups only attained moderate to good enantioselectivities (58–80% ee). Notably, the same ligand allowed the hydrogenation of methyl (*Z*)-2-acetamido-3-phenylacrylate in 97% ee (Fig. 32), which made it the first ligand that showed a good performance in the Ir-hydrogenation of dehydroamino acids that have been traditionally studied using Rh and Ru catalysts [242].

The Pfaltz's group has prepared several phosphine- and phosphinite-pyridine ligands (**L105–L108**) specially designed for the Ir-catalyzed hydrogenation of olefins. Phosphine- and phosphinite-pyridine ligands **L105–L106** (Scheme 65) were designed to be sterically similar to PHOX [243]. Phosphine ligands **L105** were prepared from cheap ethyl picolinate, which was readily alkylated by lithiated BH_3-protected methyldiphenylphosphane to yield ketone (Scheme 65). This intermediate was reduced enantioselectively by (−)-chlorodiisopinocampheyl borane [(−)-Ipc_2BCl]. As the resulting pyridyl-alcohol was an oil, it couldn't be recrystallized so the hydroxyl group was protected with $^tBuMe_2SiOTf$. After recrystallization, the hydroxyl group was deprotected and protected again with the desired silyl group. Finally, the phosphine was deprotected to give ligands **L105**. In the case of phosphinite ligands, the synthesis was even more straightforward (Scheme 65). Pyridyl-alcohols were synthesized by ketone reduction or by alkylation of aldehydes with 2-lithiopyridine. After HPLC resolution, the introduction of the phosphinite group lead to ligands **L106**.

An extensive ligand screening of [Ir(cod)(**L105-L106**)]BAr_F catalyst-precursors in the hydrogenation of *trans*-α-methylstilbene, indicated that complexes bearing phosphinites



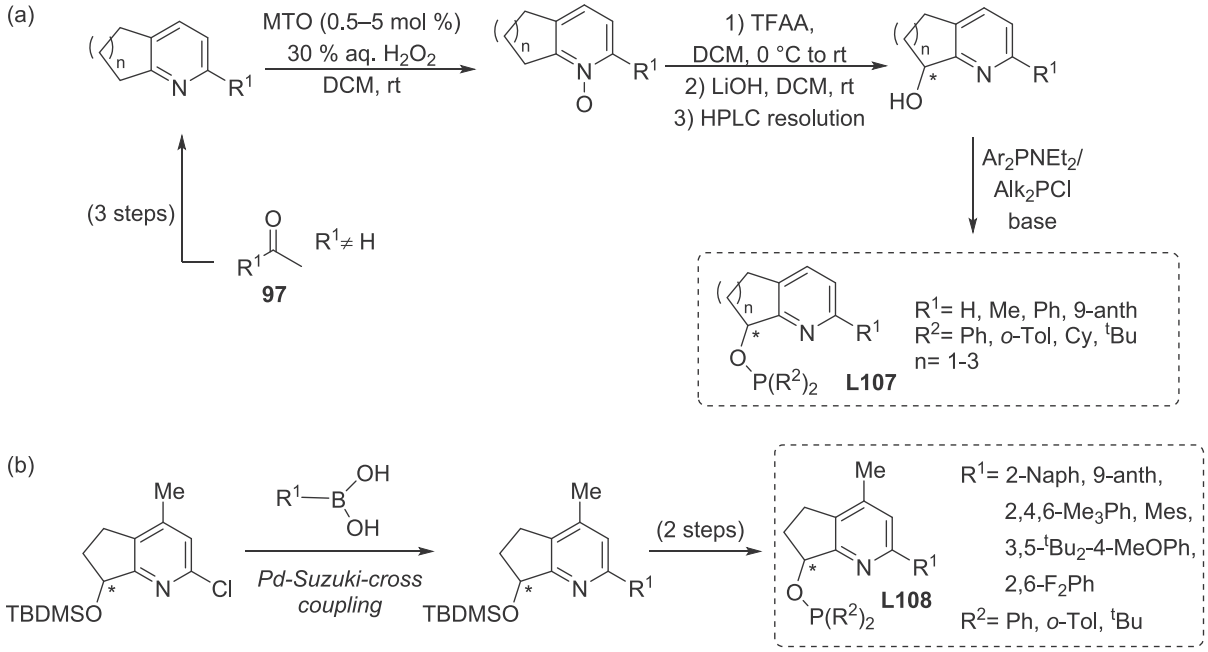
Scheme 65. Synthesis of phosphine- and phosphinite-pyridine ligands **L105**–**L106**.



Scheme 66. Asymmetric hydrogenation of a tetrasubstituted olefin using [Ir(cod)(**L106**)]BAr_F ($R^1 = R^2 = {}^tBu$).

were superior to those containing phosphines (**L105**) (up to 97% ee *vs.* 88% ee). High enantioselectivities (up to 96% ee) were also afforded with other interesting olefins. Among them, it should be highlighted that [Ir(cod)(**L106**)]BAr_F ($R^1 = R^2 = {}^tBu$) allowed the hydrogenation of the acyclic tetrasubstituted alkene shown in Scheme 66 in 81% ee and >99% conversion, which has been usually hydrogenated with low conversion and poor enantioselectivity.

Bicyclic phosphinite-pyridines **L107** (Scheme 67a) were designed to study whether the more rigid conformation due to an additional ring could increased their enantioselectivities than the provided with **L105**–**L106** [244]. Later, related disubstituted pyridine ligands with a bulky aryl group on the 2-position of the pyridyl scaffold were also developed (**L108**, Scheme 67b). Ligands **L107** are accessible from simple, available starting materials throught the pyridyl alcohols (Scheme 67a). The key step is the



Scheme 67. Synthesis of bicyclic phosphinite-pyridine ligands **L107–L108**.

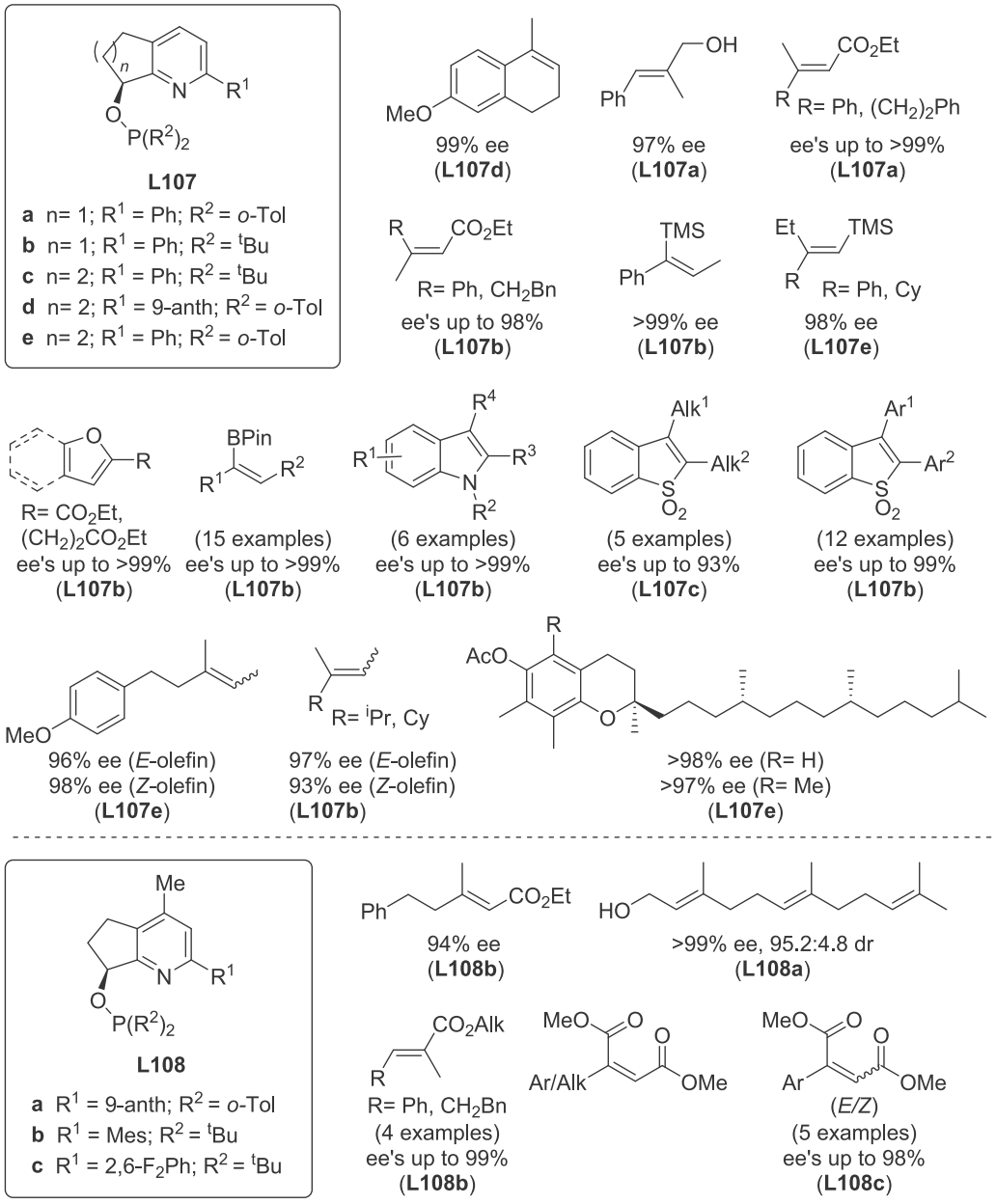


Fig. 33. Relevant results for the Ir-catalyzed hydrogenation of various olefins with bicyclic phosphinite-pyridine ligands **L107**–**L108**.

oxidation of the trisubstituted pyridines, which are prepared in three steps from the corresponding ketone, to the corresponding *N*-oxides. *N*-oxides were then subjected to a Boekelheide rearrangement to yield pyridyl alcohols, which could be resolved by preparative HPLC. Recently, the same group demonstrated that pyridyl alcohols can be easily resolved via enzymatic kinetic resolution [245]. Enantiopure pyridyl alcohols were transformed towards the desired phosphinite ligands using the same methodology than for previous ligand **L105**–**L106**. The next generation of bicyclic ligands (**L108**) were prepared from chiral silyl-protected chloropyridine precursor (Scheme 67b) [246]. The introduction of the bulky group on the 2-pyridyl scaffold was introduced through Suzuki–Miyaura cross-coupling using commercially available boronic acids.

Ligands **L107** and **L108** improved the catalyst performance of previous **L105**–**L106** in the Ir-catalyzed hydrogenation of many olefins, becoming one of the few privileged ligand family for this transformation (Fig. 33). Generally, 2-phenyl substituted ligands with a bulky ^{t}Bu and *o*-Tol phosphinite group provided the highest enantioselectivities [244]. Ligand **L107b** was initially found to be successful in the reduction of dihydronaphthalenes, allylic alcohols and α,β-conjugated esters (Fig. 33). This ligand was also successfully employed in the hydrogenation of the dihydronaphthalene core of antitumoral (+)-mutisianthol in 90% ee (see Section 6) [247]. A ligand from the **L107**-family (R^1 = Ph, R^2 = Ph) allowed the total synthesis of (+)-torrubiellone C [248] and (−)-pyridovericin [249], by catalyzing the hydrogenation of the appropriate α,β-unsaturated ester motif enantioselectively (see Section 6). (*S*)-**L107b** was also found to promote the asymmetric hydrogenation of furans with unprecedented high enantioselectivities (Fig. 33) [244]. The scope of these substrates was later extended, furnishing excellent enantioselectivities for a range of monosubstituted furans with a 3-alkyl or 3-aryl group and for benzofurans with an alkyl substituent at the 2- or 3-position [250]. Other heterocycles such as 2- and 3-substituted indoles or benzo[*b*]thiophene 1,1-dioxides could be also hydrogenated with

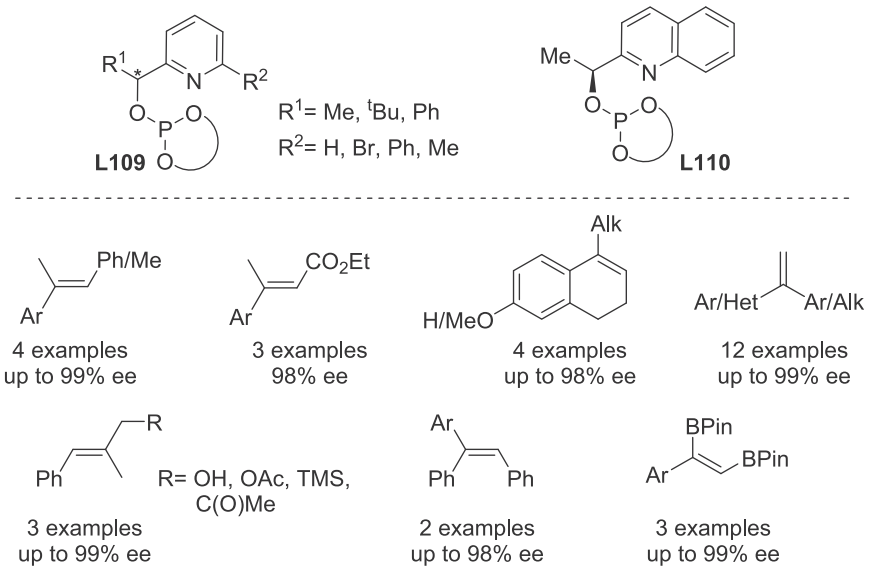


Fig. 34. Phosphite-pyridine ligands **L109–L110** and their use in the Ir-catalyzed hydrogenation of olefins.

enantioselectivities up to >99% ee (Fig. 33) [251]. Another type of substrates where ligand **L107b** proved to be successful are pinacol derived boronic esters [52b]. While the previously mentioned SimplePHIM ligands were good for terminal boronic esters, **L107b** was the optimal choice for trisubstituted substrates (Fig. 33), providing up to >99% ee. More recently, it has been found that ligands **L107** provided higher enantioselectivities than the related PHOX family in the hydrogenation of trisubstituted vinylsilanes (ee's up to >99% ee) [246]. Besides olefins with poorly coordinating groups, it was also found that phosphinite-pyridine ligands (*S*)-**L107b,e** are able to hydrogenate purely alkyl-substituted olefins with outstanding enantioselectivities (up to 99% ee, Fig. 33) [252]. Its hydrogenation has been used to prepare different biologically relevant products, such as α- and γ-tocopheryl acetates, precursors of main components of vitamin E (see Section 6) [252b,253]. Other relevant natural products, such as macrocidin A and long-chain polydeoxypropionaes have been synthesized through hydrogenation of long-chain molecules with the ligand family **L107** [254].

Later, it was found that the addition of bulkier substituents at the 2-pyridino position (e.g. R^1 = 9-Anth) led to even more enantioselective ligands for the hydrogenation of dihydronaphthalene substrates (with (*S*)-**L107d**) [246]. It was also found that disubstituted ligands (*S*)-**L108** exhibited excellent enantioselectivities in the hydrogenation of some challenging substrates. In particular, a ligand with a 9-anthracene group ((*S*)-**L108a**) showed an excellent enantioselectivity of >99% ee and 95.2:4.8 dr in the hydrogenation of (*E,E*)-farnesol (Fig. 33), even higher than the afforded with ligands **L107** (99% ee). Furthermore, unprecedented enantioselectivities (96–99% ee) were attained in the hydrogenation of α-substituted α,β-unsaturated esters ((*S*)-**L108b**) [246,255]. β-Methyl-substituted esters (Fig. 33), which resulted to be more problematic than expected, could be hydrogenated in also high enantioselectivities (up to 98% ee) [254]. The reduction of a broad range of maleic and fumaric acid diesters was also achieved with the use of ligands (*S*)-**L108c** [256]. Finally, it has been showed once again the applicability of ligands **L107-108** by the successful hydrogenation (ee's up to 98% ee and TON > 9300) of a dihydroquinoline core of agrochemical importance [257].

As for other P,N-ligands, Diéguez's group replaced the phosphinite fragment of ligands **L106** with a biaryl phosphite moiety, yielding the library of ligands **L109–L110** (Fig. 34) [18a]. Note that despite the broad substrate scope of P-pyridine ligands developed by Pfaltz et al., the catalysts were suitable mainly for trisubstituted olefins. With the incorporation of a flexible biaryl phosphite moiety (**L109**–**L110**), it was possible to increase the scope of the hydrogenated substrates to 1,1′-disubstituted terminal alkenes, successfully furnishing both enantiomers in up to 99% ee. Moreover, the catalytic performance was preserved for a range of *E*- and *Z*-trisubstituted olefins (Fig. 34). The system showed high tolerance to neighboring functional groups (such as alcohols, esters, silanes ...), leading as well to excellent enantioselectivities (up to >99% ee) [258].

The new phosphite-pyridine ligands were also successfully applied in the Pd-allylic substitution of tri- and disubstituted allylic substrates with C-, O- and N-nucleophiles (Fig. 35) [18a]. The system was highly efficient in the substitution of trisubstituted

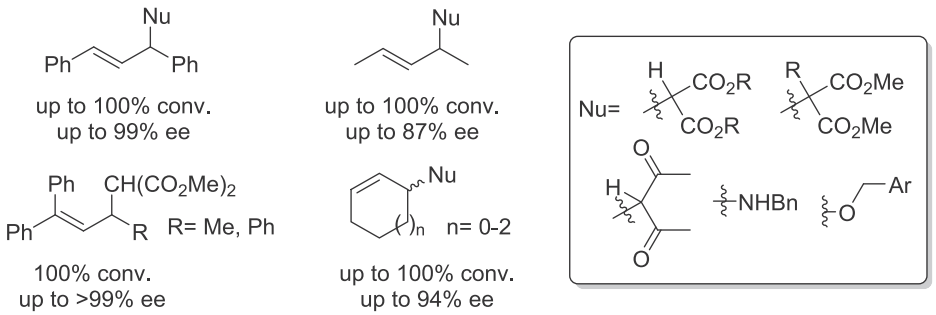


Fig. 35. Representative catalytic results furnished with **L109–L110** in the Pd-catalyzed allylic substitution.

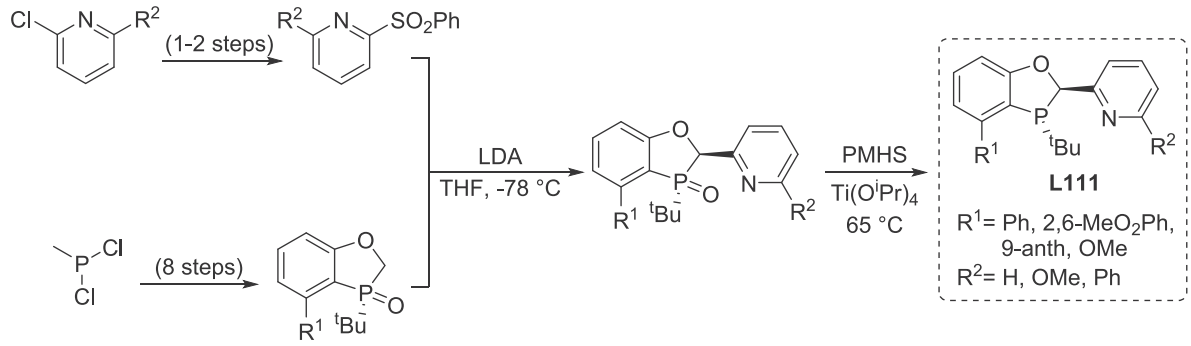
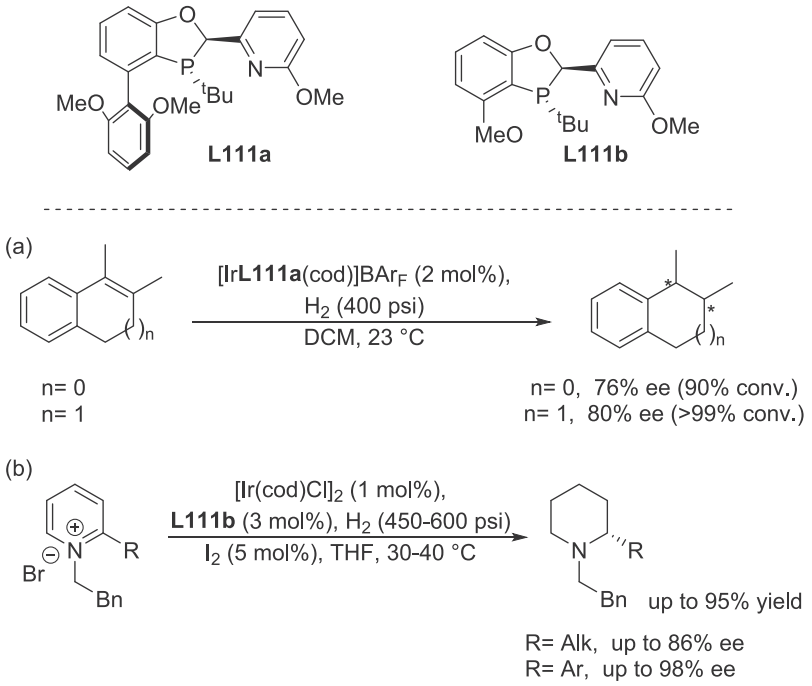


Fig. 36. BoQPhos ligands **L111**.



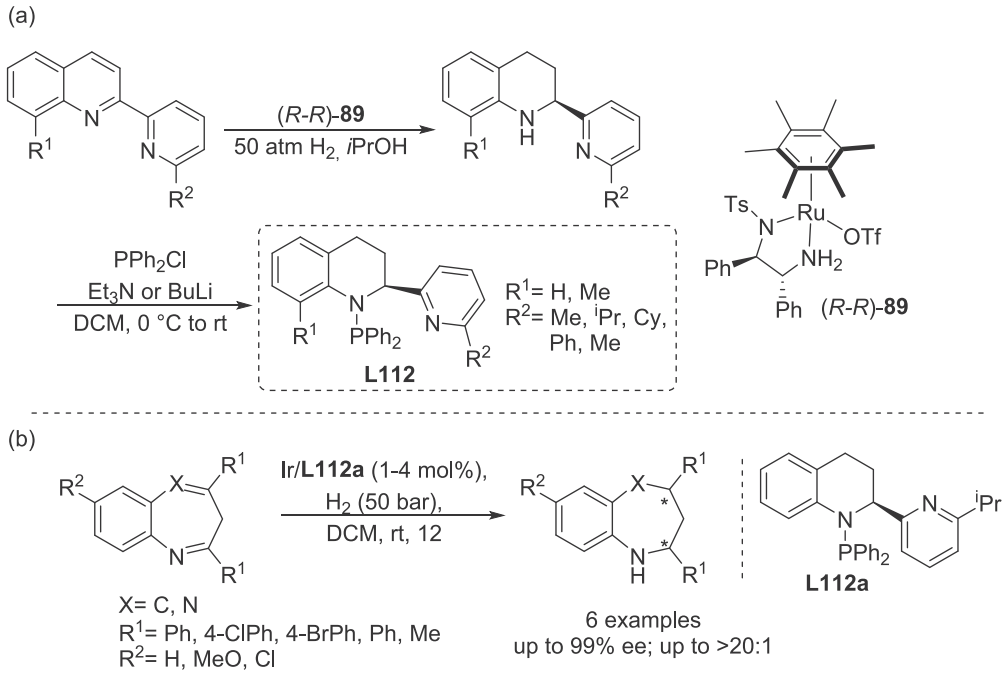
Scheme 68. Ir-catalyzed hydrogenation of tetrasubstituted olefins (a) and pyridinium salts (b) with BoQPhos ligands (**L111**).

substrates (up to >99% ee). A range of carbocyclic compounds were easily attained by combining in a sequential manner the Pd-allylic alkylation with Ru-catalyzed ring closing metathesis. Furthermore, the reaction could be performed in environmentally friendly solvents, concretely 1,2-propylene carbonate and ionic liquids (1-butyl-3-methyl imidazolium hexafluorophosphate and *N*-butyl-*N*-methyl pyrrolidinium bis(trifluoromethylsulfonyla mide). To note is that catalyst reuse could be fulfilled up to 5 runs by using the latter ionic liquids, while maintaining the excellent enantioselectivities. Studies of the Pd-1,3-diphenyl, 1,3-dimethyl and 1,3-cyclohexenyl allyl intermediates by NMR spectroscopy showed that in general, for enantioselectivities to be high the ligand parameters need to be correctly combined so that the isomer that reacts faster with the nucleophile is predominantly formed [18a].

Qu and co-workers prepared a series of air-stable P-chiral pyridyl-dihydrobenzooxaphosphole ligands, which were called BoQPhos (**L111**). These ligands could be readily obtained by a diastereoselective nucleophilic aromatic substitution of sulfonyl pyridines with P-stereogenic intermediates (Fig. 36) [259]. Sulfonyl pyridines were obtained from 2-chloropyridine or 2,6-dichloropyridine, while the P-stereogenic fragment was prepared in 8 steps from methyldichlorophosphine [260].

[Ir(cod)(**L111**)]BAr_F complexes were tested in the hydrogenation of some tri- and tetrasubstituted unfunctionalized alkenes. Although the ee 's obtained were moderately good (76–90% ee), it should be highlighted that it was possible to hydrogenate the more challenging tetrasubstituted indene and dihydronaphthalene in high conversions (90–>99%) and promising enantioselectivities (76–80% ee) with [Ir(cod)(**L11a**)]BAr_F (Scheme 68) [259]. More recently, it has been showed the utility of methoxy-substituted **L111b** for the Ir-catalyzed hydrogenation of pyridinium salts [261]. Ir/**L11b** allowed the preparation of piperidines bearing 2-alkyl and 2-aryl substituents of different nature, with enantioselectivities up to 86% and 98% respectively (Scheme 68).

Finally, Fan and co-workers have accounted the most recent family of P-pyridine ligands, consisting in aminophosphine-pyridine ligands **L112** (Scheme 69). These ligands contain 2-(pyridin-2-yl)-substituted 1,2,3,4-tetrahydroquinoline backbone that were achieved via Ru-catalyzed asymmetric hydrogenation of 2-(pyridin-2-yl)quinolines (Scheme 69a) [262]. Ligands **L112** were screened in the Ir-catalyzed hydrogenation of the model substrates *trans*-β-methylcinnamate and *E*-methylstilbene, which were reduced in >99% ee. More important are the high enantioselectivities obtained in the reduction of challenging 7-membered



Scheme 69. (a) Synthesis of phosphine-pyridine ligands **L112.** (b) Ir-catalyzed dihydrogenation of benzazepines (X = C) and benzodiazepines (X = N) with **L112a**. The dihydrogenation of benzazepines was performed as a two-step one-pot process.

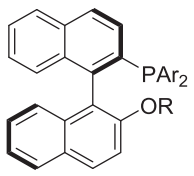


Fig. 37. (*R*)-MOP-type ligands.

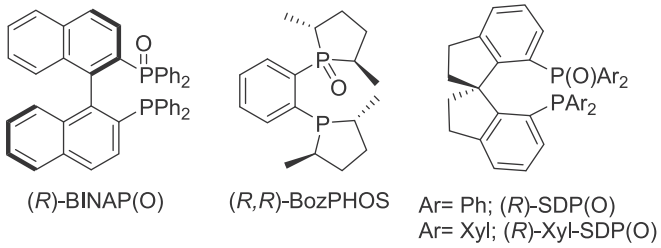
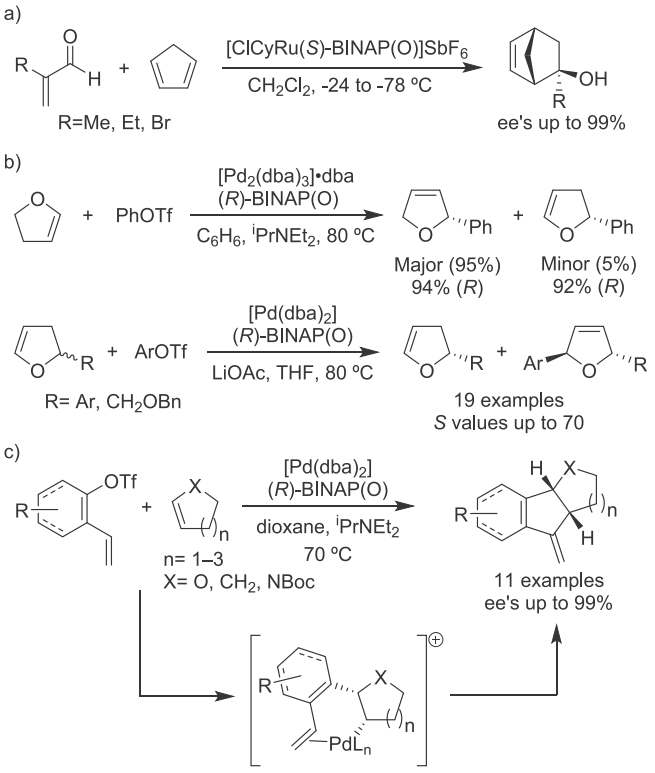


Fig. 38. Representative phosphine-phosphine oxide ligands.



Scheme 70. Selected examples of application of BINAP(O) ligand in the Pd-catalyzed asymmetric a) Diels-Alder reaction, b) intramolecular Heck reaction and c) domino Heck reaction/cyclization.

ring imines, concretely benzazepines and benzodiazepines. A ligand with a 2-isopropyl-pyridine moiety (**L112a**) proved to be the most active and enantioselective ligand, showing good diastereomeric ratios and ee's up to 99% for both types of substrates (Scheme 69b). It should be noted that the dihydrogenation of benzazepines was performed as a two-step one-pot process, otherwise only partially reduction was observed, being the C=C bond the most reactive one.

4. Heterodonor P,O-ligands in asymmetric catalysis

Chiral P,O-ligands have traditionally played a less important role than P,N-ligands in enantioselective catalysis. The hemilability of the P,O-ligands, owing to the occurrence of both a hard (O) and a soft (P) bases on the same metal center, facilitates several transformations at the metal center, such as oxidative addition, ligand exchange, isomerization, etc., that often has a positive effect on catalytic activity. However, this hemilability, can at the same time cause a detrimental effect on enantioselectivity, since the ligand can be coordinated in a monodentate fashion in the enantiodiscriminating transition state. MOP ligands constitute one of

the early examples in which a P,O-ligand acts as monodentate ligand (Fig. 37) [263,264]. Despite this, MOP-ligands have been used with great effectiveness in various asymmetric reactions [263]. In all these cases, the ligand acts as a chiral monophosphine with the ether group that produces a secondary interaction with the incoming nucleophile/reagent. Such secondary interaction, as early demonstrated by Hayashi and coworkers, is key to maximize enantioselectivities.

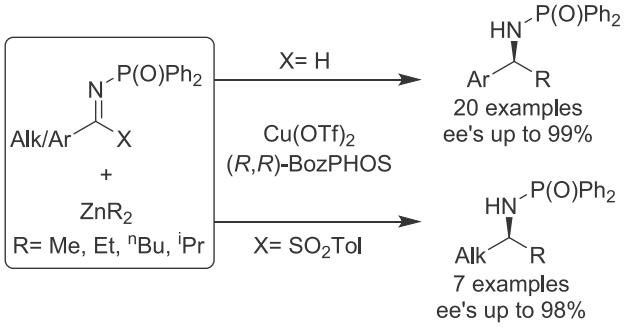
4.1. Heterodonor phosphine-phosphine oxide ligands

Heterodonor phosphine-phosphine oxide ligands have been applied with great effectiveness in different asymmetric transformations (Fig. 38) [265]. These ligands can be prepared via Pd-catalyzed monooxidation of the corresponding bidentate phosphines [266].

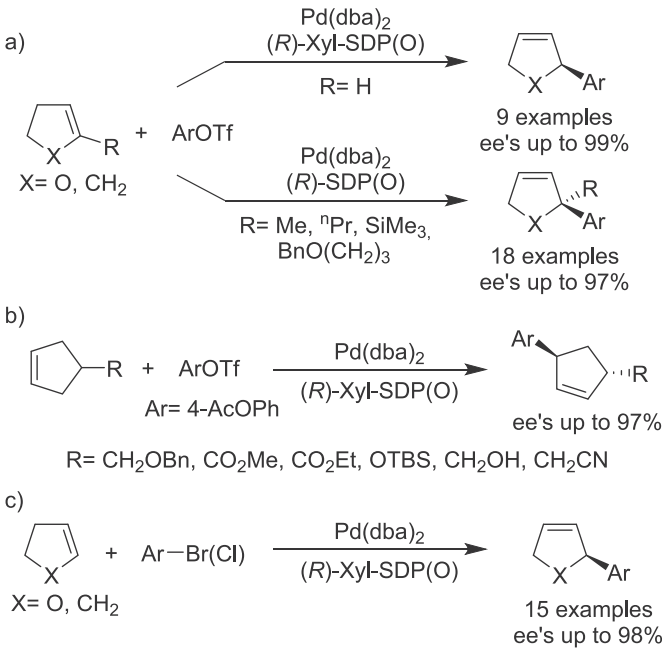
In this respect, Faller and coworkers found that BINAP(O) ligand provided high enantioselectivities in the Ru-catalyzed Diels-Alder reactions (Scheme 70a) [267]. More recently, the groups of Oestreich [268] and Hou [269] independently published the application of BINAP(O) in the Pd-catalyzed asymmetric intermolecular Heck reaction (Scheme 70b). They found an important change in the regio- and enantioselectivity of the arylation of cyclic alkenes when BINAP(O) ligand was used instead of BINAP. In this respect, the arylation of 2,3-dihydrofuran behaves as perfectly regiodivergent; while the use of BINAP favors the formation of the thermodynamically more stable 2-aryl-2,3-dihydrofuran, the use of BINAP (O) led to the preferential formation of 2-aryl-2,5-dihydrofuran. In addition, little alkene migration was observed with BINAP(O) [268]. The effectiveness of Pd-BINAP(O) in asymmetric Heck reaction was also demonstrated in the efficient kinetic resolution of 2-substituted-dihydrofurans providing optically enriched *trans*-2,5-disubstituted-dihydrofurans and 2-substituted dihydrofurans in high yield and ee's (*S* factor of up to 70; Scheme 70b) [269]. Zhou's group also reported the application of BINAP(O) in the preparation of chiral fused carbo- and heterocycles through a domino reaction involving an asymmetric intermolecular Heck reaction followed by a diastereoselective cyclization (Scheme 70c) [270].

Another relevant example of heterodonor phosphine-phosphine oxide ligands can be found in the work of Charette's group that reported the application of BozPHOS, a monoxide version of the Me-Duphos (Fig. 38), in the Cu-catalyzed 1,2-addition of diorganozinc reagents to *N*-phosphinoylarylaldimines (ee's up to 99%; Scheme 71) [271]. However, its application was in part hampered by the accessibility and stability of the *N*-phosphinoylalkylaldimines. To solve this, they demonstrated that the reaction also worked well using the sulfinic adduct of *N*-phosphinoylimines (Scheme 71) [272].

The latest heterodonor phosphine-phosphine oxide design with an outstanding applicability can be found in the work of Zhou's



Scheme 71. Synthesis of α-chiral amines using bis(phosphine) monoxide BozPHOS ligand.



Scheme 72. Application of bis(phosphine) monoxide SDP(O) ligands in asymmetric Pd-catalyzed Heck reaction.

group, that reported the successfully application of spirocyclic SDP(O) (Fig. 38) in Pd-catalyzed intermolecular Heck reactions (Scheme 72). Useful, SDP(O) ligands not only allowed the arylation of standard substrates such as 2,3-dihydrofuran or cyclopentene [273], but also of 5 substituted-2,3-dihydrofurans [274] that led to the preparation of a chiral quaternary carbon center (Scheme 72a). More interestingly, the use of SDP(O) ligands was further extended to the desymmetrization of 4-substituted-cyclopent-1-enes and other bicyclic olefins via asymmetric Heck reaction and hydroarylation, respectively (Scheme 72b) [275]. The use of spirocyclic SDP(O) ligands also allowed the unique asymmetric intermolecular Heck reaction with aryl halides as coupling partners (Scheme 72c) [276]. A wide range of aryl bromides and chlorides, including examples with heteroaromatic groups, were efficiently introduced in the Heck reaction of various cyclic olefins (35 examples with ee's typically >95%).

4.2. Heterodonor amido- and sulfinamido-phosphine ligands

Hemilabile amido-phosphine ligands have also shown their effectiveness in asymmetric catalysis. Tomioka and coworkers early demonstrated that the effectiveness of this type of ligands was mainly consequence of the coordination of the amide carbonyl oxygen to the metal [277]. Among all the amido-phosphine ligands, we should highlight ligands **L113–L119** (Fig. 39).

The synthesis of such ligands turned to be quite straightforward (Scheme 73). Thus, proline-based ligands were easily attained from (*S*)-*tert*-butyl-2-(bromomethyl)pyrrolidine-1-carboxylate through a nucleophilic substitution with a range of metallated phosphines (Scheme 73a). Elimination of the *N*-Boc protecting group, led the corresponding free amine, which reacted with the desired acetyl chlorides, isocyanates or carbamoyl chlorides. Oxygen-sensitive phosphine moieties, such as di-*tert*-butyl- or dicyclohexylphosphines, should be protected as borane adducts to avoid oxidation through the ligand synthesis. The synthesis of non-biaryl atropoisomeric ligands **L118** and **L119** starts from the corresponding aromatic tertiary amide, which is transformed to the corresponding amido-phosphine compound by lithiation followed by reaction

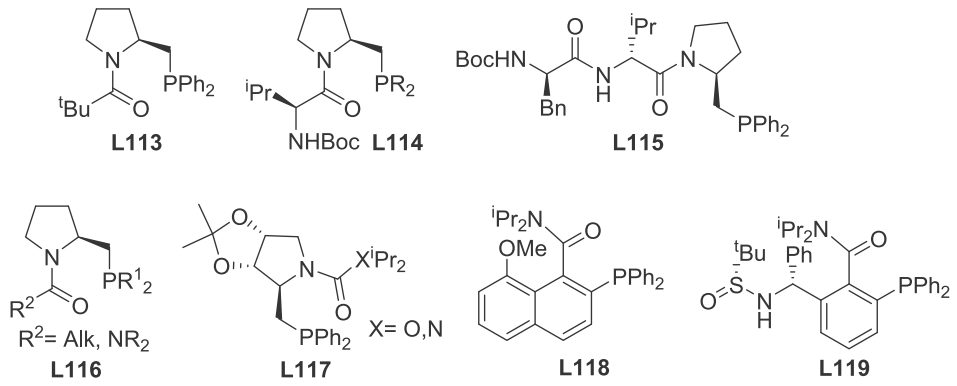
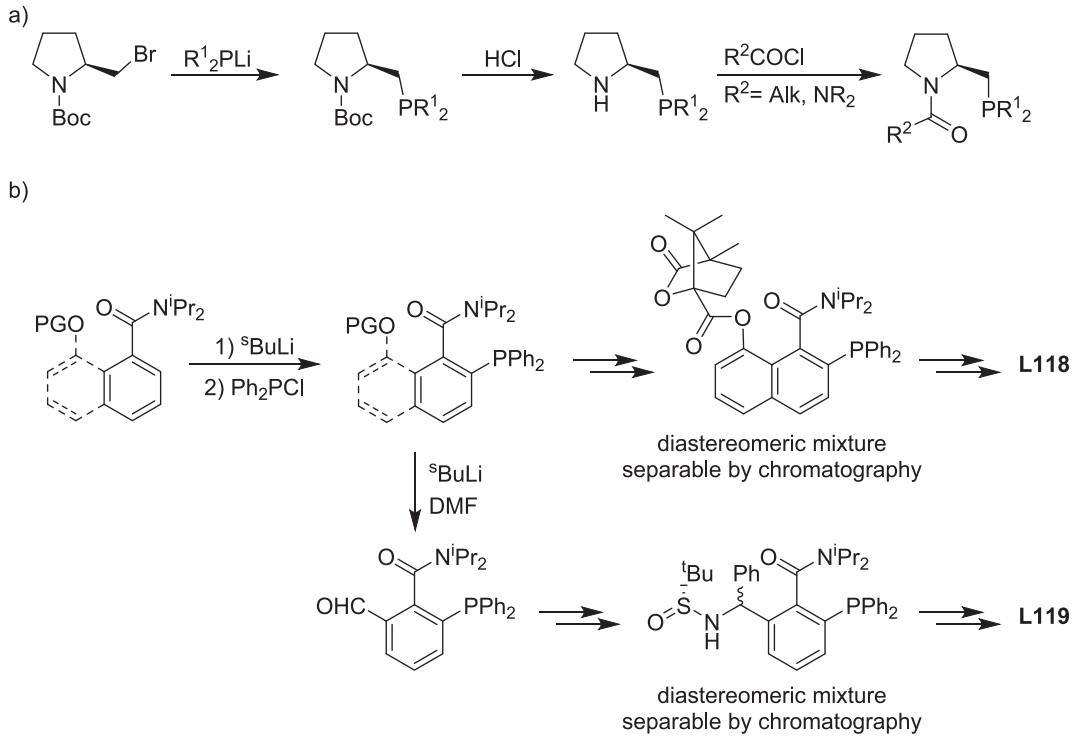


Fig. 39. Amido-phosphine ligands **L113**–**L119.**



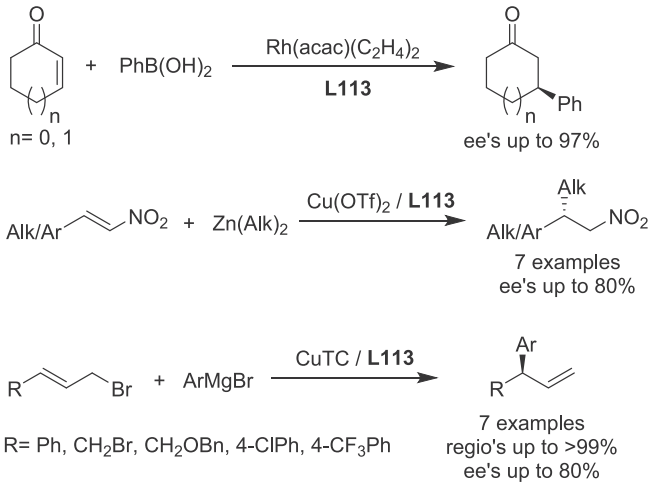
Scheme 73. Synthesis of amido-phosphine ligands a) derived from proline and b) with non-atropoisomeric chirality.

with $ClPPh_2$ (Scheme 73b). For ligand **L118**, the racemic amido-phosphine was chemically resolved by using (−)-camphanic chloride, which allowed the separation by flash chromatography of the corresponding diastereoisomers. Alkaline saponification, followed by etherification gave ligand **L118**. For ligand **L119**, the 2-(diphenylphosphaneyl)-*N*,*N*-diisopropylbenzamide was then formylated to give the corresponding aldehyde, which allowed the introduction of the chiral *N*-*tert*-butanesulfinyl imine, by condensation with (*R*)-*tert*-butanesulfinamide and subsequent 1,2-addition of PhMgBr. The diastereomeric amido-phosphines were then separated by flash chromatography.

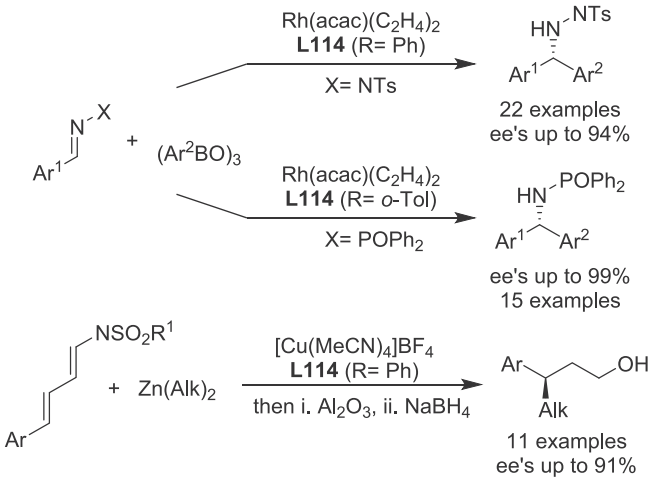
The simple proline-based ligand **L113**, prepared by Tomioka and coworkers was applied with success in several asymmetric transformation: the Rh-catalyzed 1,4-addition of arylboronic acids to cycloalkenones (ee's up to 97%) [277], the Cu-catalyzed conjugate addition of dialkylzinc reagents to nitroalkenes (ee's up to 80%) [278] and in the highly regio- and enantioselective (regio's up to >99% and ee's up to 91%) allylic substitution of Grignard reagents to cinnamyl-type allylic bromides [279] (Scheme 74).

Later, they also studied the introduction of an extra stereogenic center at the *N*-Boc amido group of ligand **L113** (ligands **L114**). The use of *N*-Boc-L-valine-connected amido-phosphine ligands **L114** allowed to extended the applicability of ligand **L113** to the Rh-catalyzed arylation of *N*-tosyl- and *N*-phosphinoyl aldimines (ee's up to 99%; Scheme 75) [280] and in the Cu-catalyzed conjugate addition of dialkylzincs to β-aryl-α,β-unsaturated sulfonylaldimines [281] (ee's up to 91%; Scheme 75).

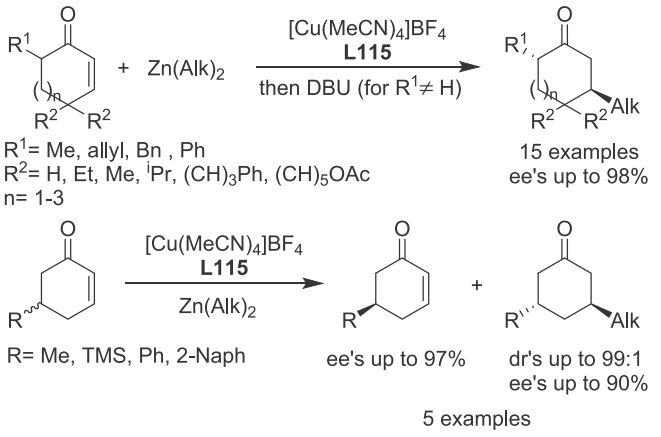
Later, they further studied other peptidic modifications of ligand **L113** and found that ligand **L115**, involving a small D-Phe-D-Val dipeptide, was useful in the asymmetric conjugate addition of organozinc reagents to cycloalkenones (ee's up to 98%; Scheme 76) [282]. Advantageously, the Cu/**L115** catalyst was also applied in the kinetic resolution of (*rac*)-5-substituted cycloalkenones to yield *trans*-3,5-disubstituted alkanones with excellent ee's (up to 90%) and excellent *trans*/*cis* ratios (up to >98/2 dr; Scheme 76) [283]. Then, they also reported the useful of Cu/**L115** system in the conjugate addition of 6-substituted cyclohexenones to give disubstituted cyclohexanones, albeit with marginally



Scheme 74. Application of proline-based amido-phosphine ligand **L113** in asymmetric catalysis.



Scheme 75. Application of proline-based amido-phosphine ligand **L114** in asymmetric catalysis.



Scheme 76. Application of proline-based amido-phosphine ligand **L115** in asymmetric catalysis.

selectivity (*cis*/*trans* ratio close to 1). Epimerization of these mixtures with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) favored the formation of the most stable *trans*-cyclohexenones as the major product in high yields and ee's (up to 96%; Scheme 76) [284].

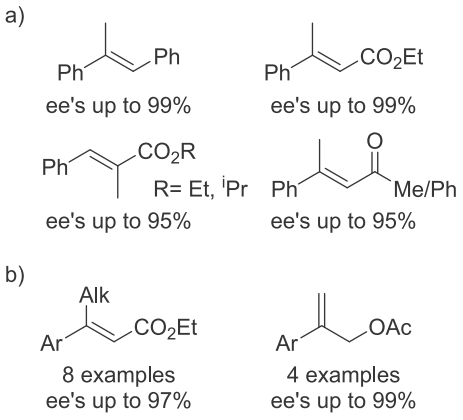
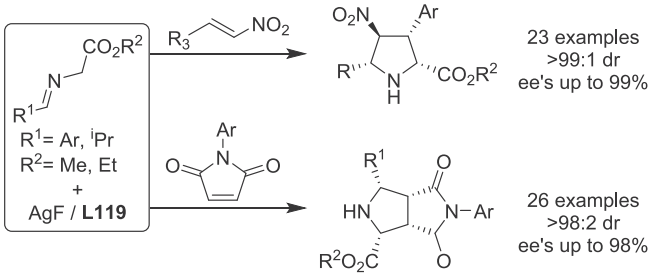


Fig. 40. Representative results in the Ir-catalyzed hydrogenation with a) proline-based P,O-ligands **L116** and b) D-mannose urea-based ligand **L117**.



Scheme 77. Application of non-biaryl atropoisomeric amido-phosphine ligand **L119** in enantioselective Ag-catalyzed [3 + 2] cycloaddition reactions.

Later, the Pfaltz's group further modified Tomioka's proline-based ligand **L113** to include several dialkyl and dialkyl phosphino groups as well as urea groups and bulky amide at the pyrrolidine N-atom (ligands **L116**; Fig. 39) [285,286]. Ligands **L116** containing bulky phosphine moieties (R^1 = Cy or ^{t}Bu) shown its effectiveness in the Ir-hydrogenation of *trans*-methylstilbene olefins and olefins with poorly coordinative groups (e.g. α,β-unsaturated ketones and carboxylic esters; Fig. 40a). These results were pretty unexpected having in mind the lability of the Ir-O bond, and unambiguously demonstrated that ligands **L116** remain coordinated in a bidentate fashion during the catalytic cycle, most likely due to the highly acidic character of the Ir^{III}/Ir^{V} intermediates.

More recently, related pyrrolidine-based P,O ligands derived from cheap carbohydrates (D-ribose, D-mannose and D-arabinose; ligands **L117**) were also screened in the Ir-catalyzed hydrogenation of olefins [287]. The presence of a rigid bicyclic skeleton in ligands **L117** had a positive effect on enantioselectivity, enabling to successful hydrogenate also 1,1′-disubstituted allylic acetates (Fig. 40b). As a further advantage and in contrast to **L116**, ligand **L117** does not require the presence of less stable, bulkier phosphine substituents for optimal performance.

Another relevant class of amido-phosphine ligands are the non-biaryl atropoisomeric ligands **L118** and **L119** (Fig. 39). Ligand **L118** provided an enantioselectivity of 95% in the Pd-catalyzed allylic substitution reaction of 1,3-diphenylallyl acetate with dimethyl malonate as nucleophile [288]. The Pd/**L118** catalyst was applied in the asymmetric Heck reaction, albeit with low ee's (up to 55%) [289]. More recently, Cia and Xu groups applied the amidophosphine ligand **L119**, which proved to be highly efficient in Ag-catalyzed [3 + 2] cycloaddition reactions. Catalyst Ag/**L119** mediated the [3 + 2] cycloaddition of aldiminoesters with nitroalkenes to yield optically enriched nitrosubstituted pyrrolidines (dr's up to >99:1 and ee's up to 99%; Scheme 77) [290]. The same catalyst was also used in the preparation of imide-containing pyrrolidines

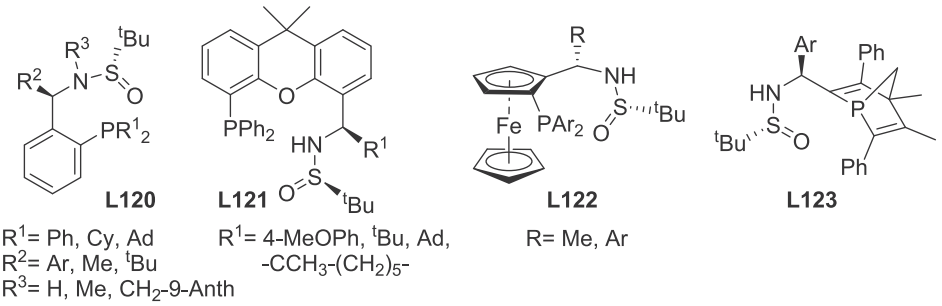
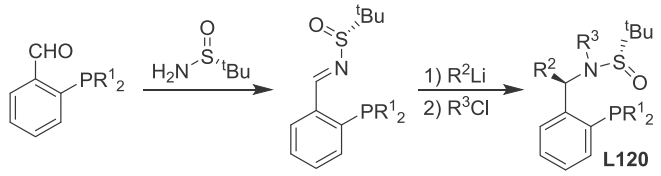


Fig. 41. Sulfinamido-phosphine ligands **L120–L123**.

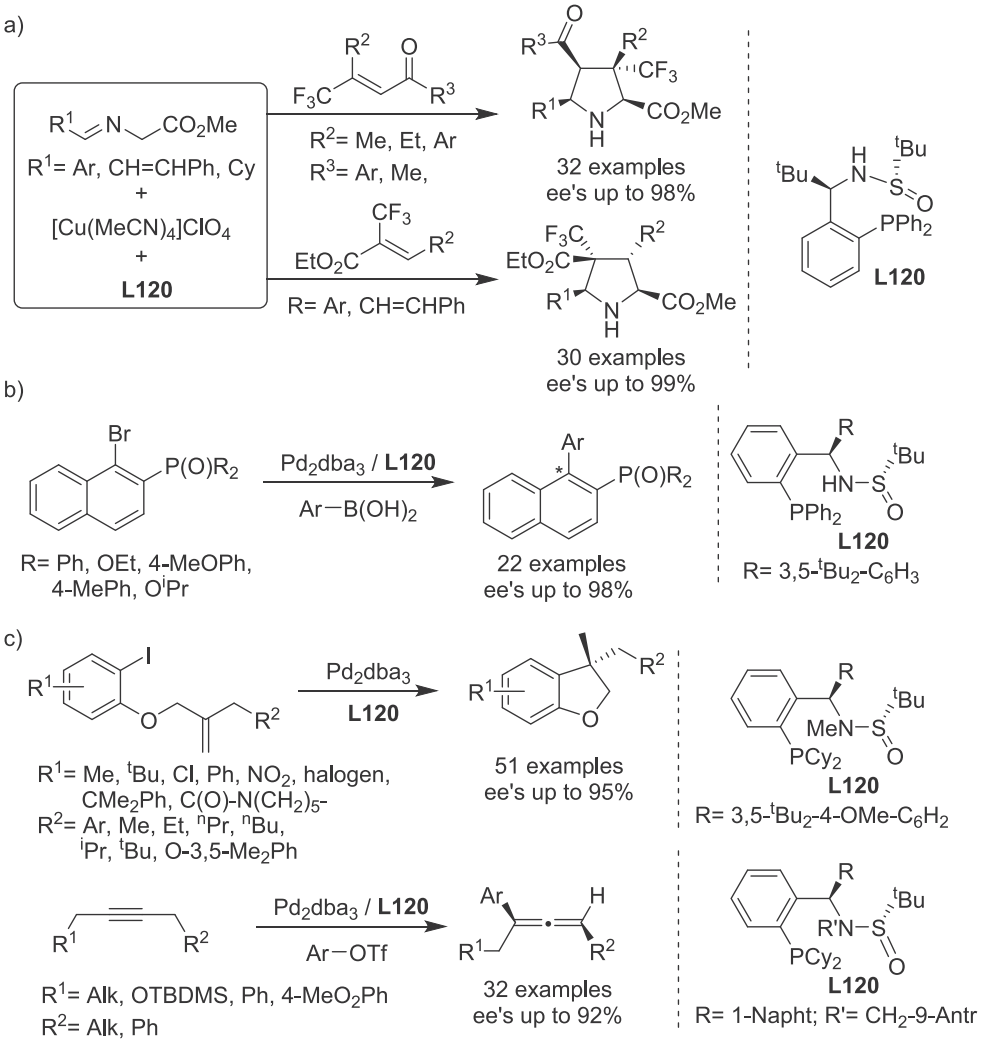


Scheme 78. Synthesis of sulfinamido-phosphine ligands **L120**.

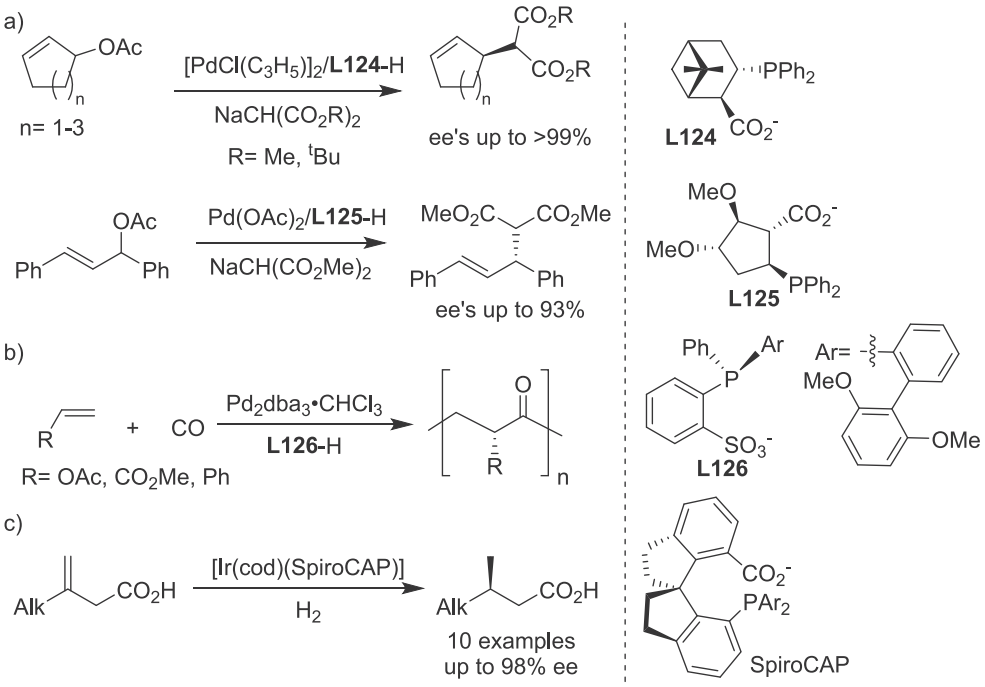
by reaction of iminoesters with maleimides (dr's up to >98:2 and ee's up to 99%; Scheme 77) [291].

Sulfinamido-phosphines **L120–L123** are another type of hetero-donor P,O ligands that has recently shown its applicability in asymmetric catalysis (Fig. 41) [292,293]. Their synthesis is again fairly straightforward, as can be seen in the short synthesis of ligands **L120** (Scheme 78). Thus, condensation of (*R*)-*tert*-butanesulfinamide with the corresponding 2-phosphinobenzaldehyde led to imino-phosphine intermediates. Stereoselective addition of R^2Li followed by reaction with R^3Cl (for $R^3 \neq H$) yielded **L120** ligands.

Ligands **L120** (R^1 = Ph, Cy, Ad; R^2 = Ar, Me, ^{t}Bu; R^3 = H, Me, CH_2-9-Anth) have proved to be useful in several asymmetric transfor-



Scheme 79. Selected successful applications of sulfinamido-phosphine ligands **L120** in asymmetric catalysis.



Scheme 80. Representative successful applications of anionic P,O ligands.

mation, such as the Cu-catalyzed [3 + 2] cycloaddition of azomethine ylides with a range of β-trifluoromethyl β,β-disubstituted enones and α-trifluoromethyl α,β-unsaturated esters [292a,b], the Pd-catalyzed Suzuki reaction for the preparation of axially chiral phosphonates and phosphine oxides [292c], the Pd-catalyzed intramolecular Heck reaction of allyl aryl ethers [292d] and the Pd-catalyzed intermolecular Heck reaction of alkynes [292e] (Scheme 79).

Ligands **L121**–**L123** have also shown its usefulness but due to their latest development the range of reactions where they have been applied is still limited. Thus, the Xantphos-inspired ligand **L121** has been applied with success in the arylation of sulfenate anions (ee's up 99%) [293a], and ligands **L122** and **L123** in the boroacylation of 1,1′-disubstituted allenes [293b] and 1,3-dipolar cycloadditions [293c-d], respectively.

4.3. Heterodonor anionic P,O ligands

The application of anionic P,O ligands is less developed than its neutral analogous despite of the early successful application of phosphine-carboxylate ligands **L124** and **L125** (Scheme 80a) [294]. These ligands attained high enantioselectivities in the Pd-catalyzed allylic substitution reactions (ee's up to >99%; Scheme 80a). More recently, phosphine-sulfonate ligands **L126** allowed the asymmetric copolymerization of polar vinyl monomers with carbon monoxide to yield highly head-to-tail isotactic γ-polyketone polymers (Scheme 80b) [295]. In 2017, Zhou's group accounted a series phosphine-carboxylate ligands (SpiroCAP) related to phosphine-oxazoline ligands **L32**, which demostrated to be efficient in the hydrogenation of terminal unsaturated carboxylic acids (Scheme 80c) [79].

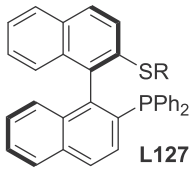


Fig. 42. Binaphthyl-based thioether-phosphine ligands **L127**.

5. Heterodonor P,S-ligands in asymmetric catalysis

5.1. P-thioether ligands

P-thioether ligands have a strong preponderancy among the P, S-ligands [3f,g,296]. In the early 90 s, researchers realized that P–thioether compounds could be of great use in asymmetric catalysis with the growth of a quite important number of P-thioether ligands. Even so, they found that the presence of diastereoisomeric mixtures of catalytically active species that arise from the sulfur coordination, which becomes an stereogenic center after coordination, made difficult to achieve high enantioselectivities. Thus, very few of the early developed P-thioether ligands had found an important impact in asymmetric catalysis. In the last decade, many efforts have been made to understand how to control the sulfur coordination. For this, mechanistic investigations had played a relevant role and they have revealed that sulfur coordination can be controlled, which have led to a new push on the use of P-thioether ligands in asymmetric catalysis. This section focuses on these new P-S ligands and the correlation between their ligand architecture and catalytic results.

BINAP and ferrocene-based ligands have shown they widely prominent useful in asymmetric catalysis. The development of their heterodonor versions was therefore an expected step. In 1994, Gladiali and coworkers used BINAP-based phosphine-thioether ligands **L127** (R = Me and ^{i}Pr; Fig. 42) in hydroformylation and transfer hydrogenation. Albeit its moderate success, this pioneering work spread the way for the use of P-S ligands in asymmetric catalysis [297]. Then, other groups reported the application of ligands **L127** (R = Me, Ph, 2-^{i}Pr-C_6H_4, 2-Naph, 3,5-Xyl and Cy) in the Pd-catalyzed allylic alkylation using as nucleophiles the model dimethyl malonate and the less studied indoles (R = 2-^{i}Pr-C_6H_4; Fig. 42) with more success (96% ee), although the high ee's are limited to the benchmark linear substrate *rac*-1,3-diphenylallyl

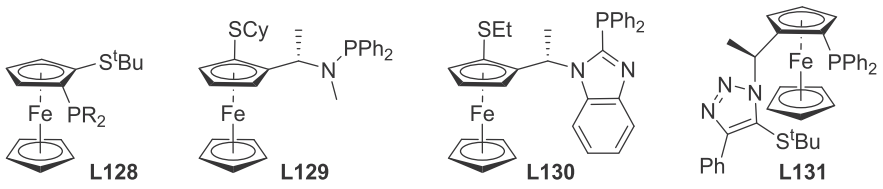
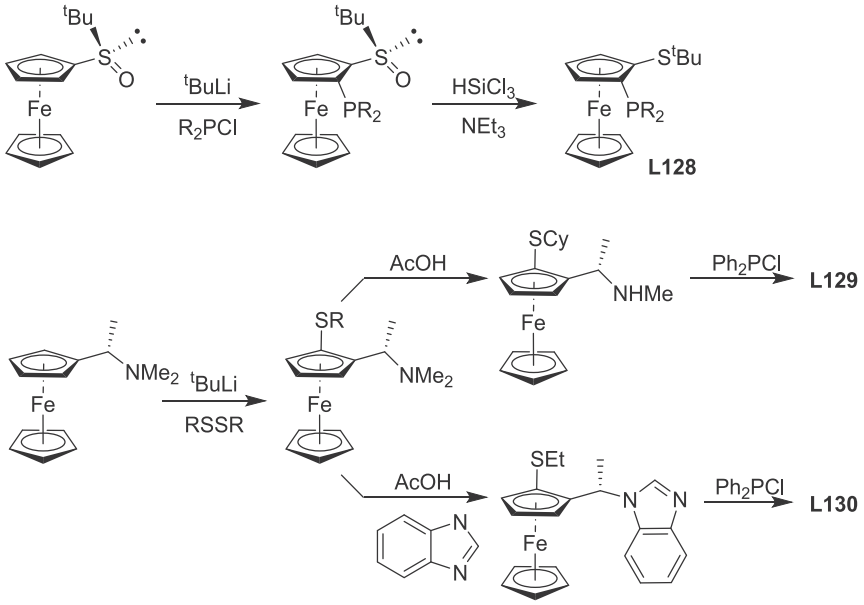


Fig. 43. Representative ferrocenyl-based thioether-phosphine ligands **L128**–**L131**.



Scheme 81. Synthesis of ferrocene-based ligands **L128**–**L130**.

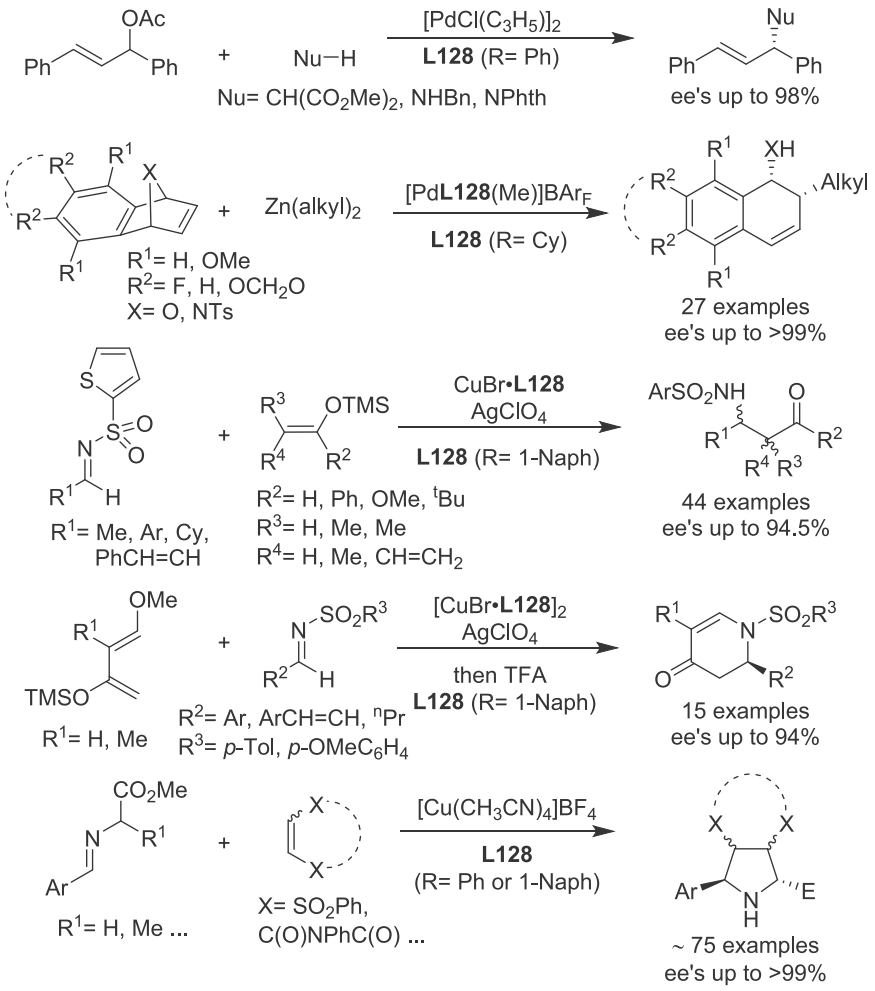
acetate [298]. More recently, a chiral biphenyl version of ligands **L127** has been developed, providing similar high ee's in the Pd-catalyzed allylic substitution with indoles [299].

In contrast to binaphtyl- and biphenyl-based P-thioether ligands, since the early development of ferrocene-based P-thioether ligands in 1996 by the groups of Pregosin [300] and Togni [301], a broad range of this type of P-thioethers have been developed [3f]. Among them, it should be underlined: the phosphine-thioether Fesulphos ligands **L128**, the *N*–phosphine-thioether FerroNPS-type ligands **L129**–**L130**, and the phosphine-thioether ThioClick-Ferrophos **L131** (Fig. 43). The synthesis of these ligands can be achieved in few steps (Scheme 81). Fesulphos ligands **L128** were prepared from *R-tert*-butylsulfenylferrocene in two steps. The first step involves the diastereoselective introduction of the desired phosphine moiety via *ortho*-lithiation. The second consists in the reduction of the sulfoxide to the thioether group with $HSiCl_3{\cdot}NEt_3$. Ligands **L129**–**L130** were achieved from Ugi's amine, which facilitates the diastereoselective introduction of the thioether group. The tertiary amine was then transformed to the secondary amine or to the benzimidazole. Finally, treatment with $ClPPh_2$ led to ligands **L129**–**L130**. ThioClick-Ferrophos ligand **L131** was synthesized following an analogous method starting from (S,R_p)-*ortho*-bromo-(1-azidoethyl)ferrocene.

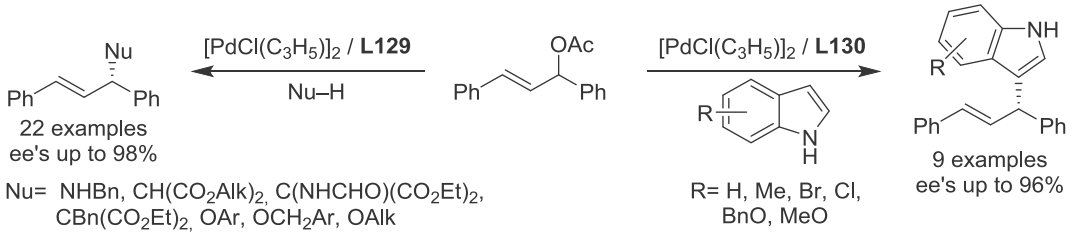
Fesulphos ligands **L128** (R = Ph, 4-FPh, 4-CF3Ph, 2-furyl, Cy, o-Tol, 1-Naph; Fig. 43), developed by Carretero's group, have become one of the most useful P–S families in asymmetric catalysis (Scheme 82). They have been used with great success in various C—C bond forming reactions, in combination with both Pd and Cu catalyst precursors [302]. Thus, in their first report they demonstrated the usefulness of Pd/**L128** catalyst in the Pd-catalyzed allylic substitution of the benchmark substrate *rac*-1,3-diphenylallyl acetate using several malonates and amines as nucleophiles (ee's up to 98%; Scheme 82) [302a,b]. Pd/**L128** also demonstrated to be efficient in the asymmetric ring opening of heterobicyclic alkenes with diorganozinc reagents (ee's up to >99%; Scheme 82) [302a,c,f]. Since then, Carretero and coworkers have also demonstrated the usefulness of Cu/**L128** catalyst precursors in a range of other metal mediatedreactions, such as Mannich-type reactions of *N*-sulfonylimines with several electrophiles [302h,l], (aza)-Diels-Alder reactions of electron rich alkenes with aldimines [302d,g] and 1,3-cycloaddition reactions of azomethine ylides with an extensive variety of activated olefins [302e,i,k,m,o-r] (ee's up to >99%; Scheme 82).

Later, Chan's group developed ligands **L129** [303] and **L130** [304] (Fig. 43), which combines both planar and central chirality, and demonstrated their versatility in Pd-catalyzed allylic substitutions. Thus, Pd/**L129** was successfully applied in the allylic substitution of benchmark *rac*-1,3-diphenylallyl acetate with dimethyl malonate, a range of amines and several aliphatic alcohols (ee's up to 98%; Scheme 83) [303a,b], being one of the first successful examples of allylic etherifications with non-aromatic alcohols. More recently, the use of ligand **L130** containing a benzimidazole unit, extended the nucleophile scope to indoles (ee's up to 96%; Scheme 83) [304a] and to the alkylation of some cyclic substrates with ee's up to 87% [304b].

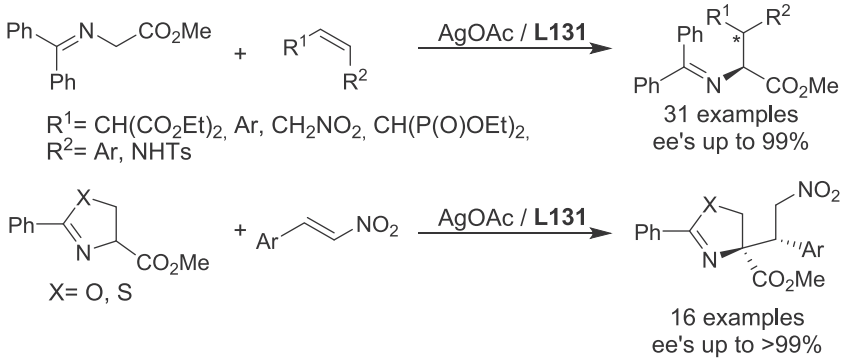
ThioClick-ferrophos ligand **L131** (Fig. 43), developed by Fukuzawa's group, was screened in the Ag-catalyzed Mannich reactions of *N*-tosylimines with a glycine Schiff base [305a] with moderate diastereoselectivities and high enantioselectivities (dr's up to 7:3 and ee's up to 98%) (Scheme 84). Ag/**L131** also efficiently catalyzed the 1,3-cycloadditions of azomethine ylides using a variety of activated alkenes providing similar enantioselectivities than those



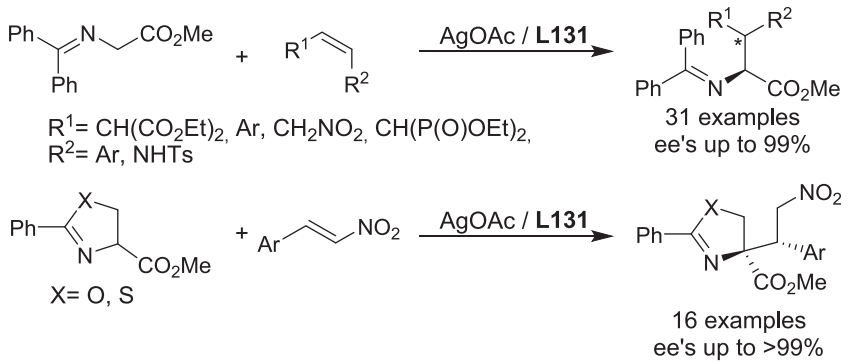
Scheme 82. Representative applications of ferrocenyl-based Fesulphos ligand **L128** in asymmetric catalysis.



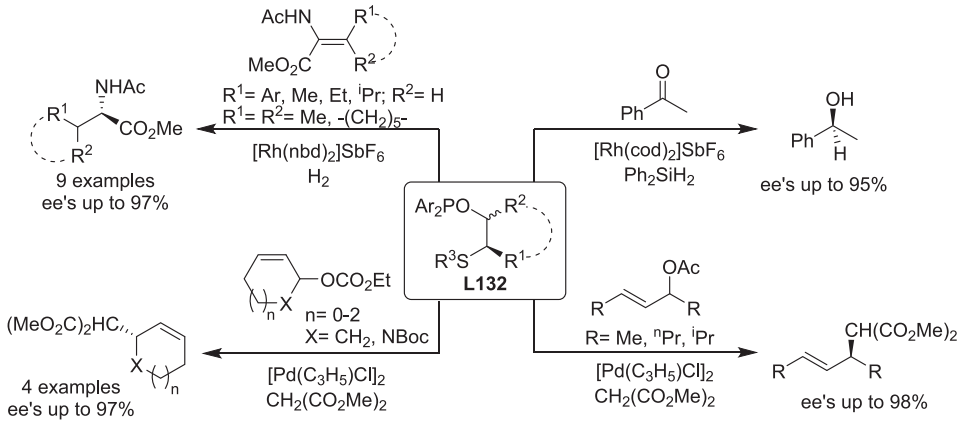
Scheme 83. Pd-catalyzed allylic substitution reactions using ferrocenyl-based ligands **L129** and **L130**.



Scheme 84. Representative examples of Ag-catalyzed conjugate addition with ferrocenyl-based P-S ligand **L131**.



Scheme 85. Synthesis of phosphinite-thioether ligands **L132**.



Scheme 86. Representative applications of Evans' phosphinite-thioether ligands **L132** in asymmetric catalysis.

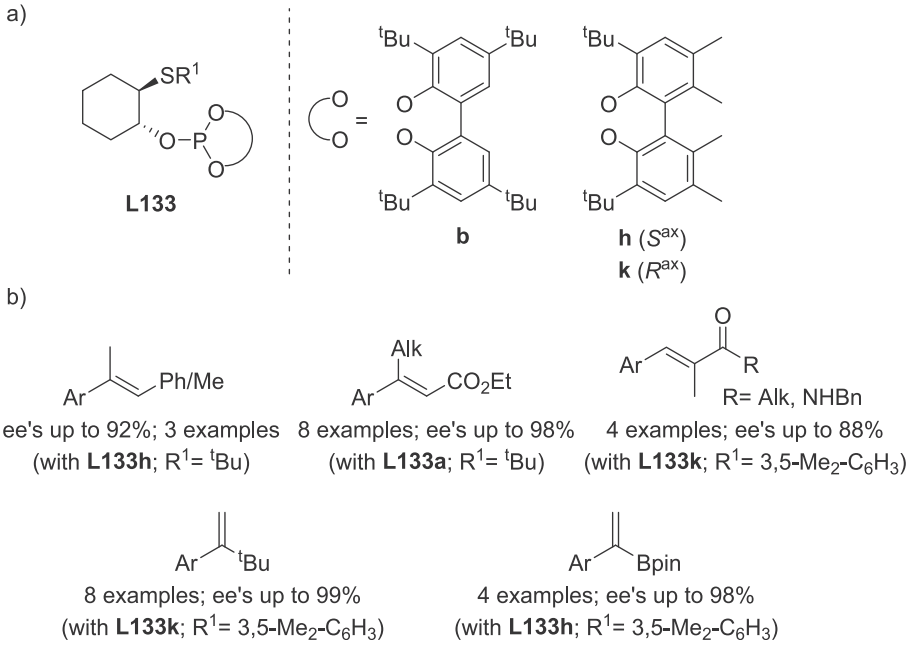


Fig. 44. a) Phosphite-thioether ligands **L133**. b) Selected asymmetric hydrogenation results using Ir/**L133** catalysts.

achieved with the Cu/Fesulphos **L128** catalyst (ee's up to 99%) [305b-g]. Later, the same group also found that Ag/**L131** catalyzed the conjugate addition of several types of Michael acceptors to different imino esters, oxazoline-esters and related substrates (ee's up to >99%; Scheme 84) [305i-l]. Finally, by switching the positions of the thioether and the phosphine moieties high

enantioselectivities can also be reached in Pd-catalyzed allylic substitution of *rac*-1,3-diphenylallyl acetate with dimethyl malonate, benzylamine and some benzylic alcohols (ee's up to 90%) [305m].

An additional group of powerful P–S ligands are those having the two donor functionalities linked by two carbon atoms [296,306]. One of the first successful examples of such a group of ligands can be found with phosphinite-thioether ligands **L132**, with a very simple ligand backbone (Scheme 85) [307] These ligands are prepared from the corresponding chiral epoxide via epoxide ring opening with the corresponding thiol or from the corresponding Evan's *N*-acyl carboximide in few steps to provide the corresponding thioether-alcohol. Treatment of the later compounds with the desired chlorophosphine gives access to ligands **L132** (Scheme 85).

The Evans' group demonstrated that by optimizing the different ligand parameters (thioether and phosphinite substituents as well as the ligand backbone) it is possible to control the thioether coordination to the metal. As a result, ligands **L132** constitutes one of the early-developed P–thioether ligands that provided excellent results to several asymmetric reaction, such as the Rh-catalyzed hydrosilylation of ketones and hydrogenation of alkenes [307c] and the Pd-catalyzed allylic substitutions [307a,b] (Scheme 86). However, the substrate/reagents scope was still low.

Much later our group decided to replace the phosphinite moiety in the Evans' ligands **L132** by the benefits of biaryl phosphite groups (ligand **L133**; R^1 = ^{t}Bu, 2,6-Me_2Ph; Fig. 44a). Air stable ligands **L133** were fruitfully applied in the hydrogenation of unfunctionalized alkenes, including terminal olefins and olefins with poorly coordinative groups (ee's up to 99%; Fig. 44b) [308]. The catalysis were carried out using the preformed catalyst precursors [Ir(cod)(**L133**)]BAr_F, prepared using the same methodology than for [Ir(cod)(**L8**)]BAr_F. One single isomer was found except for complexes containing ligands with a flexible biphenyl moiety, due to the tropoisomerization of these units. The X-Ray structure confirms the coordination of the ligand throught the P and S atoms to the metal, whith a twist-boat conformation of the chelate ring and a pseudoaxial disposition of the thioether moiety. It should be highlighted that the use of Ir/**L133** allowed the pioneering reduction of 1,1′-disubstituted aryl-substituted boronic esters. Interestingly, the enantioselectivity is mainly determined by the thioether substituent and the configuration of the phosphite group. The replacement of the phosphite moiety by several phosphinite groups provided lower ee's. The study of the reaction intermediates by HPNMR (high pressure NMR) spectroscopy and DFT calculations allowed to found the active Ir-dihydride alkene species, which follows the classical Halpern-mechanism, in which the minor species are the most active ones [309]. In addition such mechanistic study provided helpful insights to understand the influence of the different ligand elements on enantioselectivity.

Other relevant families of P–S ligands having a two carbon atoms linker are the families of P-thioethers ligands **L134** and **L135** and the phosphoroamidite-thioether ligands **L136–L138** (Fig. 45). They resemble very much to the Evans' ligands in the simplicity of the ligand backbone, which aids the recognition of key intermediates by NMR as well as speeds up the ligand optimization by DFT calculations. Ligands were prepared from the corresponding epoxides (ligands **L134** and **L135**) or aziridine (compounds **L136–L138**) following the same synthetic strategy as for the synthesis of Evan's ligands.

The arylglycidol-based phosphinite-thioether ligands **L134** (R^1 = Ar, ^{t}Bu, Ad, Cy; R^2 = Ph, Tol, Cy, Mes, R^3 = Me, Tr, Bn) (Fig. 45) have found to be useful in allylic substitutions and hydrogenation reactions [310]. A practical advantage offered by **L134** is the fact that they are made in three steps from accessible arylglycidols [310a]. In addition, both enantiomers of these P,S-ligands can be reached by simple selection of the tartrate ester used in the Sharpless epoxidation leading to the arylglycidol. Pd/**L134** catalytic systems provided similar high enantioselectivities than Evans' ligands **L132**, working under milder reactions conditions, room temperature and shorter reactions times, in the allylic substitution of di- and trisubstituted linear allylic acetates with a range of malonate-type nucleophiles and amines, and also extended the nucleophile scope to the less studied aliphatic alcohols [310a]. Ligands **L134** were also used in the Rh-catalyzed hydrogenation of dehydroamino acids, albeit with lower success than related ligands **L132** [310b]. Much more notable are the results reached in the Ir-catalyzed hydrogenation of unfunctionalized olefins [310c], in spite of the known difficulties of enantiocontrol associated to substrates lacking metal-coordinating functionalities. [Ir(cod)(**L134**)]BAr_F complexes were therefore able to reduce a large number of olefins, with similar ee's than the best ones attained with Ir–P,N catalysts (43 examples, ee 's up to 99%; Fig. 46). Unlike ligands **L133** with a cyclohexane-based backbone, the use of phosphite analogues led to lower enantioselectivities than with phosphinite-thioether ligands **L134**. The crystal structures of these Ir-catalyst precursors showed that while ligands with a phosphite moiety had the thioether group in equatorial, in the related phosphinites the thioether was in axial. This contrasts with the

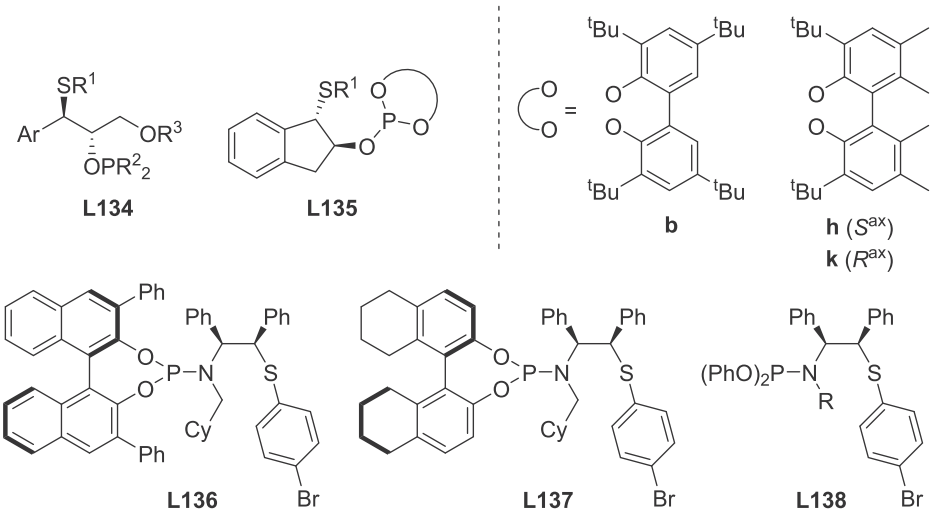


Fig. 45. P-thioether ligands **L134–L138**.

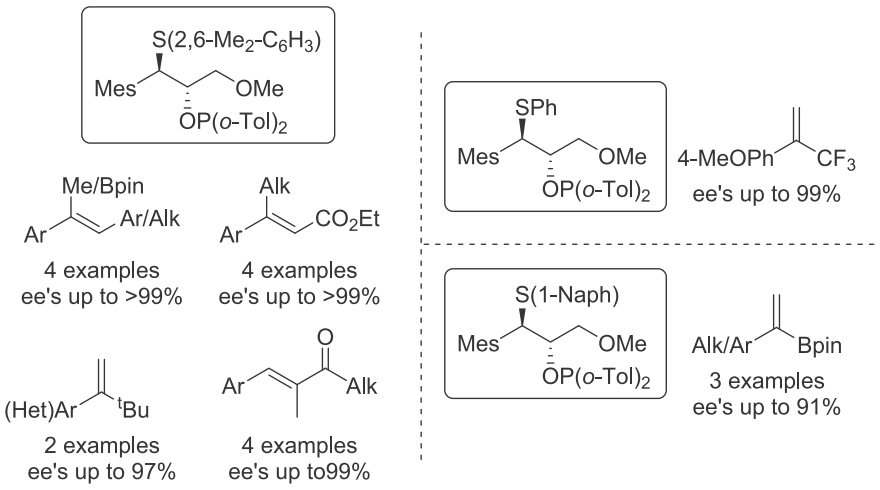
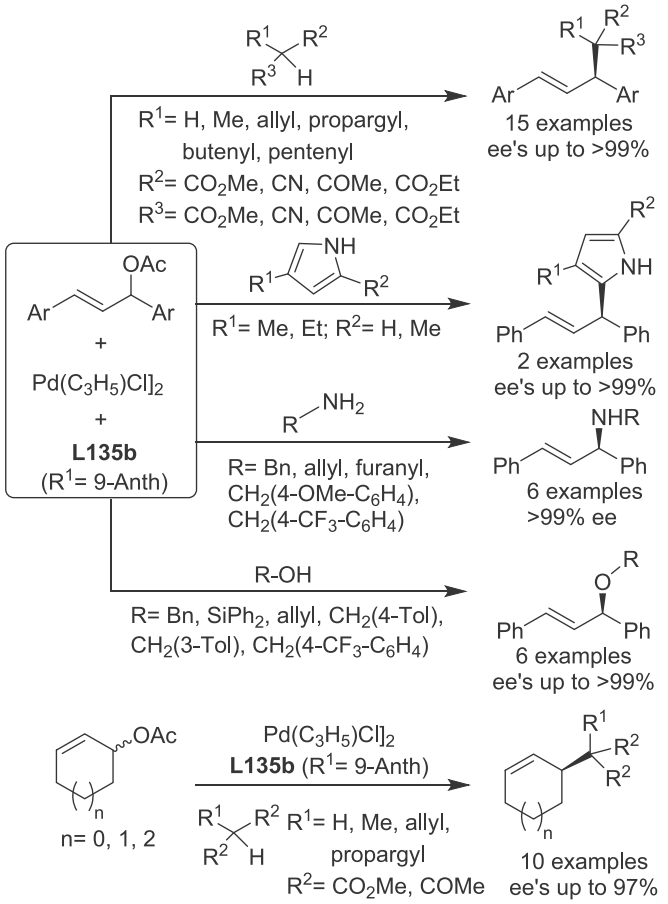


Fig. 46. Summary of the asymmetric hydrogenation results using Ir/**L134** catalysts.

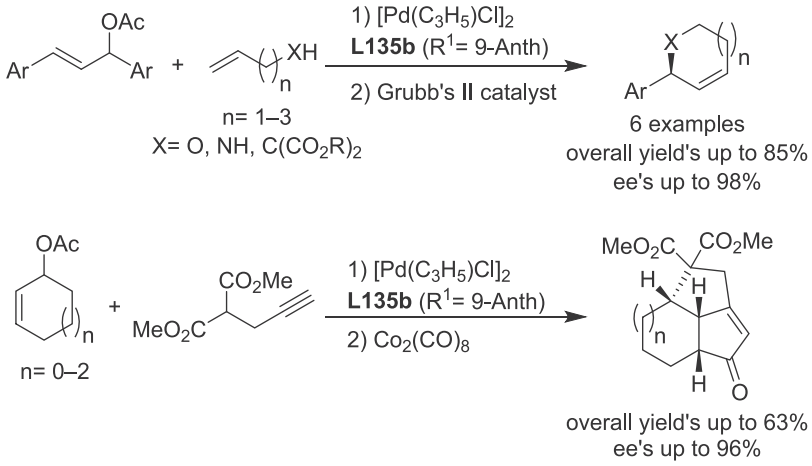


Scheme 87. Pd-catalyzed allylic substitution of disubstituted linear and cyclic substrates with C- N- and O-nucleophiles using indene-based phosphite-thioether ligand **L135b** (R^1 = 9-Anth).

pseudoaxial arrangement of the thioether substituent in Ir-structures with cyclohexane-based phosphite–thioether commented above, that also form a six-membered chelate ring. This behaviour seems to show that the disposition of the thioether substituent (in this case, axial disposition) is important to obtain high enantioselectivity. DFT calculations indicated that the reaction proceeds via an Ir(III)/Ir(V) catalytic system in which the enantioselectivity-determining step is the migration of a hydride to the coordinated alkene. In addition, the analysis of the transition states allowed to develop a quadrant model system that facilitates rationalization of the catalytic results. These DFT studies were also crucial to guide the ligand optimization process towards high enantioselectivities. They indicated the need of ligands with a mesityl group at the carbon next to the thioether group (Ar = 2,4,6-Me_3-C_6H_2) and a bulky aromatic thioether groups (2,6-dimethylphenyl or 1-naphthyl moieties, depending on the substrate). The application of mesityl-containing ligands **L134** are therefore crucial to achieve the highest ee's for a range of olefins including examples containing poorly coordinative groups and terminal alkenes (ee's up to >99%; Fig. 46). Remarkably, the catalytic systems could be also recycle up to 3 times with 1,2-propylene carbonate.

Recently, phosphite–thioether ligands **L135** (R^1 = ^{i}Pr, ^{n}Pr, ^{t}Bu, Ph, 2,6-Me_2Ph, 4-CF_3Ph, 4-MeOPh, 9-Anth) (Fig. 45), prepared in three steps from indene, were designed to maximize the substrate range in Pd-catalyzed allylic substitution reactions [18d]. The simple indene backbone facilitated both DFT and NMR studies of Pd-allyl key intermediates, which were used to optimize the thioether and phosphite substituents in the search of the best catalyst. As a result, catalyst Pd/**L135b** (R^1 = 9-Anth) is one of the very few catalysts able to afford excellent enantioselectivities (typically >95% ee) for a large number of unhindered and hindered allylic acetates with an array of C, N and O nucleophiles (Scheme 87; 40 compounds in total). Notably, the excellent performance of **L135b** was maintained using 1,2-propylene carbonate as solvent. Mechanistic investigations provided an elucidation into the exceptionally rare wide substrate scope. Enantioselectivity is therefore controlled by the relative stability of the Pd-η^3-allyl intermediates and the electrophilicity of the allylic terminal carbons. More concretely, Pd/**L135b** catalytic system not only favors the preferential formation of one of the possible Pd-allyl intermediates, but also speeds up the nucleophilic addition at the terminal allylic carbon atom *trans* to the phosphite moiety of most stable Pd-allyl intermediate. In addition, the authors took advantage of the great diversity of the allylic substitution products arising from the introduction of malonates having allyl and propargylic groups for the preparation of chiral functionalized carbo- and heterocycles as well as polycarbocyles. The former compounds were prepared by means of ring-closing metathesis, while the latter were prepared via Pauson-Khand reaction (Scheme 88).

Phosphoroamidite-thioether ligands **L136**–**L138** (Fig. 45), easily prepared in three steps from (2*S*,3*S*)-2,3-diphenylaziridine, have also been effectively applied in many asymmetric transformations



Scheme 88. Preparation of functionalized carbo- and heterocycles as well as polycarbocycles via ring-closing metathesis and Pauson-Khand reactions, respectively.

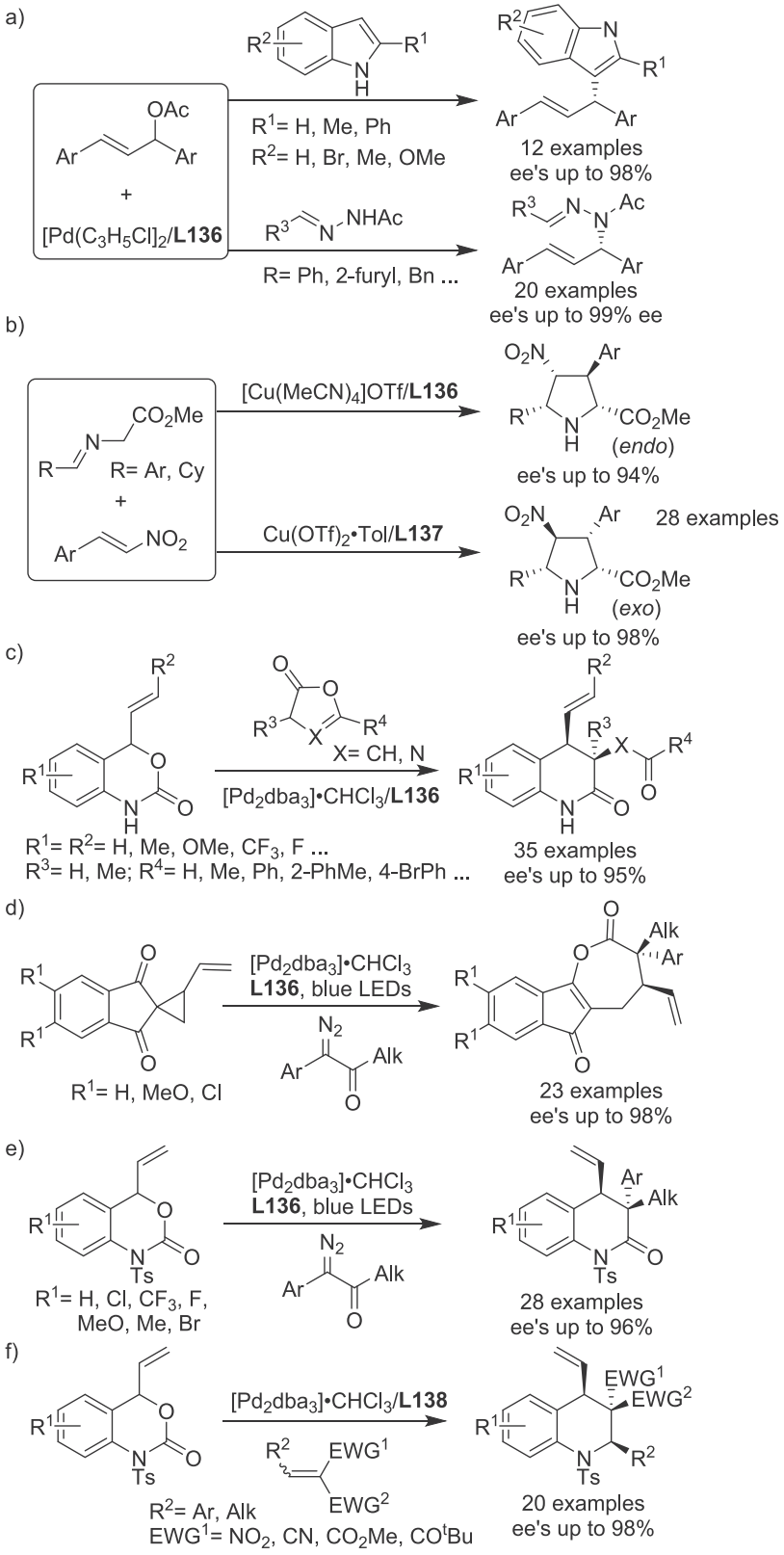
[311]. Thus, ligand **L136** been fruitfully applied in the Pd-catalyzed allylic substitution of 1,3-diarylallyl acetates with a collection of indoles and hydrazones (ee's up to 98; Scheme 89a) [311a,b]. Similar high ee's were also achieved in the allylic substitution of *rac*-1,3-diphenylallyl acetate with benzyl amine and benzyl alcohol [311a]. Ligand **L136** also evidenced to be highly competent in both Cu- and Pd-catalyzed cycloaddition reactions. Thus, for instance, catalyst Cu/**L136** afforded a range of polysubstituted *endo* pyrroles in high diastereo- and enantioselectivities *via* 1,3-cycloaddition of azomethine ylides and nitroalkenes (Scheme 89b) [311c]. Interestingly, the use of related H_8-Binol-derived ligand **L137** (Fig. 45) led to the formation of the *exo* pyrroles (Scheme 89b) [311c. Catalyst Pd/ **L136** was successfully used in inverse-electron demand decarboxylative [4 + 2] cycloaddition reactions. Thus, highly functionalized dihydroquinol-2-ones were produced with excellent selectivities (d.r. > 20:1 and ee's up to 95%; Scheme 89c) [311d]. Pd/**L136** has recently found to be beneficial in the visible-light-driven [5 + 2] cycloaddition of vinylcyclopropanes with α-diazoketones. This new methodology provides facile access to highly functionalized 7-membered ring lactones (d.r.'s up to 16:1 and ee's up to 96%; Scheme 89d) [311e]. Similarly, a series of quinolinones were synthesized via Pd-catalyzed light-driven decarboxylate [4 + 2] cycloaddition of tosylated vinyl carbamates with *in situ* generated ketenes (ee's up to 96% ee; Scheme 89e) [311g]. It should be mentioned that some Pd-catalyzed decarboxylative cycloaddition reactions do not requires the presence of a chiral biaryl phosphoroamidite moiety (ligand **L138**; Fig. 45). Thus, a range of tetrahydroquinolines bearing three contiguous stereocenters were efficiently prepared using Pd/**L138** by reaction of benzoxazinanones with activated alkenes (d.r.'s typically >95:5 and ee's up to 98% ee; Scheme 89f) [311f].

Carbohydrates have also been used as platforms for preparing P-thioether ligands. The use of carbohydrates is advantageous since they are cheap and readily available. Moreover, they have a well-established chemistry and they are highly functionalized, which favor the synthesis of highly modular ligand libraries and enable an easy ligand optimization for each particular substrate and reaction [312]. Khiar's group were the first to apply carbohydrate P–thioether ligands in catalysis. They used pyranoside ligands **L139** and **L140** (Fig. 47) in the Rh-catalyzed hydrogenation of some enamides (ee's up to 98%) and in the Pd-catalyzed allylic substitution of benchmark 1,3-diphenylallyl acetate (ee's up to 96%) [313]. The use of pseudo-enantiomeric ligands **L139** and **L140** allowed the preparation of both isomers of the products, without having to prepare the enantiomeric ligands from the expensive L-sugar series.

Furanoside phosphite-thioether ligands **L141** and **L142** (R = Ph, Me, ^{i}Pr, ^{t}Bu, 4-MePh, 4-CF_3Ph, 2,6-Me_2Ph) (Fig. 47) were prepared from D-xylose in multigram scale. Treatment of D-xylose with I_2 in acetone followed by deprotection of the more reactive isopropylidene group led to 1,2-*O*-isopropylidene-α-D-xylofuranose (key for the synthesis of ligands **L141**), which was easily transformed to the ribofuranoside anologue (key for the synthesis of **L142**). From both xylo- and ribofuranoside diols, ligands **L141** and **L142** were prepared by introducing the thioether group at the primary alcohol, via an SN_2 reaction, followed by treatment with the desired phosphorochloridite (Scheme 90).

Phosphite-thioether ligands **L141** and **L142** (Fig. 47) represented the first use of P,S-ligands in the asymmetric hydrogenation of unfunctionalized olefins or with poorly coordinative groups [314]. The catalysis were carried out using the preformed catalyst precursors [Ir(cod)(**L141–L142**)]BAr_F, prepared using the same methodology than for [Ir(cod)(**L8**)]BAr_F. The X-Ray analysis indicated that in contrast to previously commented Ir/P-S complexes, such as [Ir(cod)(**L133**)]BAr_F, the thioether substituent adopts an equatorial disposition. In this context, the use of ribofuranoside ligand **L142k** (R = 2,6-Me_2-C_6H_3) provided high ee 's in the hydrogenation of methyl stilbene-type olefins, Z-trisubstituted olefins and triarylsubstituted olefins (Fig. 48). The latter provides a feasible entry point to valuable compounds containing diarylmethine chiral centers. Ir/**L142k** catalytic system also led to high ee 's in the reduction of many 1,1′-disubstituted olefins. In addition, both enantiomers of the reduced products can be easily attained by changing the configuration of the biaryl phosphite moiety. Another interesting feature of this ligand is that the furanoside scaffold allowed to restrict efficiently the tropoisomerization of conformationally flexible biphenyl phosphite moieties. For most of the substrates studied, similar high enantioselectivities have therefore been reached with the cheap achiral bulky biphenyl phosphite moiety (ligand **L142b**). Again, these catalysts work well in 1,2-propylene carbonate, helping the catalysts to be recycled several times. Finally, the use of phosphinite or phosphine analogues led to lower enantioselectivities.

When ligands **L141** and **L142** were tested in allylic substitution of linear hindered 1,3-disubstituted allylic acetates with a range of C-nucleophiles (e.g. α-substituted malonates, diketones, cyano esters . . .) and a selection of O- and N-nucleophiles, high enantioselectivities were attained using Pd/**L142k** (R = 2,6-Me_2-C_6H_3) catalyst (ee's up to >99%; Scheme 91) [18b,315]. To achieve high



Scheme 89. Representative applications of phosphoroamidite-thioether ligands **L136**–**L138** in asymmetric catalysis.

enantioselectivities for more demanding cyclic and unhindered linear substrates, the use of xylofuranoside ligand **L141h** (R = 1-Naph) was required (ee's up to >99%; Scheme 91). This feature was rationalized with the aid of NMR studies of the Pd-allyl intermediates and DFT calculations of the TSs using cyclohex-2-en-1-yl acetate as model substrate. These studies demonstrated how the size of

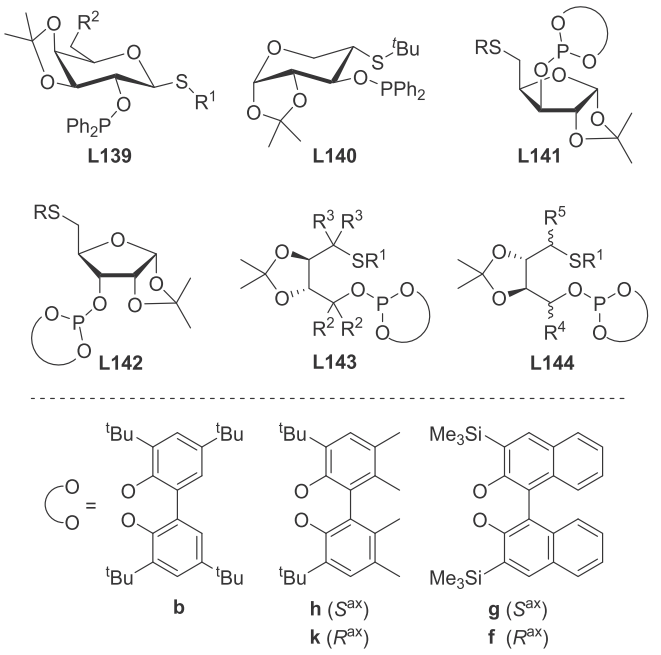


Fig. 47. Carbohydrate-based P-thioether ligands **L139–L144**.

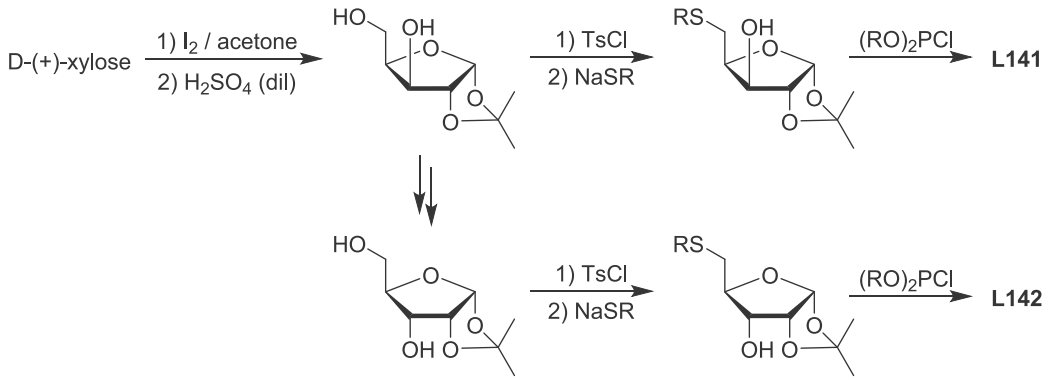
the chiral pocket in the catalytic species is affected by the configuration at C-3 of the furanoside backbone. Thus, by using catalyst Pd/**L141h**, only one of the two possible *syn*/*syn* diastereomer Pd-1,3-cyclohexenyl-allyl intermediate is predominantly formed (dr's > 20:1) [315].

Finally, Taddol-type phosphite-thioether ligands were made from L-tartaric acid (ligands **L143**) and D-mannitol (ligands **L144**) and screened in several asymmetric transformations (Fig. 47) [316]. Several positions of the ligands (R^1 = Me, 1-Ad, Ph, ^{t}Bu, 2,6-Me_2Ph, 1-Naph, 2-Naph; R^2 = Me, H, Ph; R^3 = Me, H, Ph) can be easily varied through highly efficient methods. This methods also allowed to generate at will new stereogenic centers next to the donor functionalities (R^4 = H, Me, CH_2OTBDMS, CH_2OTBDPS, CH_2OTIPS, CH_2OTr; R^5 = H, Me). [Ir(cod)(**L144f**)]BAr_F (R^1 = 1-Naph, R^4 = (*R*)-CH_2OTBDMS and R^5 = H) provided ee's up to 95% in the hydrogenation of *trans*-methylstilbene-type substrates, β,β'-disubstituted unsaturated esters, α,β-disubstituted enones, lactones and lactams bearing an exocyclic double bond [316b]. Note that for most of these substrates the selenoether version of the ligands attained slightly higher enantioselectivities than the thioether analogues [316b]. The use of catalyst [Ir(cod)(**L143h**)]BAr_F (R^1 = 1-Naph; R^2 = R^3 = H) was necessary to maximize ee's in the reduction of terminal olefins (ee's up to 99%) [316b]. Interestingly, by using [Ir(cod)(**L144g**)]BAr_F (R^1 = 1-Naph, R^4 = (*S*)-CH_2OTBDMS and R^5 = H) enantioselectivities up to 99% were attained in the hydrogenation of cyclic β-enamides (Scheme 92a). Interestingly, the exchange of the metal from Ir to Rh led to the preferential formation of the opposite enantiomer (Scheme 92a) [316a]. This is one of the rare examples of enantioswitchable metal-catalyzed transformation. This allows, for instance, access to both enantiomers of the precursors for the synthesis of rotigotine (used in the treatment of Parkinson's disease) [41a] and alnespirone (a selective 5-HT1A receptor full agonist) [41d]. In addition, the use of [Rh(cod)(**L144f**)]BF_4 (R^1 = 1-Naph, R^4 = (*R*)-CH_2OTBDMS and R^5 = H) and [Rh(cod)(**L144g**)]BF_4 (R^1 = 1-Naph, R^4 = (*S*)-CH_2OTBDMS and R^5 = H) catalyst proved also be useful in the asymmetric hydrogenation of functionalized olefins, such as dehydroamino acids (Scheme 92b) [316b]. This is again a quite unique feature, since the reduction of both unfunctionalized and functionalized alkenes follows very different catalytic cycles, and each type of substrate has been shown to require a particular catalyst type (Rh/PP-catalysts for functionalized and Ir/PN-catalysts for unfunctionalized) for optimal results [35e].

Interestingly, the use of ligand **L144g** (R^1 = 1-Naph, R^4 = (*S*)-CH_2OTBDMS and R^5 = H) and its derivatives containing different silylated protecting groups (R^4 = (*S*)-CH_2OTBPMS and (*S*)-CH_2OTIPS) also furnished high enantioselectivities in the Pd-catalyzed allylic substitutions (ee's up to 99%) [316c]. Interestingly, for cyclic substrates it is possible to select the enantiomeric series of the substitution product, as in the case of the hydrogenation of terminal alkenes, by swapping the configuration of the biaryl phosphite moiety.

5.2. P-sulfoxide ligands

Another strategy to overcome the problem of controlling the configuration of the S-thioether group after coordination to the metal center is the exchange of the thioether group by a chiral sulfoxide. Fig. 49 shows the most successful P-sulfoxide ligands developed to date. Ligands **L145** and **L146** were prepared from the corresponding bromo and 1,3-dibromobenzenes, which reacts with (*R*)-*tert*-butyl *tert*-buthanethiosulfinate to yield the corresponding sulfoxides. From the latter, the desired phosphine moiety was diastereoselectively introduced via *ortho*-lithiation (Scheme 93). Similarly, reaction of two equivalents of (*R*)-(*tert*-butylsulfinyl)benzene with 1-(dichlorophosphaneyl)piperidine led to ligand **L148**. Ligand **L147** was efficiently prepared from (2*S*, 3*S*)-2,3-diphenyl aziridine. Aziridine ring opening with 4-Br-thiophenol followed by diastereoselective oxidation led to the corresponding amino-sulfoxide compound. Reaction of the latter with 2-(diphenylphosphanyl)benzoic acid gives access to ligands **L147** (Scheme 93).



Scheme 90. Synthesis of furanoside phosphite-thioether ligands **L141** and **L142**.

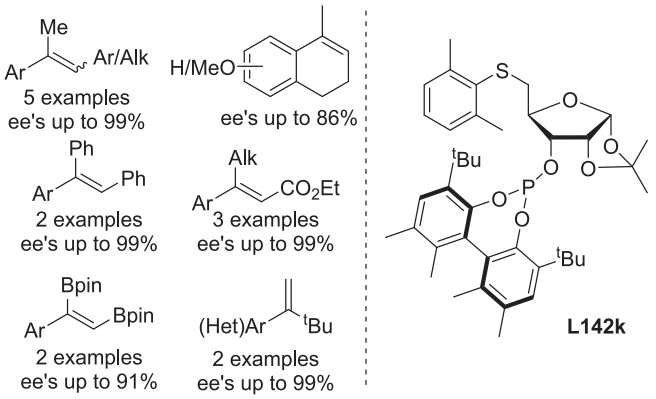


Fig. 48. Representative catalytic result of the application of Ir/**L142k** catalytic system in the asymmetric hydrogenation.

Ligands **L145** were the first successful application of P-sulfoxide ligands to several asymmetric reactions [317]. Thus, Rh/**L145** provided high enantioselectivities in the Rh-catalyzed 1,4-addition of arylboronic acids to a large number of electron-deficient olefins (up to 98% ee; Scheme 94a) [317a]. The presence of a second sulfoxide moiety at the other *ortho* position of the phosphine group (ligand **L146**; R = Ph) allowed the construction of chiral γ,γ-diaryl substituted carbonyl compounds via the same reaction, that led to the preparation of bioactive compounds such as sertraline (ee's up to >99%; Scheme 94b and Section 6) [318]. Ligands **L145** also allowed the first Cu-catalyzed formation of α-aryl-β-borylstannanes by means of a three-component borylstannation of aryl-substituted alkenes (Scheme 94c) [317b]. Such transformation relies in the efficiency in controlling the stereochemistry of B-Cu addition as well as its ability to facilitate the transmetallation of enantioenriched alkyl-Cu species with retention of configuration.

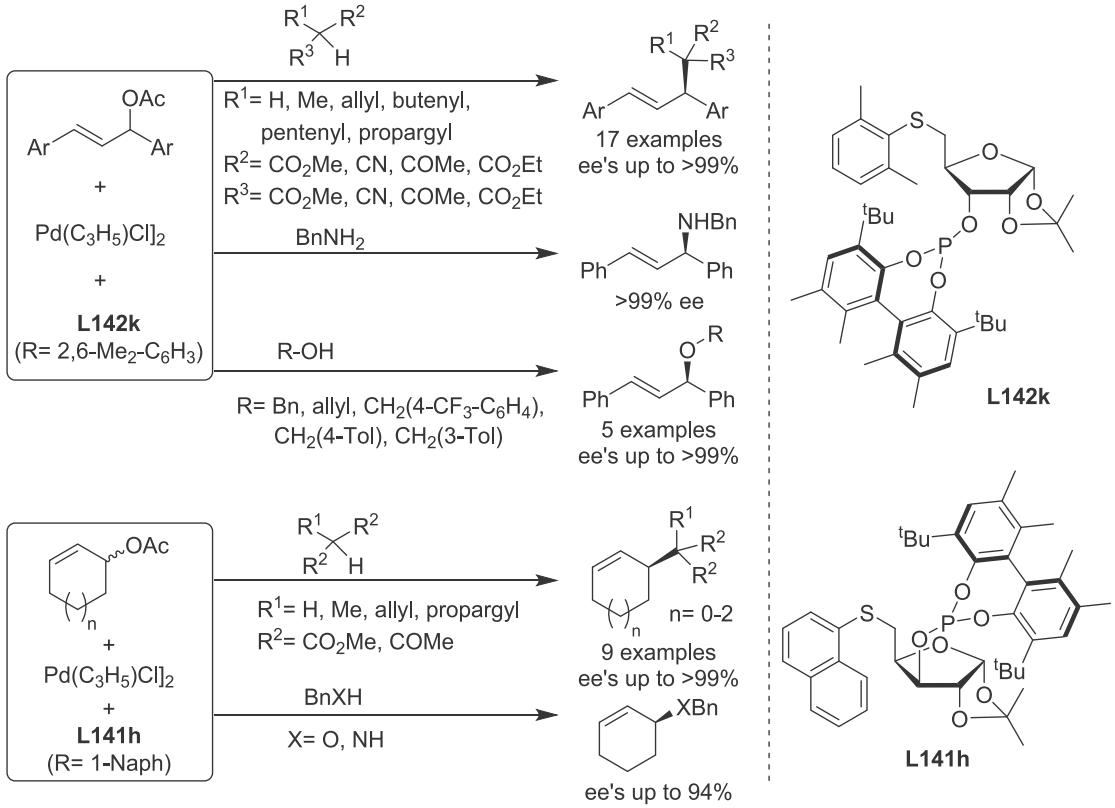
More recently, an efficient cooperative Cu/Pd-catalyzed asymmetric allylboration of alkenes has been reported (Scheme 94d) [317c]. The application of CuOAc/**L145** (R^1 = O^iPr, R^2 = ^iPr) in combination with Pd(dppf)Cl_2 catalysts allowed the three-component reaction of styrenes, $B_2(pin)_2$ and allyl carbonates to be done with ee's as high as 97%.

Phosphine-sulfoxide ligand **L147** (Fig. 49) was fruitfully applied (ee's up to 99%) in the Pd-catalyzed allylic substitution with a very broad nucleophile scope (various malonates, including examples with different functionalities at the α-position, as well as ketoesters, amines, alcohols and indoles (Scheme 95) [319].

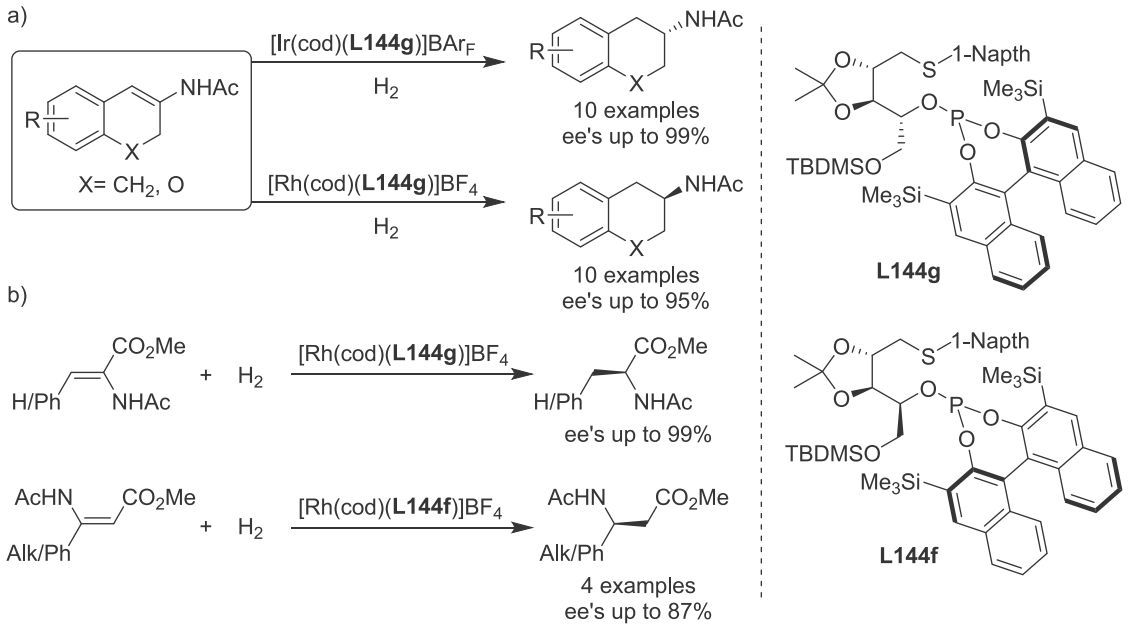
The *N*-phosphine-bis(sulfoxide) ligand **L148** (Fig. 49) have recently been used in the allylic etherification and amination of 1,3-diarylallyl acetates with benzylic alcohols and amines (ee's up to 99%; Scheme 96a) [320a]. Even more interesting are the excellent results achieved in the allylic alkylation of puzzling unsymmetrically 1,3-disubstituted allylic acetates. Pd/**L148** catalyzed the dynamic kinetic resolution of this class of substrates with indoles (up to 84% yield with up to 95% ee; Scheme 96b) [320b]. The bifunctional character of this ligand is responsible for this favorable stereocontrol. The authors postulate that the two sulfoxide moieties play a different role, while one of them tightly coordinates to Pd, the other one directs the nucleophilic attack via a hydrogen bond interaction. Finally, ligand **L148** also provided excellent enantioselectivities in the Rh-catalyzed 1,4-addition of arylboronic acids to cyclic enones (up to 98% ee) and of sodium tetraarylborates to chromenones (up to >99% ee; Scheme 96c) [320c].

6. Application in total synthesis

A ligand acquires an even greater value if, in addition to showing a high reaction and substrate applicability, it can be used in the total synthesis of relevant chiral compounds. We here compile



Scheme 91. Representative examples of the use of furanoside ligands **L141** and **L142** in the asymmetric Pd-catalyzed allylic substitution reactions.



Scheme 92. P-S ligands **L143** and **L144** in the asymmetric hydrogenation of a) cyclic β-enamides using Rh- and Ir-catalysts and b) dehydroamino acid derivatives using Rh-catalyst.

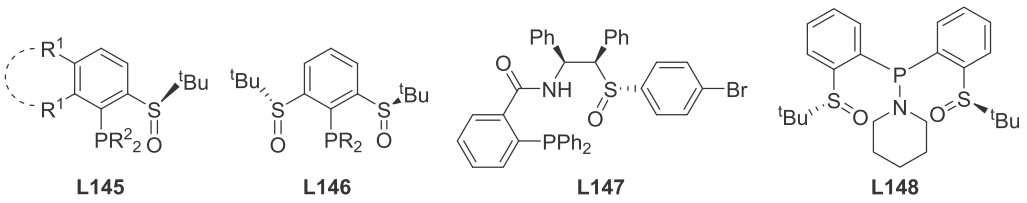
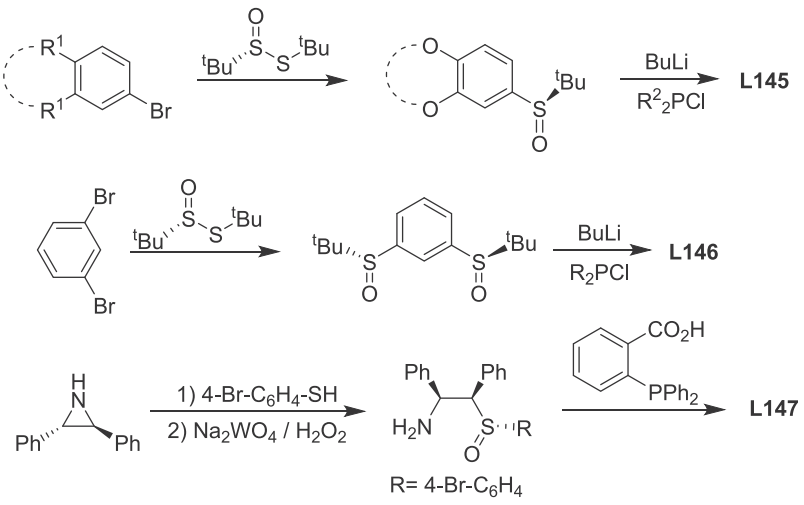
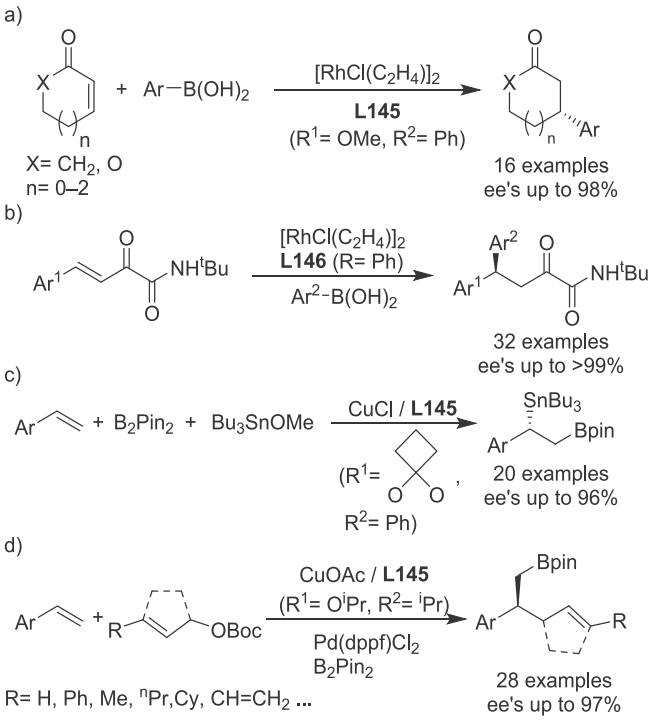


Fig. 49. Selected heterodonor P-sulfoxide ligands **L145**–**L148**.

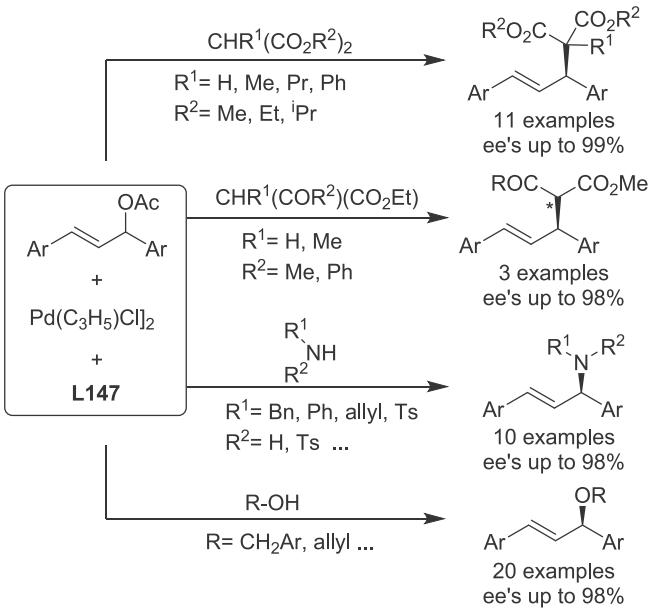


Scheme 93. Synthesis of heterodonor P-sulfoxide ligands **L145**–**L147**.

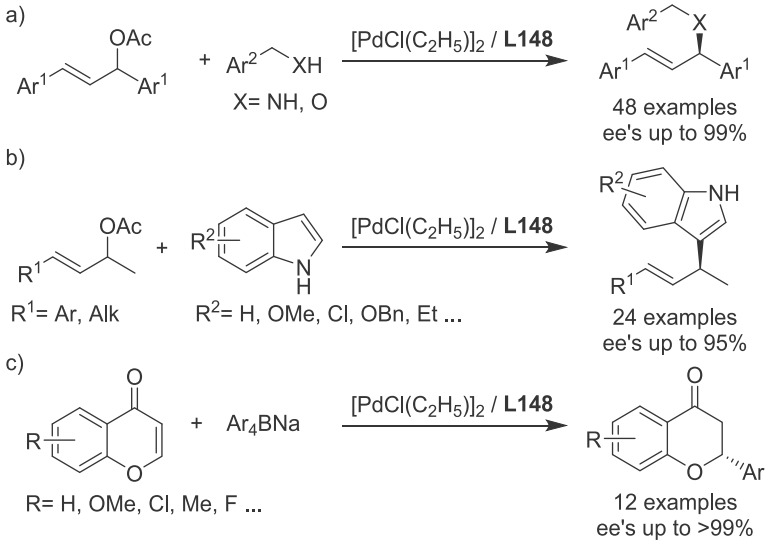
some applications of previously discussed heterodonor ligands to total synthesis (Table 1). Different P-oxazoline/pyridine/amine/imine/thiazole/imidazoline ligands, five families of P,O and three families of P-thioether/sulfoxide ligands have found applications. The examples clearly illustrate the potential of these ligands in total synthesis. However, as can be see below, only a small set of the ligands commented has found suitable application to date. Among these we have phosphine-oxazoline **L1**, with electronic withdrawing groups in the phenyl ring and the phosphine moiety of the PHOX ligand, and the spiro based-SIPHOX ligand **L32** with many applications each. The other three groups of ligands are the phosphine-amine **L75**, the phosphinite-pyridine **L107**, developed by Pfaltz, and the family of N-phosphine-thiazole ligands **L84** and **L88** developed by Andersson's group. The low application or no application for the rest of ligands may be due, in part, to the fact that research has focused mainly on finding the right ligand/s for specific asymmetric catalytic reactions. Specifically, in finding the correlation between the structure of the ligand and the catalytic



Scheme 94. Representative metal-catalyzed asymmetric transformations using phosphine-sulfoxide ligands **L145** and **L146**.



Scheme 95. Representative catalytic results using using phosphine-sulfoxide ligand **L147** in the allylic substitution of 1,3-diarylallyl acetates.



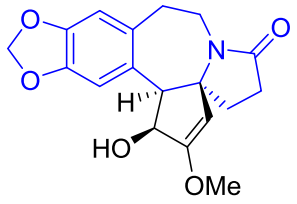
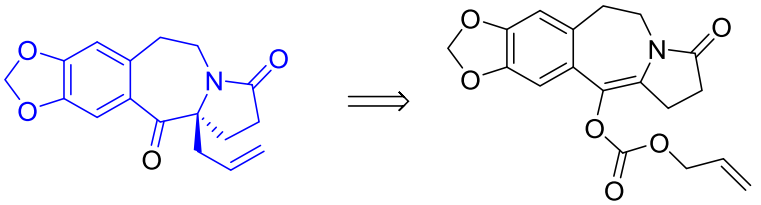
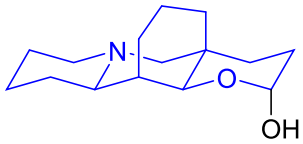
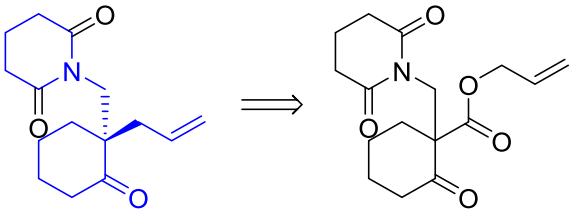
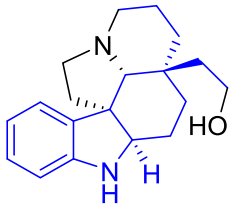
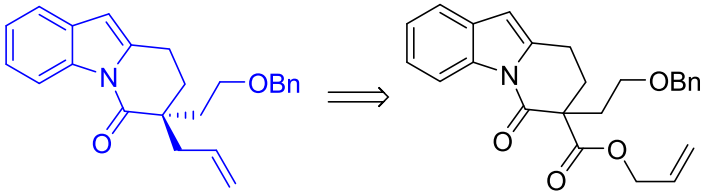
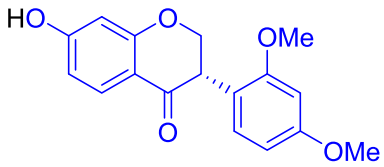
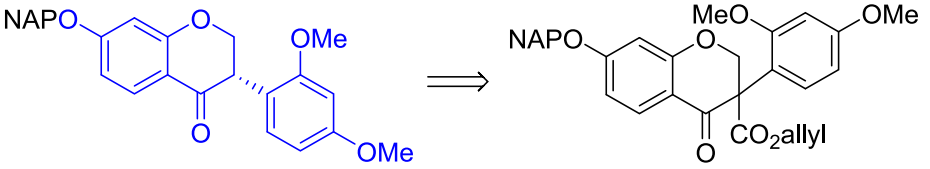
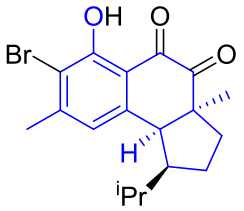
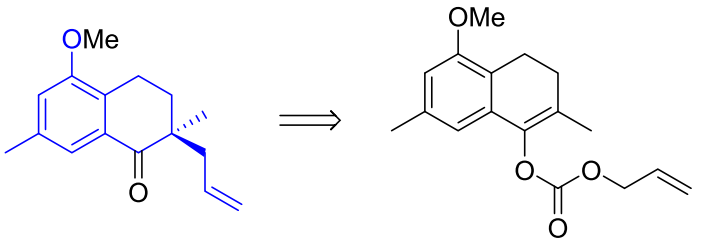
Scheme 96. Representative applications of *N*-phosphine-bis(sulfoxide) ligand **L148** in several metal-catalyzed asymmetric transformations.

capacity. Another factor to take into account is the availability of a chiral ligand. Still many of these ligands are prepared through multi-step syntheses, from costly starting material and/or toxic reagents and with low yields, which reduces their commercial interest. The progress made in the recent years to obtain ligands that are made in fewer steps and that can be manipulated in the air will hopefully widen the spectrum of chiral ligands that are commercially available.

7. Conclusions

The success of phosphine-oxazoline ligands (PHOX) inspired the development of many new P-oxazoline ligand families that cover modifications in the ligand scaffold and/or the steric /electronic characteristics of the phosphine group to the change of the phosphine group with a phosphinite or phosphite group. New development arrived also by replacing the oxazoline group by several other N-donor groups and O- and S-donor groups. The structures of these chiral heterodonor ligands have gained in diversity and new families of very efficient ligands have emerged, which have allowed to improve catalytic performance in some asymmetric transformations. In addition, the majority of these ligands maintain the short and efficient synthetic route developed with PHOX ligands. The utility of the most successful heterodonor ligand families has been described in this review. We have shown how a suitable ligand design, aided by mechanistic studies, these ligands have become versatile ligands for metal-mediated asymmetric reactions, with

Table 1
Representative applications in total synthesis using heterodonor P-N, P-S and P-O chiral ligands discussed in this review.

Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 (–)-cephalotaxine - Tratment of chronic myeloid leukemia		$Pd_2(dba)_3$ **L1**	[7c]
 (–)-myrifabral A - Natural alkaloid with antimalarial and antimicrobial properties		$Pd_2(dba)_3$ **L1**	[10e]
 (+)-limaspermidine - *Aspidosperma* alkaloid		$Pd_2(pmdba)_3$ **L1**	[10c]
 sativanone - Natural product from *Leguminosae* family		$Pd_2(dba)_3{\cdot}CHCl_3$ **L1**	[13b]
 (+)-hamerigan B - Natural product with anti-cancer and anti-viral activity		$Pd_2(dba)_3{\cdot}CHCl_3$ **L1**	[7b]

(*continued on next page*)

Table 1 (*continued*)

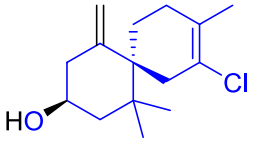
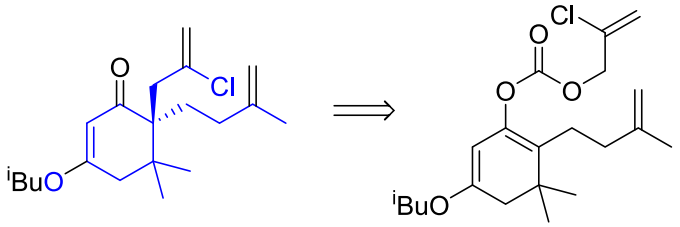
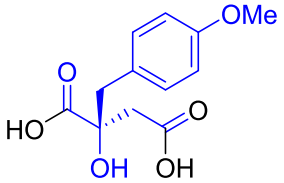
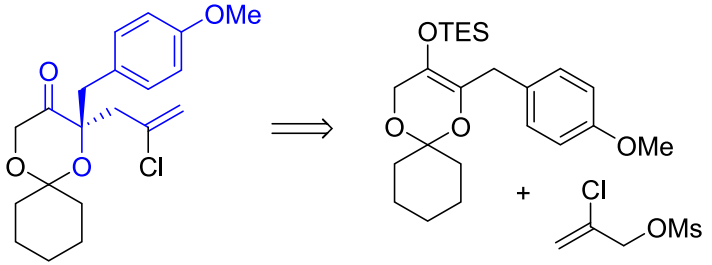
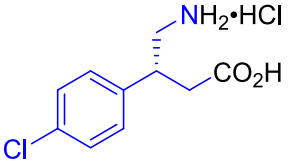
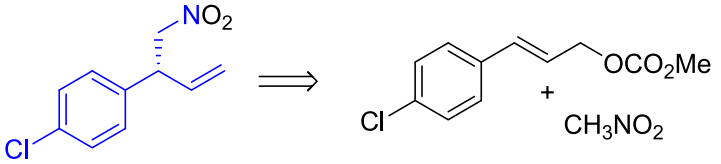
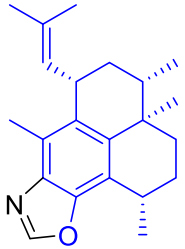
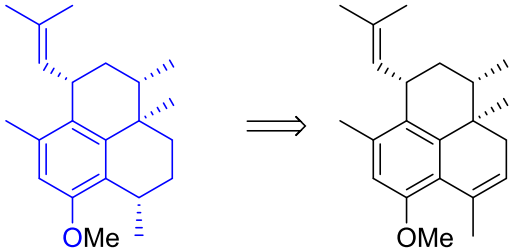
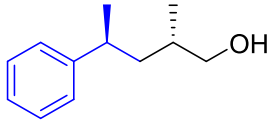
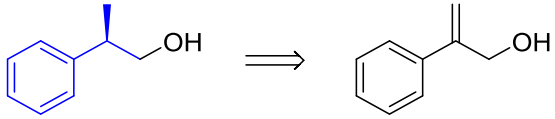
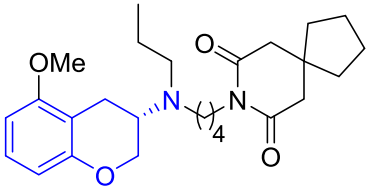
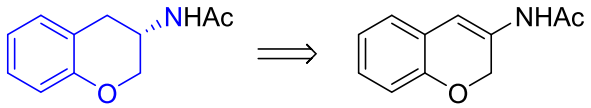
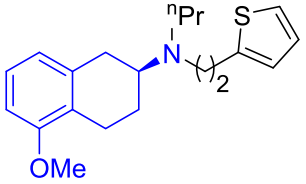
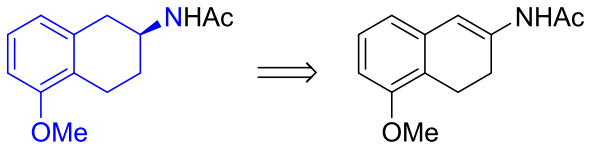
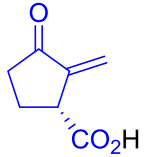
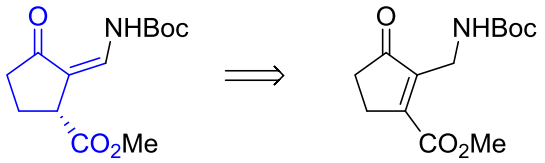
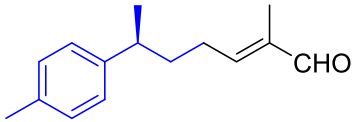
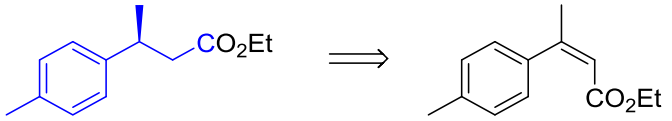
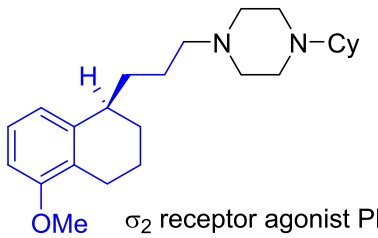
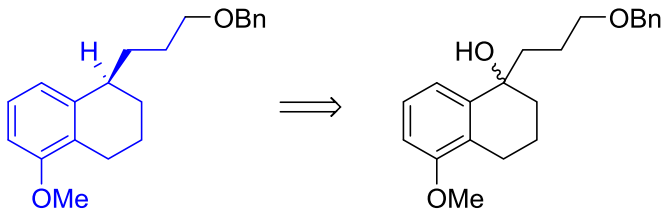
Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 (+)-elatol - Natural product with antibiofouling, antibacterial and antifungal activity		$Pd_2(pmdba)_3$ **L1**	[7a]
 (+)-eucomic acid - Natural product with skin anti-aging therapies		$Pd_2(pmdba)_3$ **L1**	[321]
 (*R*)-baclofen - Antispasmodic agent		$Pd_2(dba)_3{\cdot}CHCl_3$ (S_c,R_p,R_a)-**L14**	[322]
 pseudopteroxazole - Natural product from the marine soft coral *Pseudopterogorgia elisabethae*		[Ir(cod)**L24**] BAr_F **L24** (R^1 = *o*-Tol; R^2 = ^{t}Bu)	[53]
 (*R,S*)-pamplefeur - Commercial odorant		[Ir(cod)**L25j**] BAr_F **L25j** (R^2 = Ph)	[51a]
		[Ir(cod)**L27g**] BAr_F **L27g**	[40]

Table 1 (*continued*)

Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 alnespirone - Selective 5-HT1A receptor agonist with antidepressant and anxiolytic properties		(R^2 = R^3 = (*S*)-Ph)	
 rotigotine - Commercial dopamine agonist used in the treatment of Parkinson's disease		[Ir(cod)**L28**] BAr_F **L28** (R^2 = (*R*)-^{i}Pr; R^3 = (*S*)-^{i}Pr)	[43]
 (*R*)-sakomycin - Natural product with antibiotic activity		[Ir(cod)**L28**] BAr_F **L28** (R^2 = (*R*)-^{i}Pr; R^3 = (*S*)-^{i}Pr)	[63]
 (+)-nuciferal - Natural product from the wood oil of *Torreya nucifera*		[Ir(cod)**L29**] BAr_F **L29** (R^1 = *o*-Tol; R^2 = H; R^3 = ^{i}Pr)	[323]
 σ_2 receptor agonist PB28		[Ir(cod)**L29**] BAr_F **L29** (R^1 = *o*-Tol; R^2 = R^3 = Ph)	[64i]
		[Ir(cod)**L31**] BAr_F **L31** (R^1 = Ph;	[71a]

(*continued on next page*)

Table 1 (*continued*)

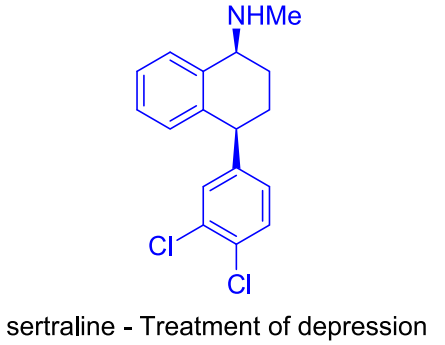
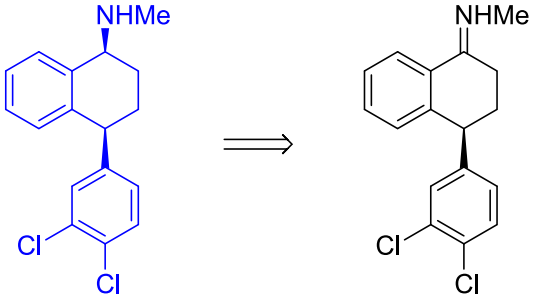
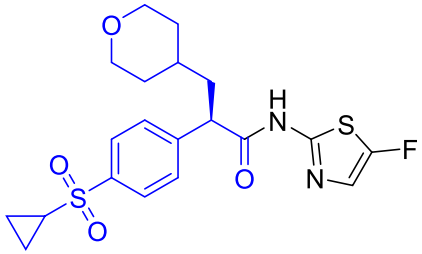
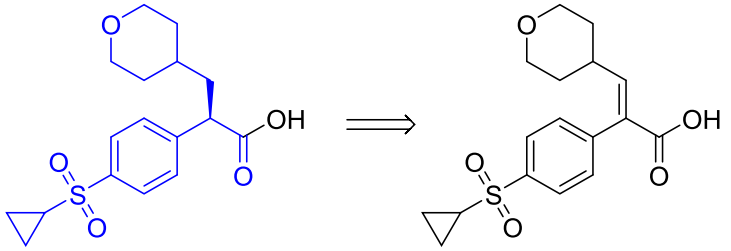
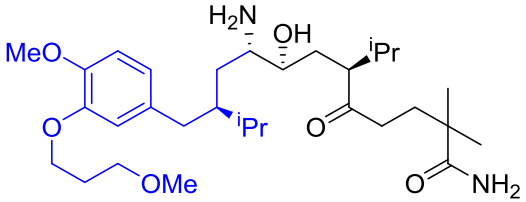
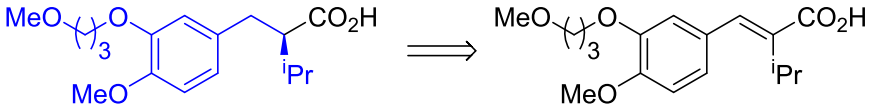
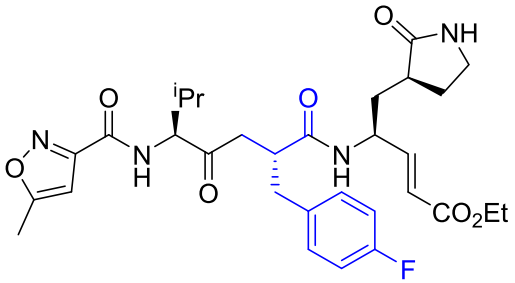
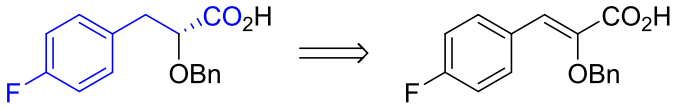
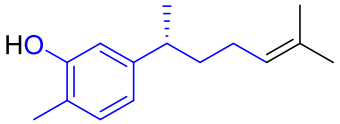
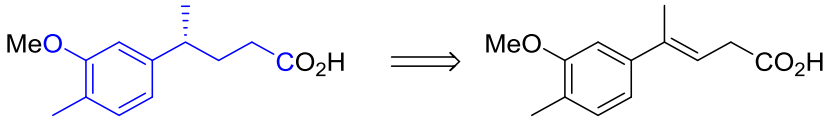
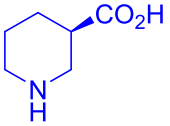
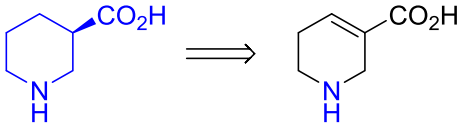
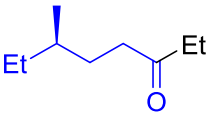
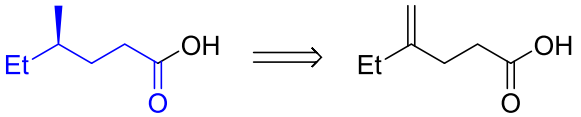
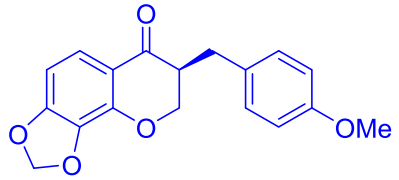
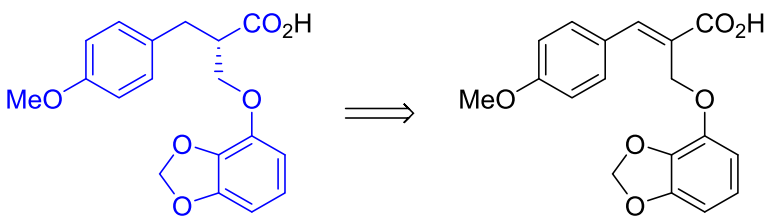
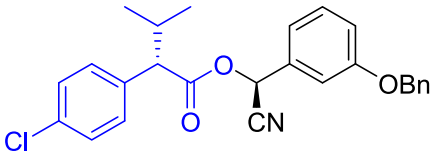
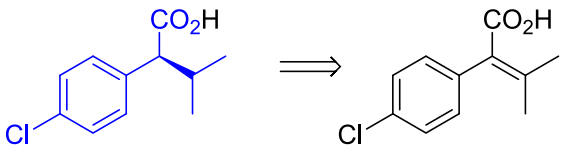
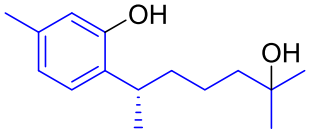
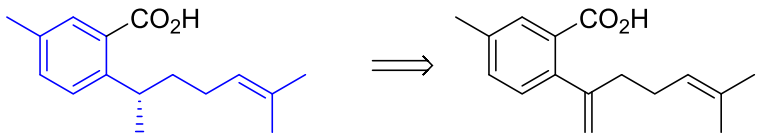
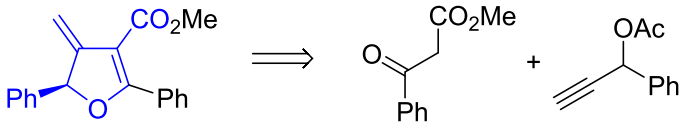
Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 sertraline - Treatment of depression		R^2 = ^{i}Bu)	
 PSN-GK1 - Antidiabetic drug		[Ir(cod)**L31**] BAr$_F$ **L31** (R^1 = *o*-Tol; R^2 = Ph)	[71b]
 (*S*)-aliskiren - Renin inhibitor drug		[Ir(cod)**L32** BAr$_F$ **L32** (R^1 = 3,5-^{t}Bu$_2$-C$_6$H$_3$; R^2 = H)	[72b]
 rupintrivir - Rhinovirus protease inhibitor		[Ir(cod)**L32** BAr$_F$ **L32** (R^1 = 3,5-^{t}Bu$_2$-C$_6$H$_3$; R^2 = H)	[72c]
		[Ir(cod)**L32** BAr$_F$	[72d]

Table 1 (*continued*)

Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 (*R*)-xanthorrizol - Natural product from *Curcuma xanthorrhiza* with cytochrome P-450 inhibition activity		**L32** (R^1 = 3,5-Me_2-C_6H_3; R^2 = α-naphthylmethyl)	
 (*R*)-nipecotic acid - GABA uptake inhibitor		[Ir(cod)**L32**]BAr_F **L32** (R^1 = 3,5-^{t}Bu$_2$-C_6H_3; R^2 = Bn)	[72e]
 Alarm pheromone of Grematogaster ants		[Ir(cod)**L32**]BAr_F **L32** (R^1 = 3,5-^{t}Bu$_2$-C_6H_3; R^2 = ^{i}Bu)	[72f]
 (S)-homoisoflavone - Natural product from plants		[Ir(cod)**L32**]BAr_F **L32** (R^1 = 3,5-^{t}Bu$_2$-C_6H_3; R^2 = H)	[80]
 fenvalerate - pyrethroid insecticide		[Ir(cod)**L32**]BAr_F **L32** (R^1 = 3,5-^{t}Bu$_2$-C_6H_3; R^2 = Bn)	[81]
 (*S*)-curcudiol - Inhibitor of gastric H, K-ATPase isolated from sponge *Epipolasis* sp.		[Ir(cod)**L32**]BAr_F **L32** (R^1 = 3,5-^{t}Bu$_2$-C_6H_3; R^2 = H)	[82]
		$Pd_2(dba)_3{\cdot}CHCl_3$ **L46**	[107]

(*continued on next page*)

Table 1 (*continued*)

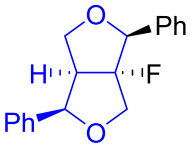
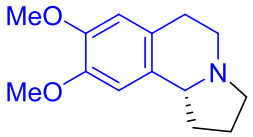
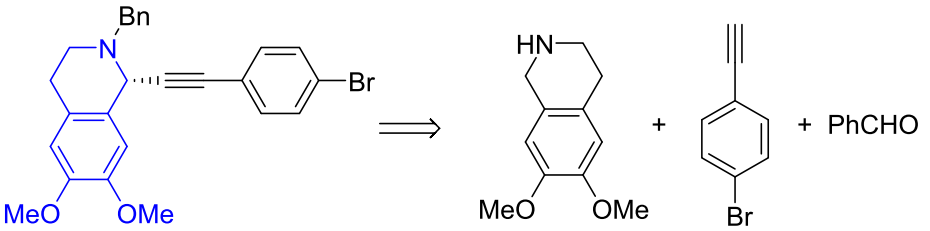
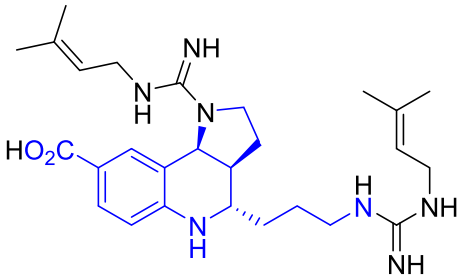
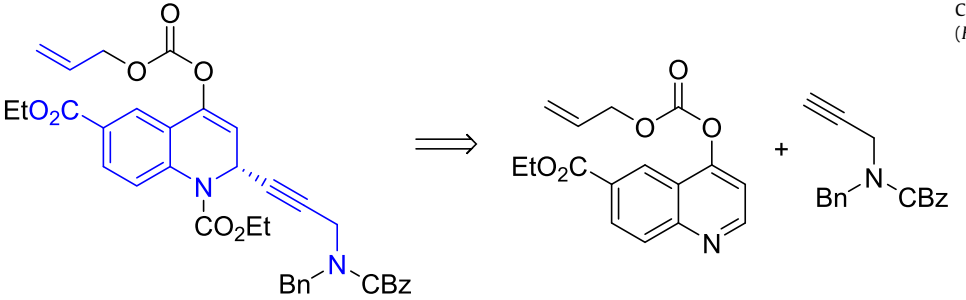
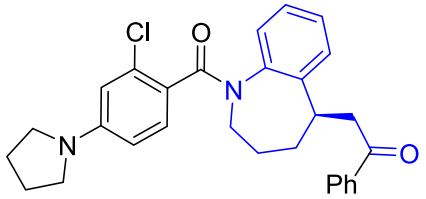
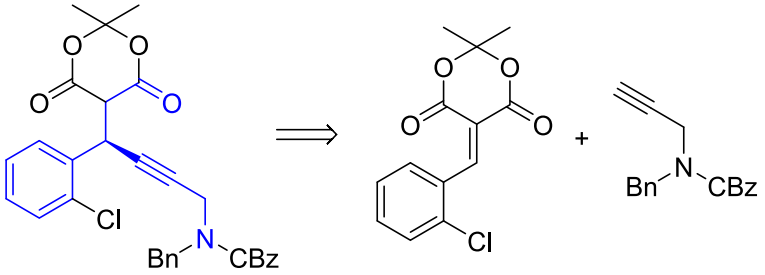
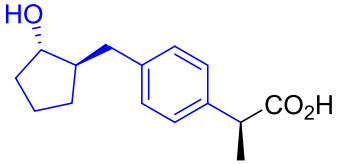
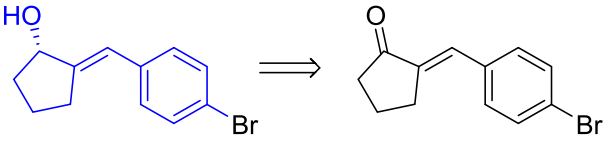
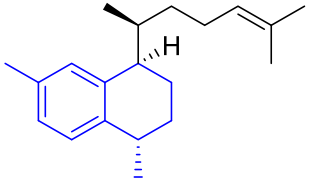
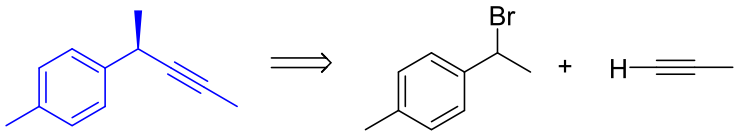
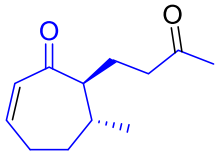
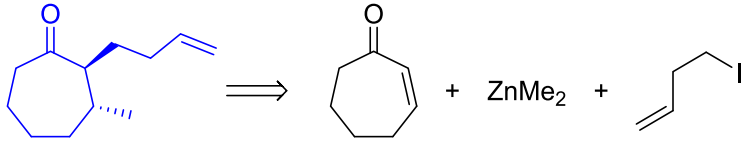
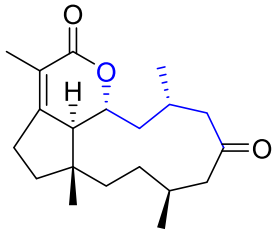
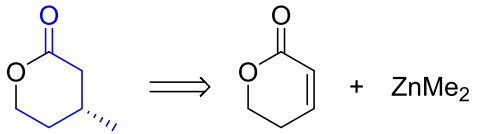
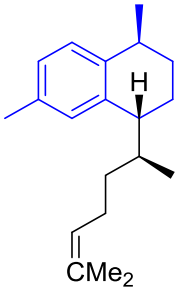
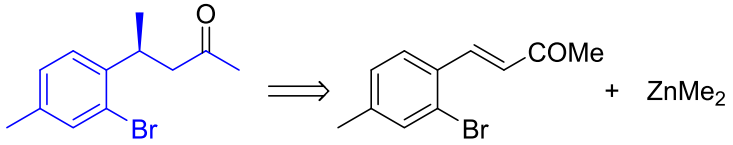
Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 Fluoromembrine analogue			
 (+)-crispine A - Natural product isolated from *Carduus crispus*		CuI (*R,R*)-**L51**	[134]
 (–)-martinellic acid - Natural product from the root bark of Martinella iquitoensis		CuBr (*R*)-**L61**	[159]
 OPC 51803 - Vasopressin V2-receptor agonist		$Cu(OAc)_2$ (*R*)-**L61**	[160]
 Ioxoprofen - Anti-inflammatory agent		$[Ir(cod)Cl]_2$ **L64** (Ar = 3,5-^{t}Bu$_2$-C_6H_3; R = H)	[163]
		CuI	[181]

Table 1 (*continued*)

Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 (+)-erogorgiaene - Natural product with antimycobacterial agent		**L72**	
 clavularin B - Anti-cancer activity		$Cu(OTf)_2{\cdot}C_6H_6$ **L75** (R^1 = ^{i}Pr; R^2 = Bn: R^3 = NHBn)	[185a]
 clavirolide C- Natural product from Pacific soft coral *Clavularia viridis*		Cu $(OTf)_2$·toluene **L75** (R^1 = ^{i}Pr; R^2 = Bn: R^3 = NEt_2)	[185f]
 (+)-erogorgiaene - Natural product with antimycobacterial agent		$Cu(OTf)_2{\cdot}C_6H_6$ **L75** (R^1 = ^{t}Bu; R^2 = CH_2-*p*-O^tBu-C_6H_4; R^3 = NH^nBu)	[185e]
		$Cu(OTf)_2{\cdot}C_6H_6$ **L75d** (R^1 = ^{t}Bu; R^2 = CH_2-*p*-OBn-C_6H_4; R^3 = NEt_3)	[187]

(*continued on next page*)

Table 1 (*continued*)

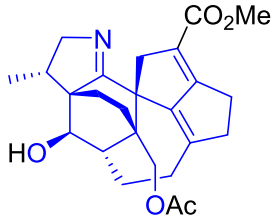
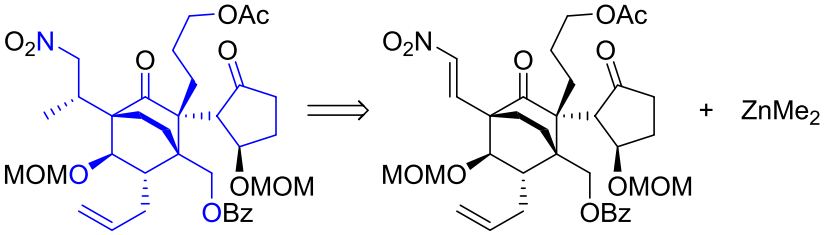
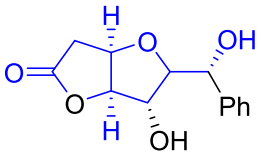
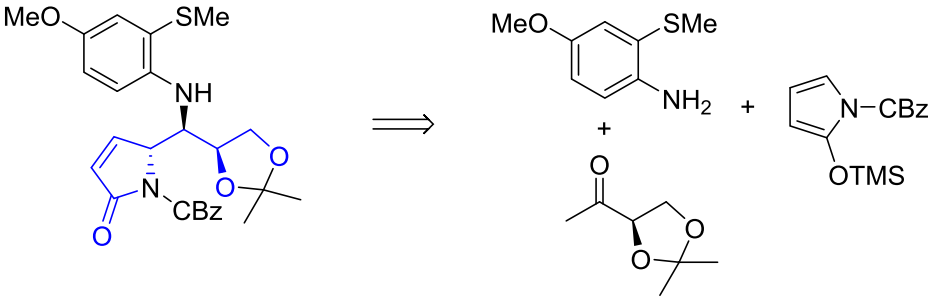
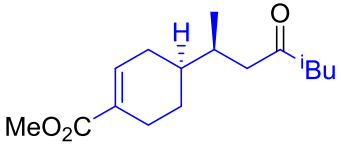
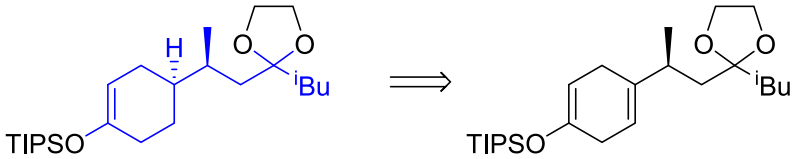
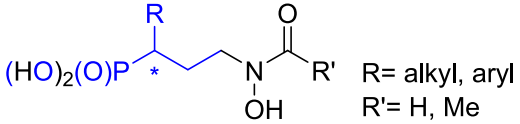
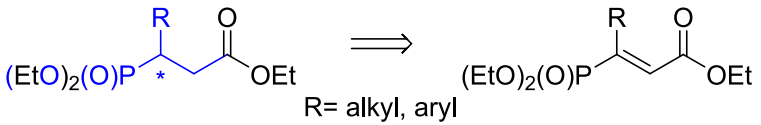
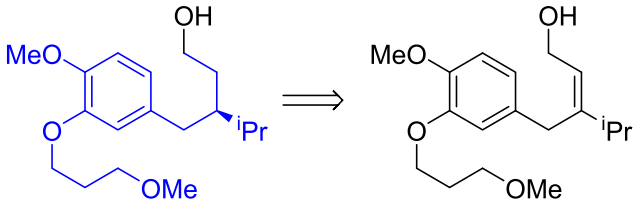
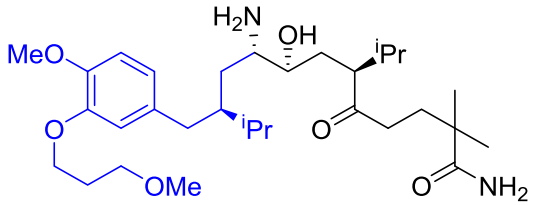
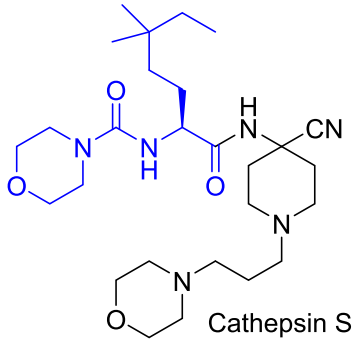
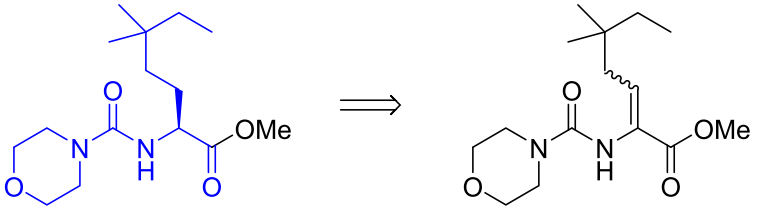
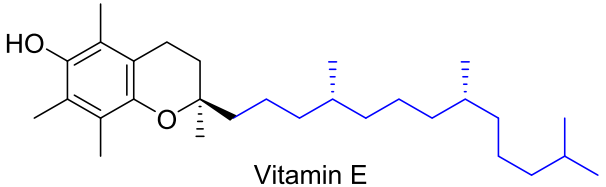
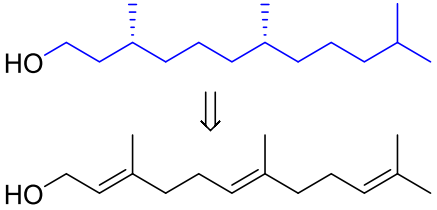
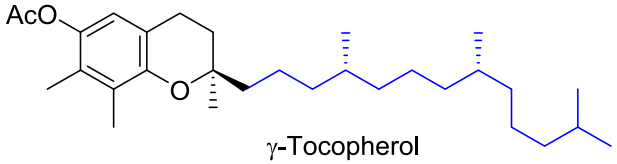
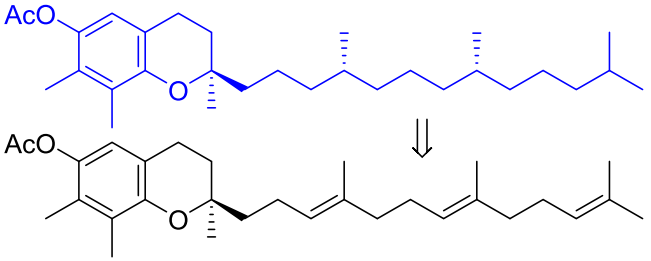
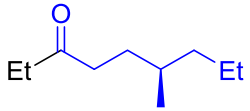
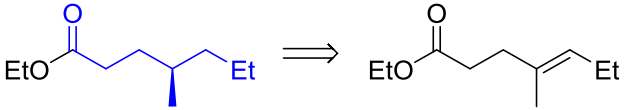
Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 (+)-daphmanidin -Natural product with moderate vasorelaxant activity			
 (+)-goniofufurone - Natural product from the stem bark of *Goniothalamus gigantius*		AgOAc **L76** (R^1 = ^{t}Bu; R^2 = *p*-OMe-C_6H_4)	[190e]
 (–)-juvabione - Natural product with juvenile insect hormone activity		[Ir(cod)**L84**] BAr_F	[324]
 Fosmidomycin analogues (FR9000098) - Antimalarial activity		[Ir(cod)**L84**] BAr_F	[204]
		[Ir(cod)**L88**] BAr_F **L88** (Ar = *o*-Tol; R = Ph)	[325]

Table 1 (*continued*)

Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 (*S*)-aliskiren - Renin inhibitor drug			
 Cathepsin S inhibitor		[Rh(nbd)$_2$]BF$_4$ **L94** (R^1 = Ph; R^2 = Cy)	[224]
 Vitamin E		[Ir(cod)**L107e**] BAr$_F$ **L107e** (n = 2; R^1 = Ph; R^2 = *o*-Tol)	[326]
 γ-Tocopherol		[Ir(cod)**L107e**] BAr$_F$ **L107e** (n = 2; R^1 = Ph; R^2 = *o*-Tol)	[252a]
 Pheromone of the caddisfly *Hesperophylax occidentalis*		[Ir(cod)**L107a**] BAr$_F$ **L107a** (n = 1; R^1 = Ph; R^2 = *o*-Tol)	[252b]

(*continued on next page*)

Table 1 (*continued*)

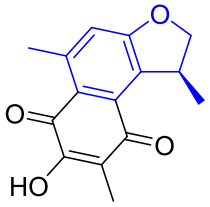
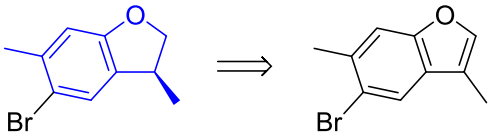
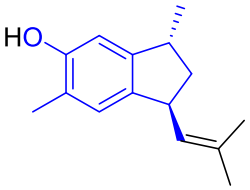
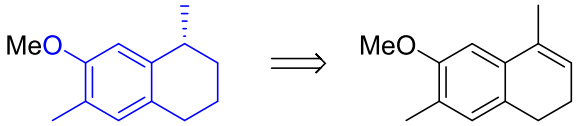
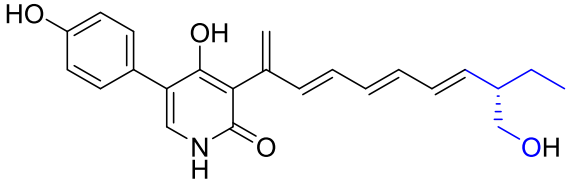
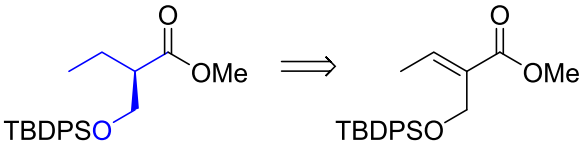
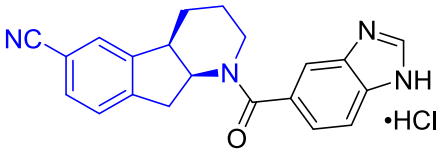
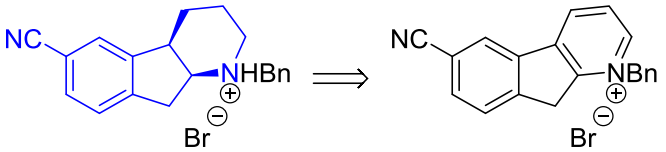
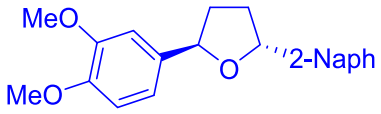
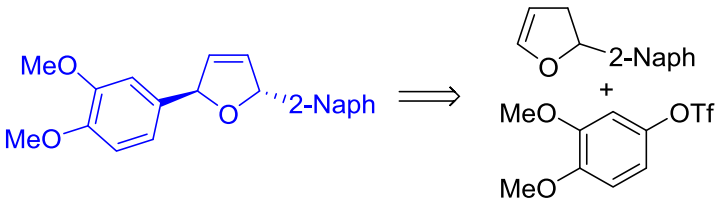
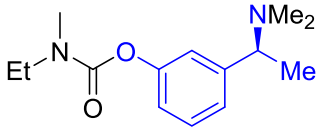
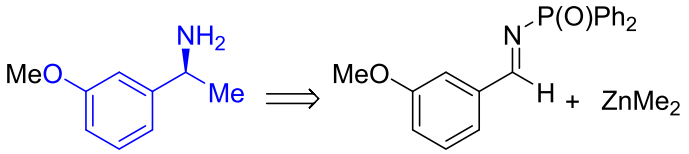
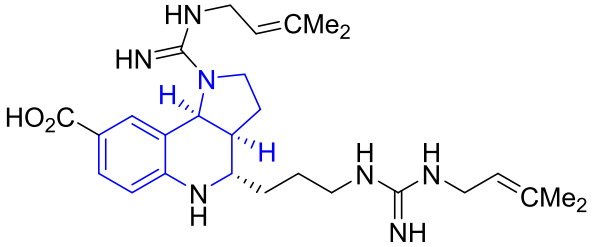
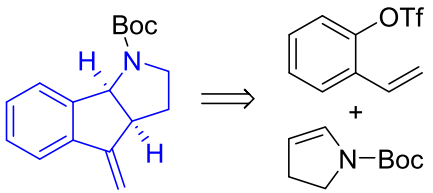
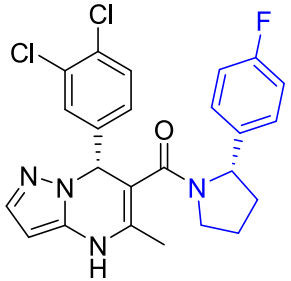
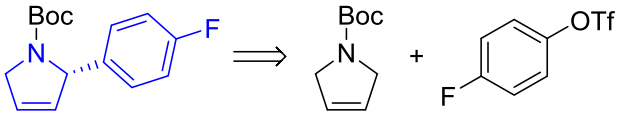
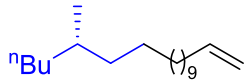
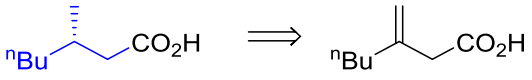
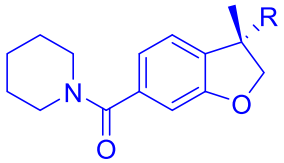
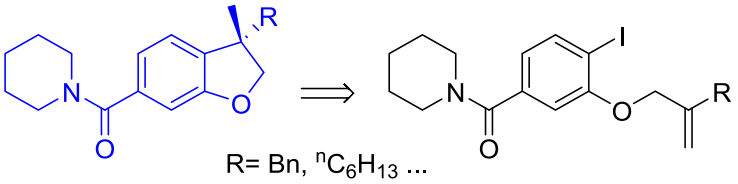
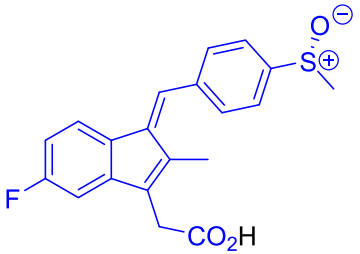
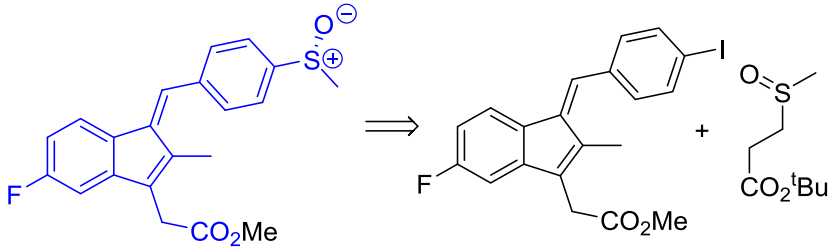
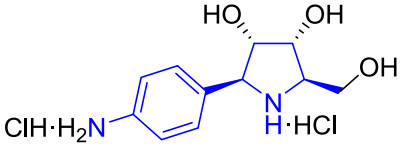
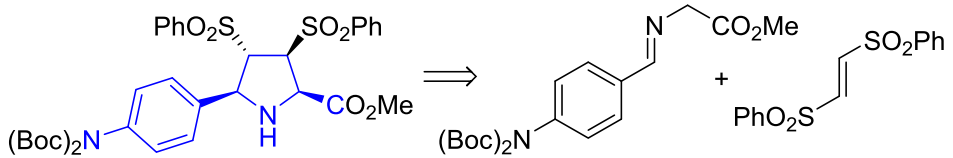
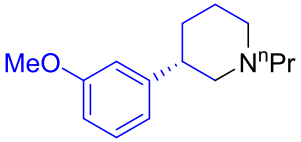
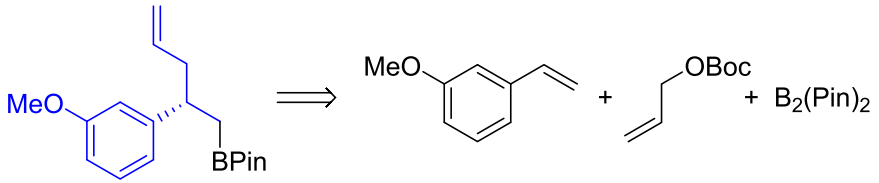
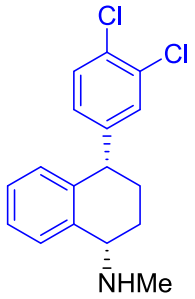
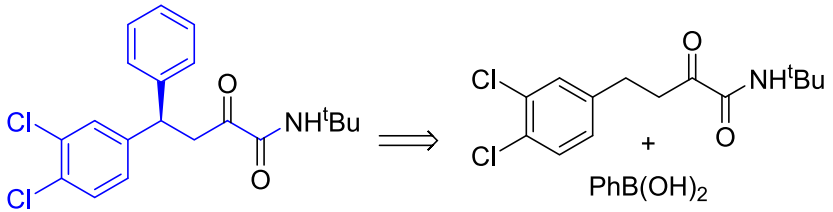
Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 thespesone- Natural product from the heartwood of the three *Thespesia populnea*		[Ir(cod)**L107**]BAr$_F$ **L107a** (n = 2; R^1 = Me; R^2 = ^{t}Bu)	[250]
 (+)-mutisianthol - Natural product from the roots of *Mutisia homoeantha*		[Ir(cod)**L107**]BAr$_F$ **L107b** (n = 1; R^1 = Ph; R^2 = ^{t}Bu)	[247]
 (+)-torrubiellone C - Natural product isolated from spiders in Nam Nao National Park		[Ir(cod)**L107**]BAr$_F$ **L107b** (n = 1; R^1 = R^2 = Ph)	[248]
 11β-HSD-1 inhibitor		[Ir(cod)Cl]$_2$ **L111** (R^1 = R^2 = OMe)	[327]
 Anti-platelet activating factor activity		Pd(dba)$_2$ (*R*)-BINAP(O)	[269]
		Cu(OTf)$_2$ (*R*,*R*)-BozPHOS	[271]

Table 1 (*continued*)

Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 rivastigmine - Treatment of Alzheimer's and Parkinson's desease			
 (–)-martinellic acid - Antagonists for the bradykinin (BK) B1 and B2 receptors		$Pd(dba)_2$ (*R*)-Xyl-SDP(O)	[270]
 BMS-394136 - Treatment of cardiac arrhythmia		$Pd(dba)_2$ (*R*)-Xyl-SDP(O)	[273]
 (*S*)-14-methyloctadec-1-ene - Sex pheromone of the peach leafminer moth		[Ir(cod)**L**]BAr_F **L** = SpiroCAP (R = Ph)	[79]
 CB2 receptor agonists	 R= Bn, $^nC_6H_{13}$ ...	$Pd_2(dba)_3{\cdot}CHCl_3$ **L120** (R^1 = Cy; R^2 = 3,5-^{t}Bu$_2$-C_6H_3; R^3 = Me)	[292d]
		$Pd_2(dba)_3{\cdot}CHCl_3$ **L121** (R^1 = 1-Ad)	[293a]

(*continued on next page*)

Table 1 (*continued*)

Product of interest/Properties	Intermediate product and its preparation	Catalyst	Ref
 (*R*)-sulindac - Anti-inflammatory drug			
 Schramm's C-aza-nucleoside - Trypanosomal nucleoside hydrolase inhibitor		$[Cu(MeCN)_4]$ PF_6 **L128** (R = 1-Naph)	[302k]
 (–)-preclamol - antipsychotic drug		CuOAc **L145** (R^1 = O^iPr; R^2 = ^iPr) $Pd(dppf)Cl_2$	[317c]
 sertraline - Treatment of depression		$[Rh(C_2H_4)Cl]_2$ **L146** (R = Ph)	[318]

superior catalytic performance in many reactions than the best C_2-symmetric N,N and P,P-ligands reported so far. Their excellent results together with its easy synthesis and tailor-made modularity spread the way to new generations of heterodonor ligands and to further enlarge the range of processes catalyzed by them. This will help the progress and will therefore drive the growth of asymmetric catalysis as a vital element to achieve the sustainable production of enantiopure compounds in the coming years.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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