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Personal Account

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Adaptable P–X Biaryl Phosphite/Phosphoroamidite-Containing Ligands for Asymmetric Hydrogenation and C–X Bond-Forming Reactions: Ligand Libraries with Exceptionally Wide Substrate Scope

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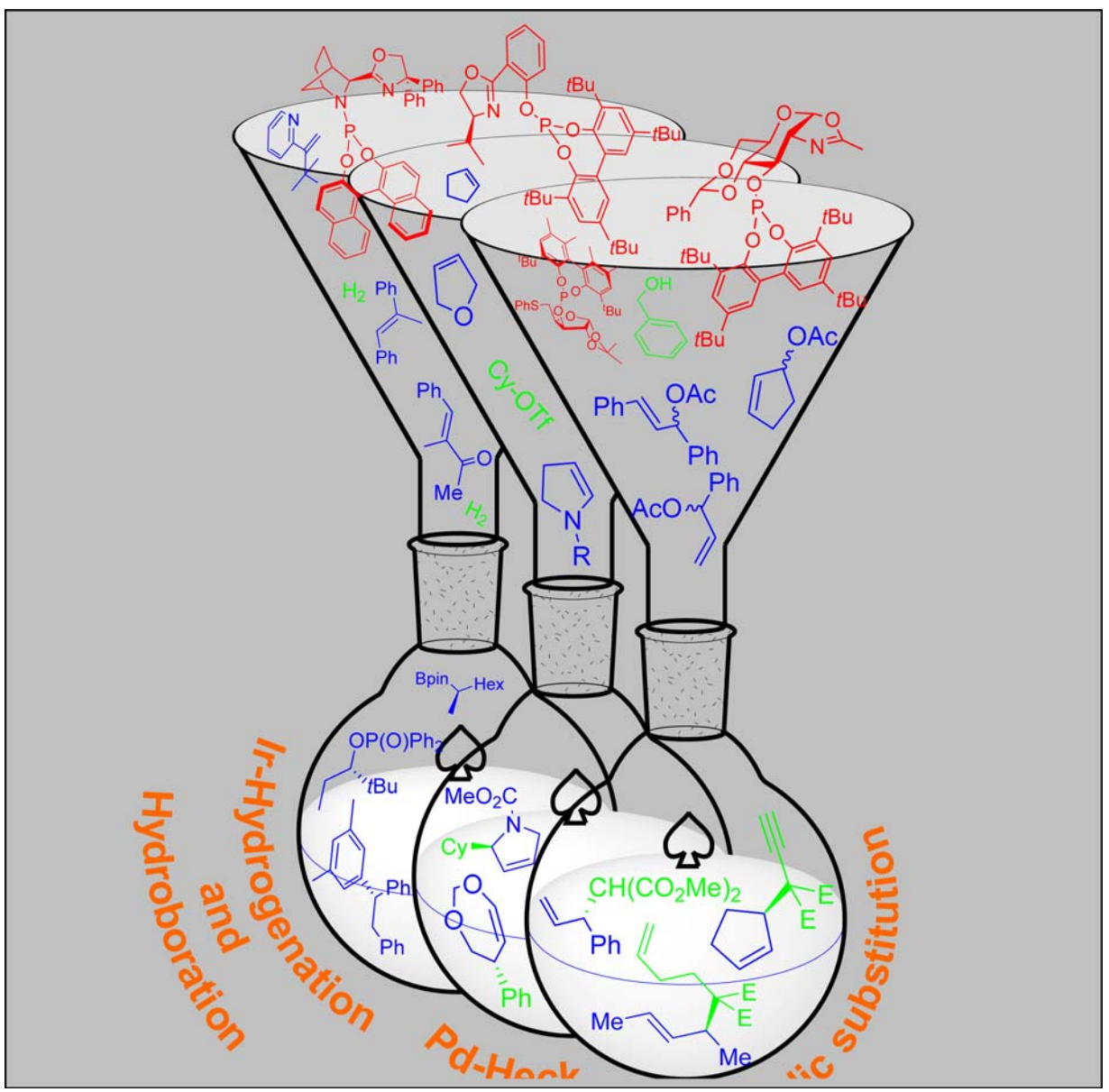

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ABSTRACT: In this personal review, we present our efforts in the design of ligand libraries for the discovery of suitable metal catalysts for asymmetric hydrogenation and C–X bond-forming reactions.

Keywords: asymmetric catalysis, ligand design, phosphanes, phosphoroamidites, transition metals

1. Introduction

Many pharmaceutical, vitamin, flavorant, and agrochemical compounds, as well as chemicals used in functional materials, are required as pure enantiomers.[1] The production of these compounds is growing and industry is searching for better synthetic procedures that are more selective, straightforward, less costly, and environmentally friendly. In achieving these goals, asymmetric catalysis plays an essential role. With only small amounts of adequate catalysts, large quantities of chiral compounds can be produced with fewer reaction steps and fewer byproducts than in non-catalyzed approaches. Clearly, research into improved activity and selectivity of these catalysts is at the core of sustainable processes, reduction of costs, and continuous growth.[1] The performance of catalytic enantioselective reactions depends, to a large extent, on the adequate selection of chiral ligands in the catalyst structure. The focus of our research group has been the development of suitable chiral ligand libraries for several enantioselective C–H, C–C, and C–X forming catalytic reactions.[2]

Among the enantioselective catalytic reactions leading to chiral products, asymmetric Ir hydrogenation of minimally functionalized olefins and Ir hydroboration of 1,1-disubstituted alkenes, together with Pd-catalyzed allylic substitution and Mizoroki–Heck reactions, are considered some of the most powerful, versatile, and sustainable processes for the preparation of complex molecules from simple ones. However, for all of them, ligands rarely tolerate a wide range of substrates and different ligands are required for different substrates to optimize the enantiopurity. In addition, new articles are continuously being published to solve the problem of using other "exotic" nucleophiles for Pd-catalyzed asymmetric allylic substitution and other triflate sources for the Pd-catalyzed Mizoroki–Heck reaction. Ligands with a wide substrate scope and suitable for a large number of nucleophiles and triflates are desirable to limit time-consuming ligand design and preparation, and for synthesizing more complex chiral organic molecules. The discovery of "privileged ligand libraries"[3] that are easy to handle (solid, robust, and air-stable) and can be prepared from simple starting materials and are good for a broad range of substrates, nucleophiles, and triflates is a relevant issue. Our group has contributed in all of these asymmetric catalytic processes with an improved generation of ligand libraries. We have found that the introduction of either biaryl phosphite and/or biaryl phosphoroamidite groups into the ligand design's library improved the ligand effectiveness in these catalytic processes.[2c]–g Metal (M) catalysts containing mixed phosphite/phosphoroamidite-X ligands have provided better versatility in terms of substrate, nucleophile, and triflate sources than previous M-phosphine/phosphinite-X catalysts. Biaryl phosphite/phosphoroamidite-containing ligands are very attractive from a synthetic point of view, since they are easy to prepare from readily accessible alcohols or amines. The availability of many alcohols and amines makes simple ligand tuning possible, which allows the synthesis of series of chiral ligands. Another advantage of phosphite/phosphoroamidite compounds is that they are less sensitive to air than phosphines. Although they are prone to decomposition reactions, such as alcoholysis, hydrolysis, and the Arbuzov reaction, these side reactions can be suppressed when bulky aryl phosphites/phosphoroamidites are used. In addition, our phosphite/phosphoroamidite-containing ligand libraries were synthesized from readily available building blocks, such as natural amino acids, and sugars. Their modular nature, well-established chemistry, and accessibility easily allowed a wide variation of the parameters that are known to influence the selectivity of the catalysts. Another important advantage of these phosphite/phosphoroamidite-containing ligands over previous ligands is that they are solid and stable to air. The ligands are therefore easier to handle and can be manipulated and stored in air.

Herein, we discuss our progress in the successful development of ligand design libraries for several relevant asymmetric C–H, C–C and C–X forming catalytic reactions. In section we rationalize the families of ligands developed. In the next sections, we cover the application of these families of ligands grouped according to the type of asymmetric catalytic reaction. For each reaction, we present an overview of the state of art and then focus on the catalytic data. We also discuss any relevant mechanistic aspects.

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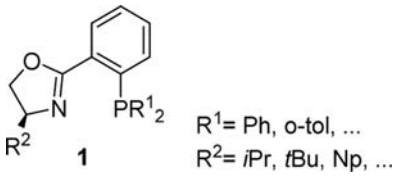

Fig. 1. Phosphine–oxazoline PHOX ligands **1**.

2. Ligand Design

Mixed phosphorus–nitrogen ligands have played a dominant role in the asymmetric catalytic processes contemplated herein. Most of the chiral P,N-ligands were phosphine/phosphinite–oxazoline compounds, and one of the most important series of ligands developed were the phosphine–oxazolines PHOX (Figure 1). These ligands have been successfully applied in several asymmetric catalytic transformations,[4] which has justified its addition to the family of privileged ligands. Despite the pioneering success of PHOX ligands in asymmetric catalysis, still more research is needed to solve the problem of substrate specificity and the use of a broad range of nucleophiles and triflate sources.

Our first approach to solve these problems was to develop ligands **L1**–**L4** (Figure 2), in which the phosphine moiety in PHOX ligands was replaced with a flexible biaryl phosphite group.[5] We thought that the higher flexibility of the biaryl phosphite group compared with phosphine moieties will help ligands **L1**–**L4** to accommodate a wider range of substrates, thereby yielding excellent enantioselectivities for a broad range of substrates and catalytic reactions. On the other hand, the greater π-accepting ability of the phosphite moiety could have important benefits for the activities.

In the search for suitable ligands in asymmetric catalysis, the use of highly modular ligand scaffolds is desirable because it facilitates the synthesis and screening of a series of chiral ligands in the search for high activities and selectivities for each of the asymmetric catalytic reactions. Therefore, we next further modified phosphite-based PHOX ligands **L1**–**L4** by developing a more highly modular biaryl phosphite–oxazoline ligand library **L5**–**L20**, in which the oxazoline and phosphite donor moieties were connected by a chiral alkyl backbone chain (Figure 2).[6] This series of ligands can be prepared efficiently from accessible hydroxyl amino acid derivatives. Interestingly, one of the advantages of this new ligand library design

Oscar Pàmies obtained his Ph.D. in Prof. Carmen Claver's group in 1999 at the Rovira i Virgili University. After three years of postdoctoral work in the group of Prof. J.-E. Bäckvall at the Department of Organic Chemistry at Stockholm University, he returned to Tarragona in 2002. He is currently working as Associate Professor at the Rovira i Virgili University. He received the Grant for Research Intensification from URV in 2008. In 2010 he was awarded with the ICREA Academia Prize 2010 from the Catalan Institution for Research and Advanced Studies. His main research interest is the development of novel, sustainable, and efficient catalytic methods for synthesizing enantiomerically enriched fine chemicals. In the design of the new catalysts, knowledge of the reaction pathways plays a crucial role. The design is therefore aided by theoretical calculations, elucidation of key reaction intermediates, as well as combinatorial techniques. In recent years, research has been focused on the use of organometallic chemistry, combinatorial synthesis, metalloenzymes, and nanocatalysis.

Montserrat Diéguez studied chemistry at the Rovira i Virgili University in Tarragona (Spain), where she received her Ph.D. in 1997 working in the group of Prof. C. Claver. Afterwards, she moved to Yale University as a Postdoctoral Fellow with Prof. R. H. Crabtree, in New Haven (USA). She returned to Tarragona in 1999 and accepted a lecturer position at the University Rovira i Virgili, becoming part of the permanent staff in 2002. In 2011 she was promoted to full Professor in Inorganic Chemistry at the University Rovira i Virgili in Tarragona. She has been involved in more than 40 research projects in the field of organometallic chemistry, stereoselective synthesis, and asymmetric catalysis. She is the author of more than 130 articles in SCI indexed journals and book chapters and of several contributions to conferences. She obtained the Distinction from the Generalitat de Catalunya for the promotion of University Research in 2004 and the Grant for Research Intensification from URV in 2008. She has also been awarded with the ICREA Academia Prize in 2009 and in 2015 from the Catalan Institution for Research and Advanced Studies. Her main research interests are focused on the sustainable design, synthesis, and screening of highly active and selective chiral catalysts for reactions of interest in the biological, pharmaceutical, and organic nanotechnological industries. Her areas of interest include organometallic chemistry, stereoselective synthesis, and asymmetric catalysis using combinatorial and biotechnological approaches.

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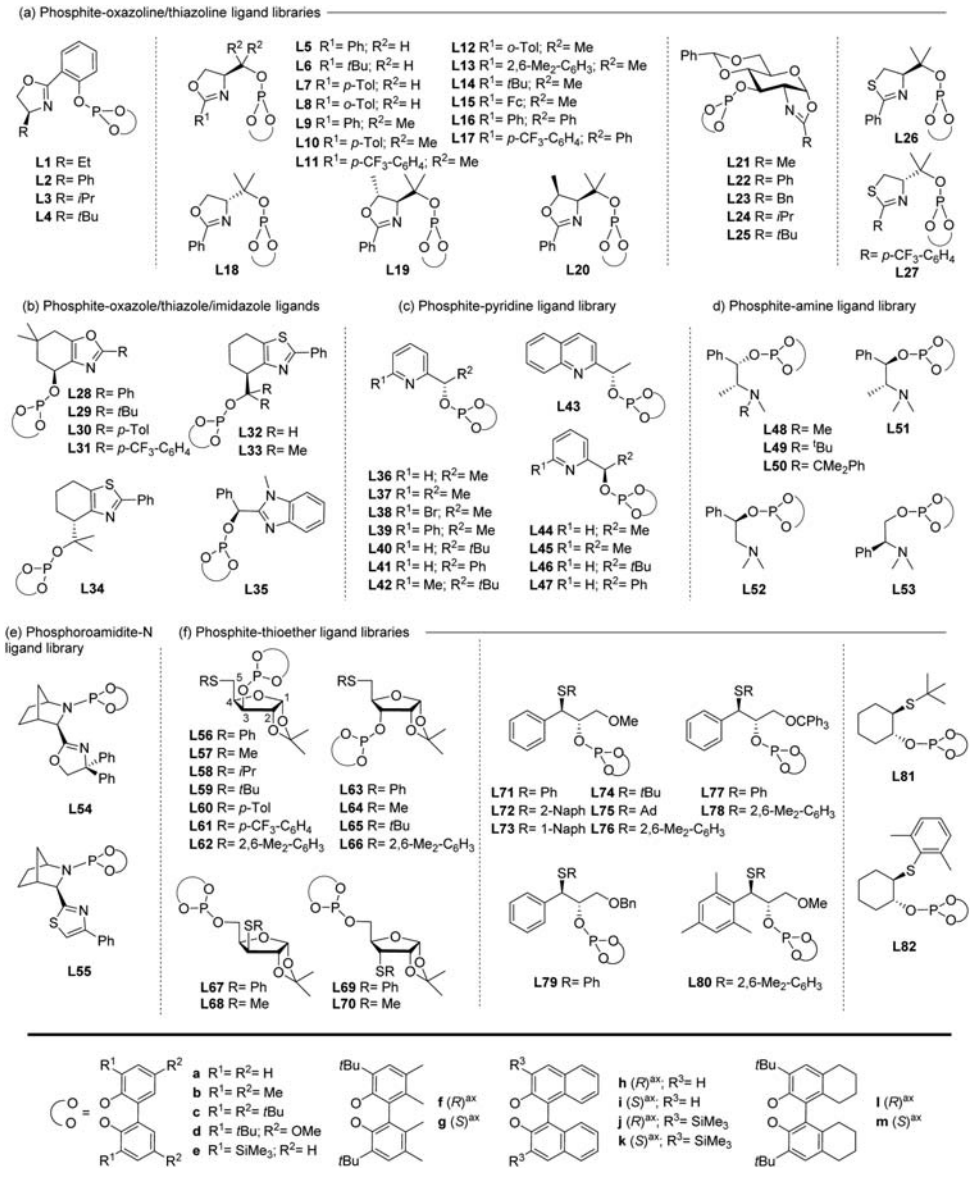

Fig. 2. Heterodonor biaryl phosphite/phosphoroamidite-based ligand libraries developed for asymmetric hydrogenation and C–X bond-forming reactions.

from previous **L1**–**L4** ligands is that more ligand parameters, which are important for asymmetric catalytic reactions, can be easily introduced, and therefore studied, than in our first generation of PHOX-type ligands **L1**–**L4**. In the first generation, for example, the oxazoline substituent was restricted to those found in readily available amino alcohols. In the second generation, these substituents are introduced from carboxylic acid derivatives; this enables the introduction of almost any substituent. With this library (Figure 2), we therefore investigated the effect of systematically varying the substituents in the oxazoline (R^1) moiety and in the alkyl backbone chain (H, **L5**–**L8**; Me, **L9**–**L15**; and Ph, **L16** and **L17**). We also studied the configuration of the alkyl backbone chain (ligands **L9** and **L18**), the presence of a second stereogenic center in the oxazoline ring and its configuration (ligands **L19** and **L20**), and the substituents and configurations in the biaryl phosphite moiety.[6,7]

Then, taking advantage of our experience in the synthesis of carbohydrate ligands,[2a,b,8] we synthesized a pyranoside phosphite–oxazoline ligand library **L21**–**L25** (Figure 2).[9] These ligands are derived from natural D-glucosamine, so they also have the advantages of carbohydrates, that is, they are cheap and can be easily constructed in modules. With these ligands, we were able to easily introduce several substituents with different electronic and steric proprieties into the

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oxazoline group and very broad range of different biaryl phosphite moieties.

We then turned our attention to replacing the oxazoline moiety in ligands **L5**–**L20** with a thiazoline group (ligands **L26** and **L27**; Figure 2).[10] We expected that subtle variations in the steric (the thiazoline brings the substituent closer to the metal center than the oxazoline) and electronic (the thiazoline group is more basic than the oxazoline) properties of the N-donor group should have important effects on the catalytic performance.

Although researchers first thought of developing ligands containing more robust groups than oxazolines/thiazolines, only a few of them have been successfully applied and these are limited in substrate, nucleophile, and catalytic process scope. With the aim of extending the substrate versatility, as well as the nucleophile and triflate sources, even further, our research progressed to heterodonor biaryl phosphite/phosphoroamidite-X ligands containing more robust X-donor groups than oxazolines/thiazolines.

In this respect, in collaboration with Andersson's group, we first studied whether the biaryl phosphite moiety was still as effective when combined with oxazole, thiazole, and imidazole groups. For this purpose, we prepared ligands **L28**–**L35** (Figure 2) from readily available hydroxyl–oxazole/thiazole/imidazole derivatives.[11] The modular construction of these ligands enabled a systematic study of the effect on the catalytic performance of bridge length (ligands **L28** and **L32**), the substituent at the heterocyclic ring (ligands **L28**–**L31**), and in the alkyl backbone chain (ligands **L32** and **L33**), the configuration of the ligand backbone (ligands **L33** vs. **L34**), and the substituents and configurations in the biaryl phosphite moiety.

We next decided to take one further step in the design of new ligand libraries using phosphite–pyridines **L36**–**L47**[12] and phosphite–amine **L48**–**L53**[13] ligand libraries (Figure 2), which incorporated the advantages of the heterodonor, the robustness of the pyridine/amine moieties, and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite group.

We also studied whether the benefits of incorporating a biaryl phosphite group were maintained when replaced by a phosphoroamidite group. For this purpose, we developed a small but structurally diverse phosphoroamidite–oxazoline/thiazole ligand library (ligands **L54** and **L55**; Figure 2).[14]

Finally, we turned our attention to the preparation of robust phosphite–thioether ligand libraries. In contrast to heterodonor P,N ligands, mixed P,S ligands have been less studied, although they have also demonstrated their potential utility in asymmetric catalysis.[15] The early pioneering works of the groups of Pregosin[16] and Evans,[17] among others, with the successful use of P-thioether ligands in Pd–allylic substitution and other relevant asymmetric processes made them a promising type of ligands for catalysis. Despite the design of new P,S ligands becoming the focus of many research groups, only a few of them were successfully applied and these were limited in substrate scope. The minor role of thioether-based ligands can be found in the formation of mixtures of diastereomeric thioether complexes (because the S atom becomes a stereogenic center when coordinated to the metal) and the difficulty of controlling their interconversion in solution. Nevertheless, if the ligand scaffold can control S coordination, this feature may be extremely beneficial because then the chirality moves closer to the metal. In this respect, we first prepared a highly modular phosphite–thioether ligand library derived from carbohydrates (Figure 2; ligands **L56**–**L70**).[18] With these ligands, we investigated the effect on the catalytic performance of varying the position of the thioether group at either C-5 or C-3 of the furanoside backbone, the configuration of C-3, the thioether substituent, and the substituents/configuration in the biaryl phosphite moiety. Then, we decided to focus our research on developing new simple P-thioether ligand libraries and optimize their application using DFT calculations. We therefore next applied a new highly modular P-thioether ligand library (Figure 2; ligands **L71**–**L80**).[19] In a simple three-step procedure, several ligand parameters were easily tuned to maximize the enantioselectivities for each substrate. Finally, we designed and applied a reduced but structurally valuable P-thioether ligand library (ligands **L81** and **L82**; Figure 2).[20] They were synthesized in only two steps and had a simple backbone, and thus, their NMR spectra were simple, with reduced signal overlap, which facilitated the identification of relevant intermediates.

3. Application of Phosphite-Based Ligands in Pd-Catalyzed Allylic Substitution Reactions

The Pd-catalyzed asymmetric allylic substitution reaction (AAA) is one of the most powerful and versatile tools for constructing chiral C–C and C–X bonds (Scheme 1).[2a,21] S1

Most of the successful ligands developed for this process use either C2-symmetrical scaffolds, to restrict the number of diastereomeric transition states, or the ability of the ligand to direct approach to one of the allylic terminal atoms, by means of either a secondary ligand–nucleophile interaction or electronic differentiation.[21] In this latter strategy, the use of heterodonor ligands allows us to electronically distinguish between the two allylic terminal carbon atoms due to the different *trans* influences of the donor atoms. All of these strategies have led to the discovery of several privileged ligands that provide high levels of enantioselectivity (i.e., DACH-phenyl Trost ligand, PHOX, etc.) However, asymmetric induction is highly dependent on the steric demands of the substrate. Thus, most of the privileged catalytic systems only afford high enantioselectivities for either hindered or unhindered substrates. Our

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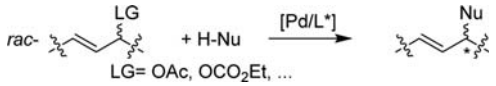


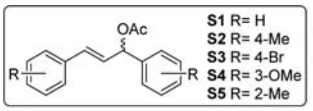
Scheme 1. Pd-catalyzed asymmetric allylic substitution reaction.

group found that the use of diphosphite and phosphite–phosphoroamidite ligands have an extremely positive effect on activity and substrate versatility.[22] The π-accepting capacity of the phosphite/phosphoroamidite moieties increases activities, and the adaptability of biaryl phosphite/phosphoroamide groups enables the catalyst to appropriately tune its chiral pocket to accommodate substrates with different steric requirements.[2f] Nevertheless, the success of these ligands is restricted to allylic alkylation using dimethyl malonate as a nucleophile and disubstituted substrates. More research was needed to expand the range of nucleophiles and substrate types with the aim of synthesizing more demanding organic compounds.

So bearing in mind the excellent enantioselectivities obtained with heterodonor ligands in this process, we next concentrated our efforts on the development of new heterodonor ligand libraries containing a biaryl phosphite moiety. In Sections 3.1–3.3, we present our progress in the development of new heterodonor phosphite-containing ligand libraries and their successful application in Pd-AAA.

3.1. Application of Phosphite–Oxazoline/Thiazoline Ligands

With the aim of solving the limitations of activity and substrate and nucleophile versatility in the Pd-AAA, our group took one of the most successful ligand families developed for this process, the PHOX ligands **1** and replaced the phosphine moiety with biaryl phosphite groups (Figure 2; ligands **L1**–**L4**). Whereas the Pd-PHOX catalyst gives excellent results with the model *rac*-(*E*)−1,3-diphenyl-2-propenyl substrate **S1**, modest to good results with 1,3-dialkyl-2-propenyl substrates, and racemic results for cyclic substrates,[4a] the application of analogues **L1**–**L4a**,**c**–**d**,**l**,**m** was very successful in all of them.[5a,c] Excellent activities (turnover frequencies (TOFs)>2400 $mol_{substrate}\ mol_{Pd}^{-1}\ h^{-1}$, regio- (up to 99%) and enantioselectivities (*ee* values up to 99%) were therefore achieved for hindered and unhindered mono-, di-, and trisubstituted substrates. The highest enantioselectivities in the asymmetric allylic substitution of substrate **S1** were achieved using simple tropoisomeric ligand **L3c**. Pd/**L3c** is very tolerant to variation of the nucleophile sources (Figure 3). A broad range of malonates provided alkylated products in high yields, and enantioselectivities, comparable to those obtained with dimethyl malonate (*ee* values up to >99%). Notably, high enantioselectivities achieved with allyl-, butenyl-, pentenyl-, and propargyl-substituted malonates (Figure 3), the products



S1

H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	94	>99 (*S*)
H-CH(CO_2Et)$_2$	93	>99 (*S*)
H-CH(CO_2Bn)$_2$	95	>99 (*S*)
H-CMe(CO_2Me)$_2$	91	99 (*R*)
H-Callyl(CO_2Me)$_2$	92	>99 (*R*)
H-Cbutenyl(CO_2Et)$_2$	89	>99 (*R*)
H-Cpentenyl(CO_2Et)$_2$	93	93 (*R*)
H-propargyl(CO_2Et)$_2$	91	>99 (*R*)
H-CH(COMe)$_2$	89	98 (*S*)
H-CF(SO_2Ph)$_2$	76	99 (*R*)
H-OCH$_2$(*p*-CF_3-C_6H_4)	93	97 (-)
H-OSiMe$_2$Ph	79	98 (*R*)
H-OSiPh$_3$	91	99 (*R*)

S2

H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	93	99 (*S*)
H-Callyl(CO_2Me)$_2$	91	99 (*R*)
H-Cbutenyl(CO_2Et)$_2$	92	94 (*R*)

S3

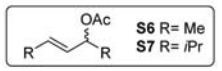
H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	89	99 (*S*)

S4

H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	91	99 (*S*)

S5

H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	90	99 (*S*)



S6

H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	89	93 (*S*)
H-CMe(CO_2Me)$_2$	86	80 (*S*)
H-Callyl(CO_2Me)$_2$	89	90 (*S*)
H-Cbutenyl(CO_2Et)$_2$	90	87 (*S*)

S7

H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	92	>95 (*S*)

Fig. 3. Summary of the catalytic results in the allylic substitution of linear substrates **S1**–**S7** using the Pd/**L3c** catalyst. Reactions carried out using 0.5 mol% [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base (except for O-nucleophiles, for which Cs_2CO_3 was used as base), r.t. (except for substrate **S6**, for which 0°C was used).

are key intermediates in the synthesis of more complex chiral products.

The addition of acetylacetone also provided similar high enantioselectivities (*ee* values up to 98%). We could also obtain *ee* values up to 99% in the allylic fluorobis(phenylsulfonyl)methylation of **S1**. The efficient allylic substitution with this type of nucleophile opens up a path for obtaining highly appealing chiral monofluoromethylated compounds, which are attracting significant attention in the field of medicinal chemistry.[23] Despite this, only one catalytic system has previously been successfully applied, although it resulted in lower enantioselectivity (*ee* values up to 96%) than the present system and also required lower temperature (0 °C) than our Pd/**L3c** catalyst.[24] Pd/**L3c** also provides high yields and enantioselectivities (*ee* values up to 97%) using 4-(trifluoromethyl)benzyl alcohol as the O-nucleophile (Figure 3). Even more remarkable are the almost perfect enantioselectivities (*ee* values up to 99%) and high yields obtained in the etherification of **S1** with silanols. The results surpass those of the only Pd/CycloN2P2-Phos catalytic type system that has provided high enantioselectivities (up to 94%) so far.[25] Therefore, Pd/**L3c** can be used for preparing chiral silyl ethers that can be easily transformed into high-value compounds, such as chiral aromatic allylic alcohols. Pd/**L3c** was also successfully applied to other symmetrical linear substrates with different steric and electronic requirements (**S2**–**S7**) different from those of **S1** (Figure 3). The present results are among the best in the literature for substrate **S6**, even using highly appealing nucleophiles, such as

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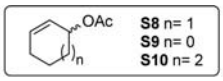


S8

H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	92	99 (*S*)
H-CH(CO_2Et)$_2$	93	>99 (*S*)
H-CH(CO_2Bn)$_2$	90	97 (*S*)
H-CMe(CO_2Me)$_2$	89	99 (+)
H-Callyl(CO_2Me)$_2$	91	>99 (-)
H-propargyl(CO_2Et)$_2$	88	92 (*S*)
H-CH(COMe)$_2$	93	99 (-)

S9

H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	86	>95 (-)
H-propargyl(CO_2Et)$_2$	87	96 (*S*)

S10

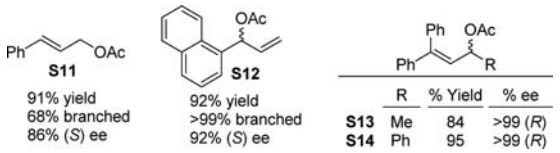
H-Nu	% Yield	% ee
H-CH(CO_2Me)$_2$	92	>99 (*S*)
H-propargyl(CO_2Et)$_2$	65	>99 (*S*)

Fig. 4. Summary of the catalytic results in the allylic substitution of cyclic substrates **S8**–**S10** using Pd/**L3m** catalyst. Reactions carried out using 0.5 mol% [Pd(η^3-C_3H_5)Cl]$_2$, 1.1 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t.

α-substituted with methyl, allyl, and butenyl groups, for which very few catalytic systems have provided high enantioselectivities. This substrate is less sterically demanding, and therefore, enantioselectivities tend to be lower than those with model substrate **S1**. Interestingly, Pd/**L3c** can also successfully be used for the alkylation of **S7** (*ee* values up to >95%).

F4 Figure 4 shows that a wide range of C-nucleophiles, including the less studied α-substituted malonates and acetylacetone, can also efficiently react with more demanding cyclic substrate **S8** to provide the corresponding compounds with high yields and enantioselectivities (*ee* values up to >99%), comparable to those obtained with dimethyl malonate. The exception was propargyl-substituted malonate, which led to somewhat lower enantioselectivity (*ee* values up to 92%), but still good for this challenging C-nucleophile. Remarkably, excellent enantioselectivities (*ee* values between 96 and >99%) were obtained, even with **S9**, which usually provided products with much lower enantioselectivities than those with cyclic **S8**. In contrast to previous substrates, for cyclic substrates the best enantioselectivities were obtained with ligands **L3c** and **L3m**, although ligand **L3m** provided somewhat higher enantioselectivity.

Finally, the good performance of Pd/**L3c** and Pd/**L3m** also extended to the allylic substitution of challenging unsymmetrical monosubstituted allylic substrates **S11** and **S12** (Fig-
F5 ure 5). Most Pd catalysts favor the formation of the usually undesired achiral linear product.[21,26] The increases in regioselectivity toward the desired branched isomer in monosubstituted linear substrates can be explained by the high π-accepting ability of the phosphite moiety, which decreases the electron density of the most substituted allylic terminal carbon atom through the *trans* influence, favoring nucleophilic attack to this carbon atom. Also, excellent enantioselectivities were achieved in 1,3,3,-trisubstituted allylic substrates **S13** and **S14** (Figure 5). Again, the flexibility conferred by the biaryl phosphite moiety was enough to adequately control the size of the chiral pocket to achieve enantioselectivities comparable to the best one reported.



	R	% Yield	% ee
S13	Me	84	>99 (*R*)
S14	Ph	95	>99 (*R*)

Fig. 5. Summary of the catalytic results in the allylic substitution of mono- and trisubsituted substrates **S11**–**S14** using the Pd/**L3c** catalyst. Reactions carried out using 1 mol% [Pd(η^3-C_3H_5)Cl]$_2$, 2.2 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t.

To explain the unusually wide substrate scope of Pd/**L3c**, we performed experimental and theoretical studies of its η^3-allyl and η^2-olefin complexes by NMR spectroscopy and DFT calculations.[5c] We found, in contrast with previously studied flexible ligands, the tropoisomeric biaryl phosphite moiety in ligand **L3c** adopts an *S* configuration in complexes mimicking product olefin complexes obtained in palladium-catalyzed allylic alkylations of both "broad" and "narrow" allylic substrates. Although the olefins coordinate with the same face to palladium in diastereomeric rigid ligands **L3l** and **L3m**, with *S* and *R* configurations, respectively, products with opposite absolute configuration were obtained. The explanation was found in the different energies of the transition-state complexes. The NMR spectroscopy and DFT studies confirmed that the exceptionally broad substrate scope of these ligands was due to the ability of the ligands to adapt the size of the substrate-binding pocket to the reacting substrate. This ability also serves as an explanation for its excellent performance in other types of catalytic processes (see below). In contrast, PHOX ligands interact with the substrate mainly at its wings. As a consequence, allylic systems with bulky substituents show high *exo*/*endo* ratios and high enantioselectivities, whereas unhindered substrates give low selectivity.

Therefore, by the simple substitution of the phosphine moiety by a biaryl phosphite in the PHOX ligand, we were able to identify unprecedented catalytic systems that, with high enantiocontrol, generated C–C, C–N, and C–O bonds for a number of hindered and unhindered mono, di-, and trisubstituted substrates using a wide range of C-, N-, and O-nucleophiles.

Following this significant contribution, we next developed new more highly modular biaryl phosphite–oxazoline/thiazoline ligand libraries.

The first of these were based on previous ligands **L1**–**L4**, in which the oxazoline and phosphite donor moieties were connected by a chiral alkyl backbone chain (**L5**–**L20a**,**c**–**e**,**h**–**j**; Figure 2).[6,10a] By selecting the ligand parameters, Pd/**L9c**,**I**,**k** and Pd/**L17i** catalysts provided high regio- and enantioselectivities (*ee* values up to 99%) in the Pd-catalyzed allylic substitution of a broad range of mono, di-, and trisubstituted linear hindered and unhindered linear substrates (Figure 6) F6 using a range of C- and N-nucleophiles. In addition, both

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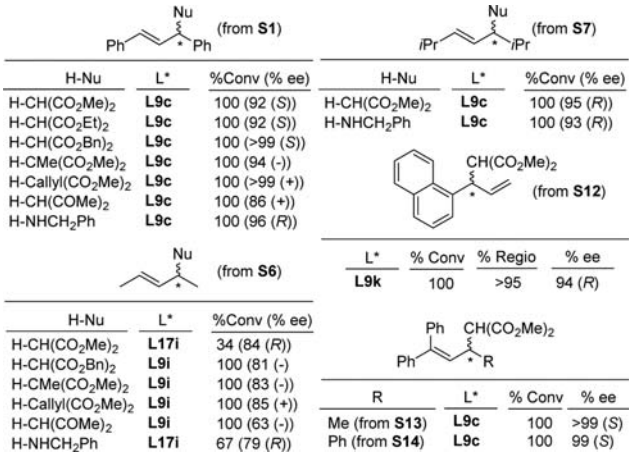

Fig. 6. Summary of the catalytic results in the allylic substitution of several substrates using Pd/**L9c**,**I** and Pd/**L17i** catalysts. Reactions carried out using 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t.

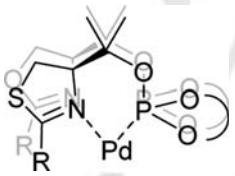

Fig. 7. Superimposed structures of phosphite–thiazoline (black) and phosphite–oxazoline (gray) for comparison.

enantiomers of substitution products can be obtained with high enantioselectivities by simply changing either the absolute configuration of the alkyl backbone chain or the absolute configuration of the biaryl phosphite moiety.

Despite success with this readily accessible and highly modular ligand library **L5**–**L20**, the enantioselectivity obtained in unhindered cyclic substrates was not completely satisfactory. To address this limitation, we decided to expand the ligand design by replacing the oxazoline group of ligands **L9** and **L18** with a thiazoline moiety (ligands **L26** and **L27**; Figure 2).[10a] The reason for this modification is that the introduction of a thiazoline moiety will create a smaller chiral pocket more suitable for unhindered cyclic substrates, while maintaining the flexibility conferred by the biaryl phosphite group (Figure 7).

We were pleased to see that enantioselectivities for unhindered cyclic substrates improved considerably with these new phosphite–thiazoline ligands (Figure 8). For hindered substrates, such as **S1**, and trisubstituted substrate enantioselectivities were still best with previous phosphite–oxazoline ligands. Therefore, by correctly combining substrate and ligand type (phosphite–oxazoline or phosphite–thiazoline), we have identified another catalytic system that provided high regio- and

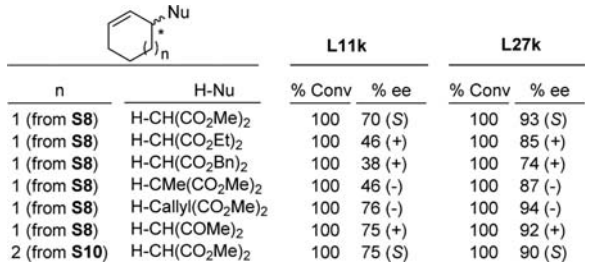

Fig. 8. Comparison of the catalytic results in the allylic substitution of several cyclic substrates using phosphite–oxazoline **L11k** versus phosphite–thiazoline **L27k** ligands. Reactions carried out using 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t.

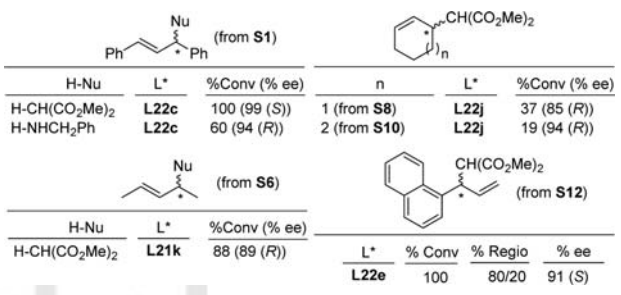

Fig. 9. Summary of the catalytic results in the allylic substitution of several substrates using Pd/**L21**–**L25** catalysts. Reactions carried out using 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t.

enantioselectivities in both enantiomers of the substitution products for a wide range of hindered and unhindered mono- and disubstituted substrates with several carbon nucleophiles. We even achieved unprecedented *ee* values (>99%) for the challenging class of trisubstituted olefins. By studying the Pd-1,3-diphenyl, 1,3-dimethyl, and 1,3-cyclohexenyl allyl intermediates by means of NMR spectroscopy, we found that the changes in enantioselectivities observed by replacing the oxazoline with a thiazoline could be explained by variations in the relative amount of species formed in solution. Thus, although for hindered substrates the relative amount of the fastest reacting isomer increases with phosphite–oxazoline ligands, for cyclic substrates it increases with phosphite–thiazoline ligands.[10a]

The second phosphite–oxazoline ligand library developed by our group was based on a sugar backbone. A pyranoside phosphite–oxazoline ligand library **L21**–**L25a**–**e**,**h**–**k** (Figure 2) was therefore successfully applied in the Pd-catalyzed asymmetric allylic substitution.[9a],d We found that the ligand components must be selected to suit each substrate to obtain the highest enantioselectivity. High enantioselectivities (*ee* values up to 99%), comparable to the best one reported, and good activities (turnover numbers (TONs) up to 600 $mol_{substrate}$ mol_{Pd}^{-1} h^{-1}) have been achieved in a broad range of mono- and disubstituted hindered and unhindered linear and cyclic substrates (Figure 9).

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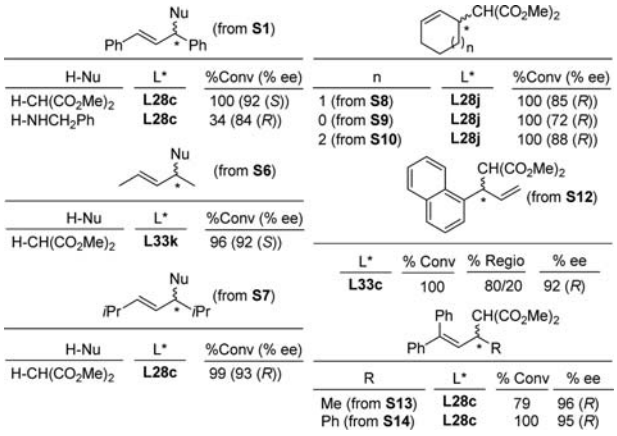

Fig. 10. Summary of the catalytic results in the allylic substitution of several substrates using Pd/**L28**–**L34** catalysts. Reactions carried out using 1 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.2 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base, r.t.

In addition, the efficiency of this ligand design is corroborated by the fact that these Pd/phosphite–oxazoline catalysts provided higher enantioselectivity than their phosphinite–oxazoline analogues[27] in several substrate types. The study of the Pd-1,3-diphenyl, 1,3-dimethyl, and 1,3-cyclohexenyl allyl intermediates indicates that, for enantioselectivities to be high, the substituents in the biaryl phosphite moiety and the electronic and steric properties at the oxazoline substituents need to be correctly combined to form predominantly the isomer that reacts faster with the nucleophile and also to avoid the formation of species with ligands coordinated in monodentate fashion.[9d]

3.2. Application of Phosphite–Oxazole/Thiazole/Pyridine/Amine Ligands

Then, we concentrated our efforts on developing ligands containing more robust groups than oxazoline/thiazoline moieties. We first, in collaboration with Andersson's group, studied whether the biaryl phosphite moiety was still as effective when combined with oxazole and thiazole groups. For this purpose, we prepared ligands **L28**–**L34c**–**e**,**h**–**k** (Figure 2), from readily available hydroxyl–oxazole/thiazole derivatives.[11a] We found again that the ability of the catalysts to transfer chiral information to the product could be tuned by choosing suitable ligand components (bridge length, the substituents in the heterocyclic ring and the alkyl backbone chain, the configuration of the ligand backbone, and the substituents/configurations in the biaryl phosphite moiety), so that enantioselectivities could be maximized for each substrate, as required. We found that the flexibility and larger bite angle created by the biaryl phosphite moiety and the different bridge lengths increased substrate versatility (Figure 10).

For hindered substrates **S1**, **S7**, **S13**, and **S14**, the best enantioselectivities were obtained with ligand **L28c**, whereas for substrate **S6** and cyclic substrates **S8**–**S10** the best enantioselectivities were obtained with ligands **L33k** and **L34k** and **L28j**, respectively. We also found that the π-accepting character of the phosphite moiety increases reaction rates. To sum up, high regio- and enantioselectivities (*ee* values up to 96%) and good activities were obtained for a broad range of mono-, di-, and trisubstituted linear hindered and unhindered substrates and cyclic substrates. In addition, for all substrates, both enantiomers of the substitution products were obtained with high enantioselectivities. By studying the Pd-1,3-diphenylallyl, Pd-1,3-dimethylallyl, and Pd-1,3-cyclohexenylallyl intermediates by means of NMR spectroscopy and DFT calculations, we conclude that, for enantioselectivities to be high, the ligand parameters need to be correctly combined to predominantly form the Pd intermediate that has the fastest reaction with the nucleophile.

We next decided to synthesize and screen a library of 84 potential new phosphite–pyridine ligands (**L36**–**L47c**–**g**,**j**–**k**; Figure 2).[12a] These ligands incorporate the advantages of the heterodonor, the robustness of the pyridine moiety, and the extra control of the chiral pocket through the presence of biaryl phosphite groups. By a systematic variation of the substituents at the ligand backbone (R^1 and R^2, ligands **L36**–**L42**), the configuration of the carbon next to the phosphite moiety (ligands **L36**–**L42** vs. **L44**–**L47**), and the substituents and configurations in the biaryl phosphite moiety (**c**–**g**, **j**–**k**), we could achieve high enantioselectivities and activities in several di- and trisubstituted substrates by using a wide range of C-, N- and O-nucleophiles, including the less studied α-substituted malonates, β-diketones and alkyl alcohols (Figure 11).[12a]

The potential application of these catalysts was demonstrated by the practical synthesis of chiral carbocyclic compounds using a simple sequential allylic alkylation and ring-closing metathesis reaction (Scheme 2).[12a]

The new phosphite–pyridine ligand library not only performs well in traditional organic solvents, but also in alternative environmentally friendly solvents, such as propylene carbonate. The use of ionic liquids allowed the palladium catalyst to be reused, while maintaining excellent enantioselectivities up to five times.[12a] By studying the Pd-1,3-diphenyl, 1,3-dimethyl, and 1,3-cyclohexenyl allyl intermediates with NMR spectroscopy, we found that, for enantioselectivities to be high in the substitution of hindered substrate **S1**, the ligand parameters needed to be correctly combined, so that electronic differentiation increased between the most electrophilic allylic terminus carbon atoms of the isomers formed and/or the isomer that reacted faster with the nucleophile was predominantly formed. Likewise, for unhindered substrates **S6** and **S8**, the Pd intermediate that has the fastest reaction with the

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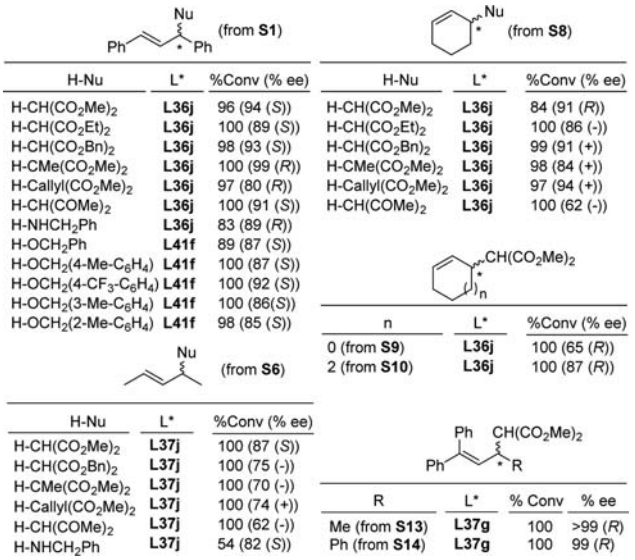
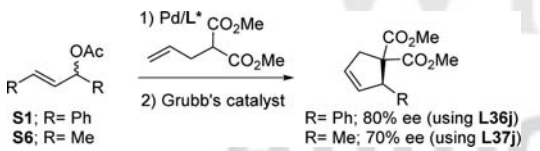


Fig. 11. Summary of the catalytic results in the allylic substitution of several substrates using Pd/**L36–L42** catalysts. Reactions carried out using 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base (except for O-nucleophiles, for which Cs_2CO_3 was used as base), r.t.



Scheme 2. Synthesis of chiral carbocycles using a sequential allylic alkylation and ring-closing metathesis reactions.

nucleophile should be predominantly formed, which leads to high enantioselectivities.[11a]

To speed up the search for ligands for asymmetric catalysis, we more recently focused our research in alternating DFT and experimental work. The usual approach to find new suitable ligands is to use DFT calculations to explain why a certain ligand provides good enantioselectivities, but development stops there. Our new strategy uses the conclusions from DFT to restart the design process, and requires the development of families of ligands, which must be modular and simple to facilitate DFT calculations, NMR spectroscopy characterization of the relevant intermediates, and synthesis of new ligands. In this respect, a library of simple modular phosphite–amine ligands (**L48–L53c–g,j–k**; Figure 2) has been tested successfully in the asymmetric Pd-catalyzed allylic substitution of substrates with different steric and electronic requirements with a large variety of nucleophiles (Figure 12).[13] These ligands, which are prepared in two or three steps from readily available enantiopure amino alcohols, include the benefits of high stability of the amine moiety and additional control provided by both the adaptability of the chiral cavity caused by the biaryl phosphite

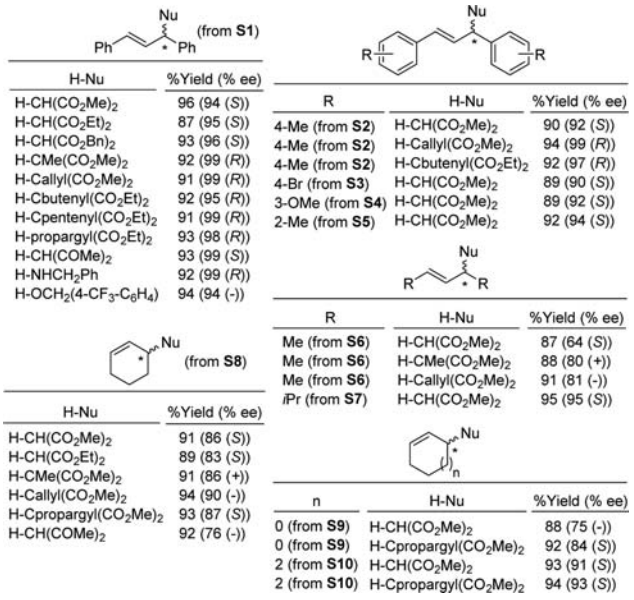


Fig. 12. Summary of the catalytic results in the allylic substitution of several substrates using the Pd/**L52g** catalyst. Reactions carried out using 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base (except for O-nucleophiles, for which Cs_2CO_3 was used as base), 5 °C.

groups and the flexibility of the chiral pocket through a highly modular ligand scaffold. We found that enantioselectivity was controlled mainly by the substituents/configuration at the biaryl phosphite moiety and by the amine substituents, whereas the configuration of the ephedrine backbone had less effect. Theoretically guided optimization based on DFT studies of the relevant intermediates (Pd–allyl and Pd–olefin) and transition states allowed us to rationalize the modifications required in the ligand to improve selectivity. We found that the best results were achieved using ligands **L52f–g**, whereas the analogous ephedrine-based ligands **L48–L51,** with a methyl group in the ligand backbone, provided lower enantioselectivities. Enantioselectivities up to 99% have been achieved for a range of disubstituted hindered and unhindered substrates using a broad range of C-, N-, and O-nucleophiles (Figure 12). Although these results do not surpass the enantioselectivities achieved with Pd/**L1–L4** catalysts, which have emerged as one of the most versatile catalysts for this transformation, it shows that alternating DFT and experimental work in simple ligand systems is a good strategy to find suitable ligands for this process.

By using the Pd/**L52f,g** catalysts, we were able to synthesize a range of chiral five-, six-, and seven-membered carbocyclic compounds by simple sequential allylic substitution and ring-closing metathesis reactions with no loss of enantioselectivity (Scheme 3a).[13] Also, the carbobicycle hydrindane was obtained by cycloisomerization of the corresponding 1,6-

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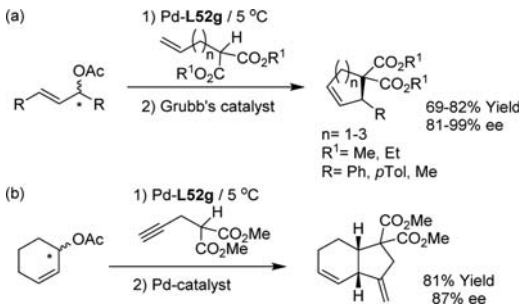

Scheme 3. Preparation of chiral carbocycles by the sequential allylic substitution of functionalized olefins/cyclization reactions.

enyne, produced from the allylic alkylation of **S8** with dimethyl propargylmalonate (Scheme 3b).[13]

3.3. Application of Phosphite–Thioether Ligands

P,S ligands have scarcely been evaluated, although some have proved to be potentially useful in this reaction.[28] Notably, Evans and co-workers reported the successful application of phosphinite–thioether ligands derived from chiral β-hydroxysulfoxides. These ligands were effective in the allylic substitution of model substrates **S1** (*rac*−1,3-diphenyl-3-acetoxyprop-1-ene) and **S8** (*rac*−3-acetoxycyclo-hexene), but had low enantioselectivity for such unhindered linear substrates as **S6** (*rac*−1,3-dimethyl-3-acetoxyprop-1-ene).[17b] They also required low temperature (−20 °C) to achieve high *ee*. To solve the substrate versatility reported with P,S ligands, we need to control S coordination in the Pd intermediates responsible for enantioselectivity. For this purpose, the use of modular ligand scaffolds can be a good strategy. In this context, we decided to apply a sugar-based phosphite–thioether ligand library (**L56**, **L62**–**L63** and **L66c,f,g**; Figure 2).[18c] These ligands, which are prepared from inexpensive D-xylose, also incorporate the advantages of the heterodonor, the robustness of the thioether moiety, and the extra control provided by the flexibility of the chiral pocket through the presence of a biaryl phosphite group and a modular ligand scaffold. By selecting the ligand components, we were able to control sulfur coordination to Pd, and therefore, to achieve, with xylofuranoside ligands **L62g**, excellent enantioselectivities (*ee* values up to >99%) in several substrate types (hindered and unhindered) using a wide range of C-, N-, and O-nucleophiles (Figure 13).[18c] Of particular note are the excellent enantioselectivities obtained in the etherification of linear and cyclic substrates; this represents the first example of successful etherification of both substrate types. The results are comparable with the best ones reported in the literature, including Pd/phosphite-oxazoline **L1**–**L4**, which are considered the most versatile Pd catalysts developed to date for this transformation. This catalytic system has also been successfully applied in the synthesis of

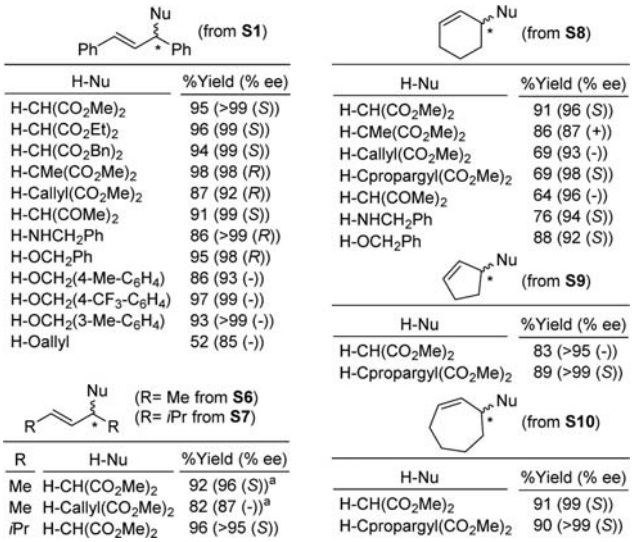

Fig. 13. Summary of the catalytic results in the allylic substitution of several substrates using the Pd/**L62g** catalyst. Reactions carried out using 0.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, CH_2Cl_2 as solvent, BSA/KOAc as base (except for O-nucleophiles, for which Cs_2CO_3 was used as base), r.t. [a] Reaction carried out using Pd/**L66f** catalyst.

chiral carbo- and heterocycles using a simple sequential allylic alkylation/ring-closing metathesis or allylic alkylation/cycloisomerization of 1,6-enyne reactions.[18c]

4. Application of Phosphite-Based Ligands in Pd-Catalyzed Intermolecular Mizoroki–Heck Reactions

The asymmetric Pd-catalyzed Mizoroki–Heck reaction, that is, the coupling of an aryl of alkenyl halide or triflate to an alkene, is also a powerful, highly versatile procedure for the construction of C–C chiral bonds because it tolerates several functional groups.[29] During past decades, research into the Mizoroki–Heck reaction has focused on the possibility of controlling its enantioselectivity. The bulk of the reported examples involve intramolecular reactions, which have the advantage that the alkene regiochemistry and product geometry can be easily controlled. Fewer studies, however, have been conducted on the asymmetric intermolecular version, mainly because regioselectivity is also often a problem.[29] So, for example, the intermolecular Mizoroki–Heck reaction of 2,3-dihydrofuran **S15** with phenyl triflate provides a mixture of two products: the expected product 2-phenyl-2,5-dihydrofuran and 2-phenyl-2,3-dihydrofuran (Scheme 4). The latter is formed as the result of an isomerization process. Although diphosphines (such as BINAP) were used early on this process,[30] heterodonor phosphine–oxazolines have next emerged as more suitable ligands for the intermolecular Mizoroki–Heck reaction.[31] Interestingly, both ligand types offer

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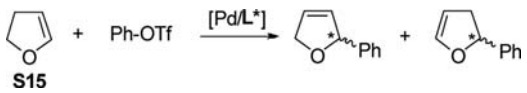

Scheme 4. Model Pd-catalyzed Mizoroki–Heck reaction of 2,3-dihydrofuran **S15** with phenyl triflate.

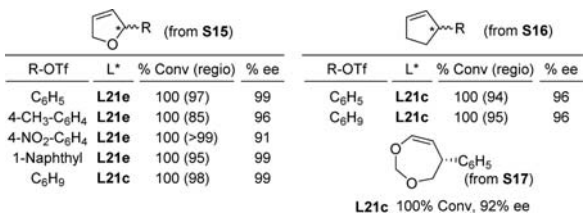

Fig. 14. Summary of the catalytic results achieved in the Pd-catalyzed Mizoroki–Heck reaction of several substrates and triflate sources using **p**yranoside ligands **L21**–**L25**. Reactions carried out using 2.5 mol% $[Pd_2(dba)_3]$dba, 5.2 mol% ligand, THF as solvent, iPr$_2$NEt as base, 70°C.

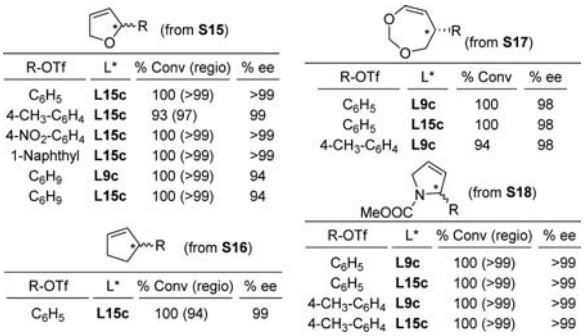

Fig. 15. Summary of the catalytic results achieved in the Pd-catalyzed Mizoroki–Heck reaction of several substrates and triflate sources using ligands **L1**–**L20**. Reactions carried out using 2.5 mol% $[Pd_2(dba)_3]$dba, 5.2 mol% ligand, THF as solvent, iPr$_2$NEt as base, 70°C.

complementary results. Although diphosphines favor the formation of 2-phenyl-2,3-dihydrofuran, regioisomer 2-phenyl-2,5-dihydrofuran is preferentially formed using P,N ligands. Despite all of the advances, there are two main drawbacks in this reaction: the long reaction times usually required to achieve full conversion and the substrate specificity.

4.1. Application of Phosphite–Oxazoline Ligands

Our first approach to tackle the drawbacks of the Mizoroki–Heck reaction was to use the pyranoside phosphite–oxazoline ligand library **L21**–**L25a**–**e**,**h**,**i** (Figure 2). We envisaged that, as for the Pd–allylic substitution reactions, the π-accepting character and flexibility of the biaryl phosphite moiety may have a beneficial effect on activities and substrate versatility, respectively. We were pleased to find out that the introduction, for the first time, of a phosphite moiety in the ligand design proved to be highly advantageous in terms of activity, selectivity, and substrate versatility.[9b],c These ligands have therefore provided high activities (full conversion in hours using thermal conditions or minutes using microwave conditions) and regio- and enantioselectivities (up to 99% in both cases) for a range of substrates (including challenging cyclopentene **S16** and 4,7-dihydro-1,3-dioxepin **S17**) and triflate sources (Figure 14). The catalytic results showed that the catalytic performance was highly influenced by the steric properties of the oxazoline and phosphite substituents. Thus, in contrast to successful phosphine–oxazoline ligands, the presence of bulky oxazoline substituents has a negative effect on both activities and selectivities. On the other hand, bulky substituents in the *ortho* position of the biaryl phosphite moiety are needed for high activity, as well as regio- and enantioselectivity. The best catalytic performance was therefore obtained with ligands **L21**.

Bearing in mind the benefits of incorporating a biaryl phosphite moiety and the fact that phosphine–oxazoline PHOX ligands were one of the most successful ligand backbones developed for this process, we decided to study the application of other phosphite–oxazoline ligands based on a PHOX ligand backbone. We therefore tested ligands **L1**–**L20a**–**e**,**h**,**i**.[7c] We were pleased to see that by using Pd/phosphite–oxazolines **L9c** and **L15c**, excellent activities, combined with high regio- and enantioselectivities, could be reached for a wide range of substrates and triflate sources (Figure 15).

The best results were obtained with ligands **L9c** and **L15c**. Under microwave-irradiation conditions, reaction times were considerably shorter (from 24 h reported for phosphine–oxazoline PHOX to 10 min with ligands **L9c** and **L15c**) and regio- and enantioselectivities were still excellent. Therefore, we found that by selecting the ligands parameters we could improve the results obtained with the previous Pd/**L21** catalysts considerably. A larger number of substrates could be successfully coupled using a bigger number of triflate sources. These results compete favorably with the best ones published in the literature.[29]

4.2. Application of Phosphite–Oxazole/Imidazole Ligands

Finally, we studied whether the introduction of a biaryl phosphite moiety also had a positive effect when combined to other N-donor groups than oxazolines. For this purpose, we applied phosphite–oxazole ligands **L28**–**L31c**–**e**,**h**–**k** and phosphite–imidazole ligands **L35c**–**e**,**h**–**k** (Figure 2) in asymmetric intermolecular Pd-catalyzed Mizoroki–Heck reactions under thermal and microwave conditions and compared the results with those of the phosphinite analogues.[11c] The results showed again the benefits of incorporating a phosphite moiety. Thus, phosphite-based ligands provided higher activities and selectivities than their phosphinite analogues (i.e., the use of Pd/**L28c** in the phenylation of **S15**, the Mizoroki–Heck adduct

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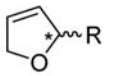
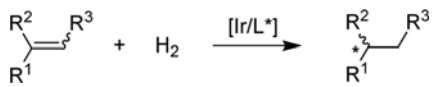


R-OTf	L*	% Conv (regio)	% ee
C_6H_5	**L28c**	77 (97)	98
4-CH_3-C_6H_4	**L28c**	69 (92)	99
4-NO_2-C_6H_4	**L28c**	99 (>99)	99
1-Naphthyl	**L28c**	98 (95)	>99
C_6H_9	**L28c**	92 (99)	69

Fig. 16. Summary of the catalytic results achieved in the Pd-catalyzed Mizoroki–Heck reaction of **S15** using several triflate sources using ligands **L28**–**L31** and **L35**. Reactions carried out using 2.5 mol% $[Pd_2(dba)_3]dba$, 5.2 mol% ligand, THF as solvent, *i*Pr_2NEt as base, 70°C.



Scheme 5. Asymmetric hydrogenation of minimally functionalized olefins.

2-phenyl-2,5-dihydrofuran is achieved in 77% conversion, 97% regioselectivity, and 98% *ee*, whereas the phosphinite analogue provided 2-phenyl-2,5-dihydrofuran in 9% conversion, 81% regioselectivity, and 56% *ee*). By suitably tuning the ligand components, we could achieve high regio- and enantioselectivities, although activities were lower than those previously reported phosphite–oxazoline ligands **L9c** and **L15c** (Figure 16).

5. Application of Phosphite/Phosphoroamidite-Based Ligands in Ir-Catalyzed Hydrogenation of Minimally Functionalized Olefins

Asymmetric hydrogenation is one of the most efficient, sustainable, and straightforward routes to create stereogenic centers. It has perfect atom economy and is operationally simple.[32] Compared with the Rh/Ru-catalyzed hydrogenation of substrates with a good coordinative group close to the C=C bond, enantiodiscrimination in the hydrogenation of minimally functionalized olefins is still challenging and requires more sophisticated ligand design (Scheme 5).[2d,e,33] Ir catalysts modified with phosphine/phosphinite/carbene–oxazoline, phosphine/phosphinite–oxazole/thiazole and phosphinite–pyridine were developed and successfully applied in this process. Despite this success, the reduction of minimally functionalized olefins was still highly substrate-dependent and other types of substrates still required much attention.

Although phosphites first emerged as successful ligands for Rh hydrogenation of functionalized olefins,[34] it was not until 2008 that a publication reported their use in the reduction of minimally functionalized olefins with limited success. A TADDOL-based phosphite–oxazoline ligand library was applied in the Ir hydrogenation of some model minimally functionalized substrates, with lower activities and selectivities than their related phosphinite/phosphine–oxazoline ligands, and required higher pressures (100 bars) and higher catalyst loadings (4 mol%) to obtain full conversions.[35] With the aim of taking advantage of phosphite/phosphoroamidite-containing ligands for asymmetric catalysis our group decided to find more versatile heterodonor phosphite/phosphoroamidite-containing ligands for the Ir hydrogenation of minimally functionalized olefins.

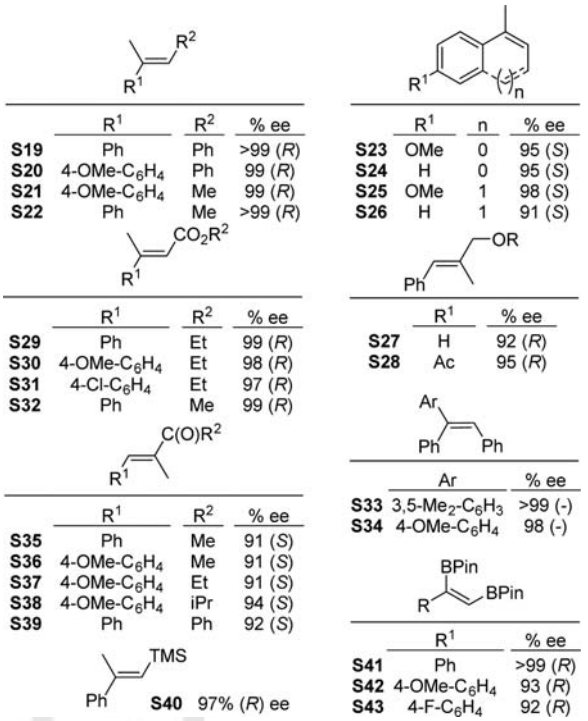


Fig. 17. Summary of the catalytic results in the hydrogenation of several minimally functionalized trisubstituted olefins using [Ir(**L22c**)(cod)]BAr_F catalyst precursor. Reaction conditions: 0.2 mol% catalyst, CH_2Cl_2 as solvent, 50 bar H_2, 2 h.

5.1. Application of Phosphite/Phosphoroamidite–Oxazoline/Thiazoline Ligands

Our group first applied previously mentioned phosphite–oxazoline ligand libraries **L5**–**L20** and **L21**–**L25** in this process.[7a,b,9e] We were able to identify representative ligands in each ligand library (**L9c**, **L9i**, **L22c** and **L22e**) with good performance in the reduction of 50 substrates (Figures 17 and 18), including challenging terminal disubstituted olefins (*ee* values up to 99% for a range of substrates) at low catalyst loadings (0.2 mol%) and under mild reaction conditions (1 bar of H_2). Although both ligand libraries provide similar levels of enantioselectivity for the reduction of trisubstituted olefins, the use of pyranoside ligands **L22c** and **L22e** allows the range

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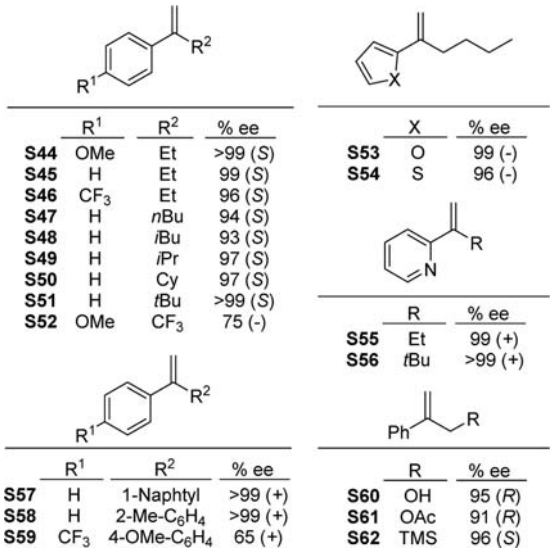

Fig. 18. Summary of the catalytic results in the hydrogenation of several minimally functionalized disubstituted olefins using [Ir(**L9i**)(cod)]BAr_F catalyst precursor. Reaction conditions: 0.5 mol% catalyst, CH_2Cl_2 as solvent, 1 bar H_2 for **S43–S55** or 50 bar of H_2 for **S56–S61**, 2 h.

of substrates to be expanded to include α,β-unsaturated ketones, vinyl silanes, vinyl boronates, and triaryl-substituted olefins.[9e,f] The successful hydrogenation of substrates with poorly coordinative groups is of particular importance because they can be further converted into relevant intermediates for synthesizing more complex chiral molecules. In this respect, the effective hydrogenation of vinylboronates opened up an appealing route for obtaining chiral borane compounds, which could be easily transformed into high-value compounds because C–B can be readily converted into C–O, C–N, and C–C bonds with the retention of chirality. The hydrogenation of α,β-unsaturated ketones have also received much consideration because it is an elegant and easy route to produce ketones with a chiral center in the α position of the carbonyl moiety. Another relevant set of substrates are the triaryl-substituted olefins, the hydrogenation of which provides an easy entry point into diarylmethine chiral centers, which are present in several important drugs (such as ®-tolterodine and sertraline) and natural products (i.e., podohyllotoxin).[36] In addition, high enantioselectivities (*ee* values up to 98%) were also obtained for more demanding *Z* isomers, which usually reacted with a lower enantioselectivity than that of the corresponding *E* isomers.[2d,33]

More remarkably, these ligands represent the first ones that were successfully applied in a broad range of minimally functionalized 1,1-disubstituted olefins (29 examples; Figure 18).[7a,b,9e,f] Unlike trisubstituted substrates, at that moment disubstituted substrates were not successfully hydrogenated and finding a ligand with a broad substrate scope was highly appealing. This is because the catalyst has the added difficulty of controlling not only the isomerization of the olefins to form the more stable *E*-trisubstituted substrates, which are hydrogenated to form the opposite enantiomer, but also face-selectivity coordination. Although both ligand families provided similar levels of enantioselectivity, in contrast to the reduction of trisubstituted olefins, the use of phosphite–oxazoline ligands **L9c** and **L9i**, allowed the range of substrates to be expanded to include substrate classes that had never been asymmetrically hydrogenated before (i.e., trifluoromethyl-containing olefins **S52**, 1,1-hetereoraryl-alkyl olefins **S53–S56**, 1,1-diaryl olefins **S60–S62**, . . .).[7b]

Notably, high enantioselectivities were obtained, for the first time, in the hydrogenation of diaryl terminal olefins **S60–S62**, the hydrogenation products of which were important intermediates for the preparation of drugs and research materials.[37] To date, chiral diarylalkanes are prepared through some rather laborious approaches.[37,38] It was also found that these catalytic systems had high tolerance to the steric and electronic requirements of the substrate and also to the presence of poorly coordinative groups. High enantioselectivities were achieved in the reduction of allylic alcohols, acetates, and silanes as well as in the hydrogenation of trifluoromethyl-containing olefins. The hydrogenation of these latter compounds is used in the development of important organic intermediates (such as fragrances) and in a number of new organosilicon and -fluorine drugs.[39]

The introduction of a thiazoline moiety, with ligands **L26** and **L27**, allowed the substrate scope of the Ir/**L9** catalysts to be increased. High enantioselectivities of up to >99% were therefore achieved for a range of α,β-unsaturated ketones **S35–S39**, vinyl silane **S40**, and trifluoromethyl olefins **S52**.[10b] The use of Ir/**L26c** has also increased the enantioselectivities of simple Z-trisubstituted olefins, such as **S23**, up to 96%, while maintaining excellent enantioselectivities for the rest of *E*-trisubstituted and 1,1-disubstituted minimally functionalized olefins.

Catalyst libraries Ir/**L5–L20** and Ir/**L21–L25** were also effective using propylene carbonate, an alternative environmentally friendly solvent, which allowed the catalyst to be reused, while maintaining excellent enantioselectivities.[7b,9f] Again, the simple substitution of the phosphine by a biaryl phosphite group extended the range of olefins that could be successfully hydrogenated, and gave enantioselectivities that surpassed the best reported so far.

In collaboration with Profs. P.-O. Norrby and P. G. Andersson, we also performed a detailed computational study that identified the preferred reaction path: an Ir^{III}/Ir^{V} cycle with migratory insertion of a hydride as the selectivity-determining step (Scheme 6).[9f]

We also found that the favored enantiomer and the effect of ligand modifications could be rationalized by using a simple

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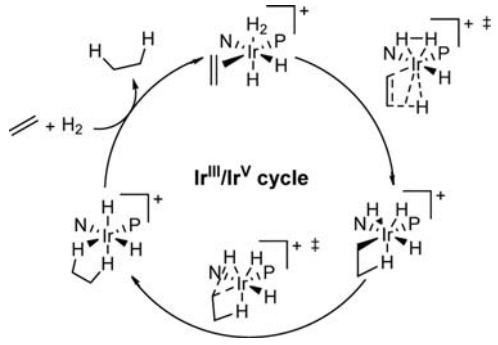


Scheme 6. The Ir^{III}/Ir^{V} migratory-insertion/reductive-elimination catalytic cycle for the hydrogenation of minimally functionalized olefins.

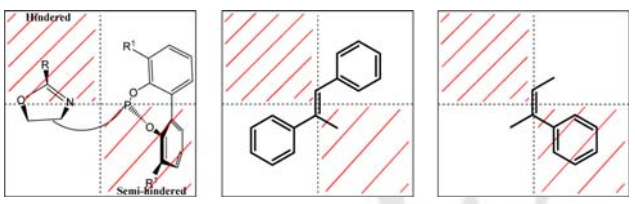
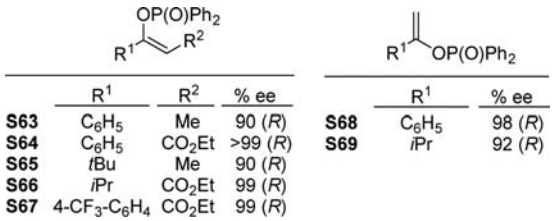


Fig. 19. Quadrant diagram describing the enantioselective substrate–ligand interactions.

quadrant model (Figure 19). In this quadrant model, the oxazoline substituent occupies the upper-left quadrant, and the biaryl phosphite group partly blocks the lower-right quadrant. The other two quadrants are free (Figure 19). This quadrant model therefore generates a chiral pocket that is well suited to (*E*)-olefins. However, the use of flexible biaryl phosphite moieties allows the tuning of the steric hindrance of the lower right quadrant, which is key for the successful asymmetric hydrogenation of Z-trisubstituted, triaryl-substituted, and 1,1-disubstituted olefins. The DFT studies therefore verify that the flexibility of the biaryl phosphite groups seems to be crucial in expanding the substrate scope.[9f]

More recently, our group in collaboration with Andersson's group decided to prepare Ir catalysts containing bicyclic phosphoroamidite–oxazoline ligands (Figure 2; **L54h**,**i**), for application to the Ir hydrogenation of minimally functionalized olefins.[14] These catalytic systems were derived from a previously successful generation of Ir bicyclic N-phosphine–oxazoline catalysts, by replacing the N-phosphine group of the ligand with a π-accepting biaryl phosphoroamidite moiety. The simple substitution of the N-phosphine by a phosphoroamidite group extended the range of olefins that could be successfully hydrogenated. Thus, a wide range of tri- and disubstituted enol phosphinites were hydrogenated in enantioselectivities that were comparable, for most of the substrates, to the best reported so far (Figure 20). The effective hydrogenation of this type of substrate opened up an appealing route for



	R^1	R^2	% ee
S63	C_6H_5	Me	90 (*R*)
S64	C_6H_5	CO_2Et	>99 (*R*)
S65	*t*Bu	Me	90 (*R*)
S66	*i*Pr	CO_2Et	99 (*R*)
S67	4-CF_3-C_6H_4	CO_2Et	99 (*R*)

	R^1	% ee
S68	C_6H_5	98 (*R*)
S69	*i*Pr	92 (*R*)

Fig. 20. Summary of the catalytic results in the hydrogenation of several enol phosphinites using ligand **L54i**. Reactions carried out using 1 mol% of catalyst, CH_2Cl_2 as solvent at 50 bar of H_2 for 12 h.

obtaining chiral organophosphinates, which could be easily transformed into high-value compounds, such as alcohols and phosphines.

5.2. Application of Other P–X Biaryl Phosphite-Containing Ligands

Despite advances in Ir-based phosphite/phosphoroamidite–oxazoline/thiazoline ligand libraries, more research was still needed to improve the substrate scope even further. For this reason, our research progressed to heterodonor biaryl phosphite-X ligands bearing more robust X-donor groups than oxazolines. In this respect, we synthesized several families of heterodonor phosphite/phosphoroamidite–oxazole, thiazole, pyridines, and thioether ligands.[11b,12b,14,18a,b,19,20] The best results were obtained with phosphite–pyridine and phosphite–thioether ligand families.

5.2.1. Application of Phosphite–Pyridine Ligands

Pfaltz et al. first prepared a new class of P,N-containing Ir catalysts with the synthesis of iridium complexes containing chiral phosphinite–pyridine ligands, to mimic the Crabtree catalyst even more.[40] They first applied phosphinite–pyridine ligands **2** in the Ir hydrogenation of a limited range of minimally functionalized alkenes. The performance of Ir/**2** was then further improved with the use of ligands **3**, which had a more rigid bicyclic ligand backbone. However, there was still a problem of substrate range limitation, since high performance was mainly limited to trisubstituted olefins.

To further increase the substrate scope, our group decided to take the first generation of Pfaltz's phosphinite–pyridine ligands **2** and replace the phosphinite group with biaryl phosphite moieties (ligands **L36–L47c–g**,**j**,**k**; Figure 2).[12b] Enantioselectivities were excellent (*ee* values up to >99%) in both enantiomers of the reduction products and in a wide range of *E*- and *Z*-trisubstituted and 1,1-disubstituted terminal alkenes (Figure 22).[12b] It should be noted that these catalytic systems also have high tolerance to the presence of a neighboring polar group, and therefore, tri- and disubstituted allylic alcohols, acetates, α,β-unsaturated esters ketones, allylic silanes, vinylboronates, and trifluoromethyl olefins can be hydrogenated in

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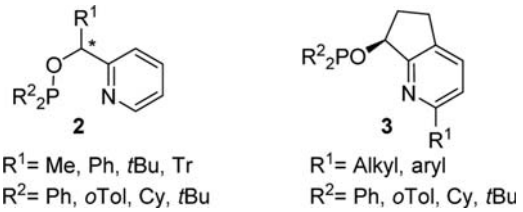
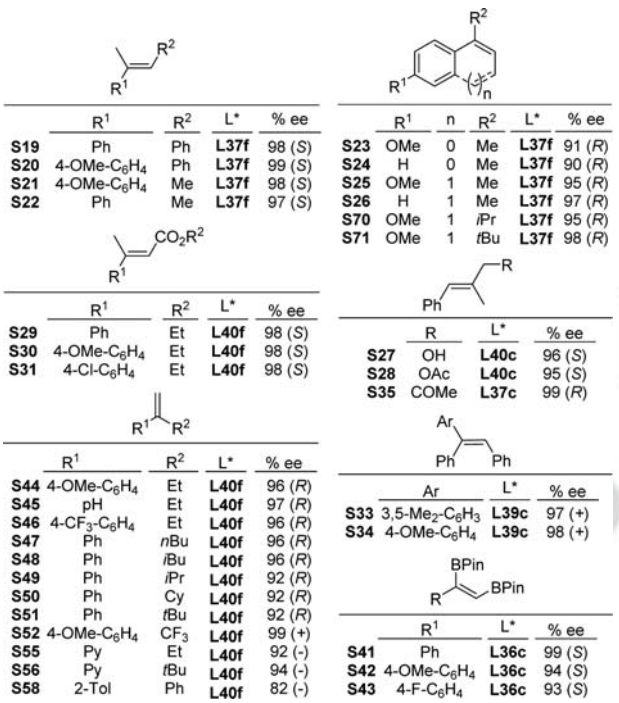


Fig. 21. First (ligands **2**) and second (ligands **3**) generation phosphinite–pyridine ligands developed by Pfaltz et al.



	R^1	R^2	L*	% ee
S19	Ph	Ph	**L37f**	98 (*S*)
S20	4-OMe-C_6H_4	Ph	**L37f**	99 (*S*)
S21	4-OMe-C_6H_4	Me	**L37f**	98 (*S*)
S22	Ph	Me	**L37f**	97 (*S*)

	R^1	n	R^2	L*	% ee
S23	OMe	0	Me	**L37f**	91 (*R*)
S24	H	0	Me	**L37f**	90 (*R*)
S25	OMe	1	Me	**L37f**	95 (*R*)
S26	H	1	Me	**L37f**	97 (*R*)
S70	OMe	1	*i*Pr	**L37f**	95 (*R*)
S71	OMe	1	*t*Bu	**L37f**	98 (*R*)

	R^1	R^2	L*	% ee
S29	Ph	Et	**L40f**	98 (*S*)
S30	4-OMe-C_6H_4	Et	**L40f**	98 (*S*)
S31	4-Cl-C_6H_4	Et	**L40f**	98 (*S*)

	R	L*	% ee
S27	OH	**L40c**	96 (*S*)
S28	OAc	**L40c**	95 (*S*)
S35	COMe	**L37c**	99 (*R*)

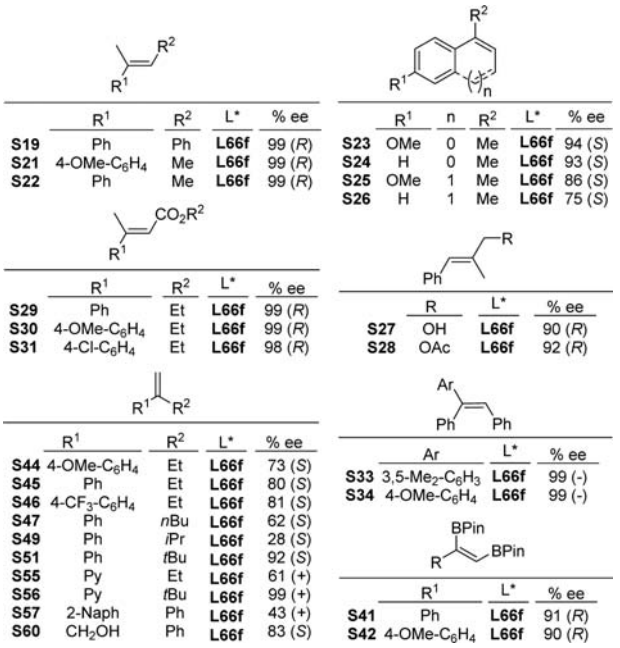
	R^1	R^2	L*	% ee
S44	4-OMe-C_6H_4	Et	**L40f**	96 (*R*)
S45	pH	Et	**L40f**	97 (*R*)
S46	4-CF_3-C_6H_4	Et	**L40f**	96 (*R*)
S47	Ph	*n*Bu	**L40f**	96 (*R*)
S48	Ph	*i*Bu	**L40f**	96 (*R*)
S49	Ph	*i*Pr	**L40f**	92 (*R*)
S50	Ph	Cy	**L40f**	92 (*R*)
S51	Ph	*t*Bu	**L40f**	92 (*R*)
S52	4-OMe-C_6H_4	CF_3	**L40f**	99 (+)
S55	Py	Et	**L40f**	92 (-)
S56	Py	*t*Bu	**L40f**	94 (-)
S58	2-Tol	Ph	**L40f**	82 (-)

	Ar	L*	% ee
S33	3,5-Me_2-C_6H_3	**L39c**	97 (+)
S34	4-OMe-C_6H_4	**L39c**	98 (+)

	R^1	L*	% ee
S41	Ph	**L36c**	99 (*S*)
S42	4-OMe-C_6H_4	**L36c**	94 (*S*)
S43	4-F-C_6H_4	**L36c**	93 (*S*)

Fig. 22. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphite–pyridine ligands **L36**–**L47c**–**g**,**j**,**k**. Reactions carried out using 0.25–1 mol% of catalyst, CH_2Cl_2 as solvent at 50 bar of H_2 (except for **S44**–**S52** and **S55**–**S56**, which were performed at 1 bar of H_2) for 2 h.

high enantioselectivities. The effectiveness of these ligands was also corroborated by the fact that Ir/**L36**–**L47c**–**g**,**j**,**k** catalysts provided higher enantioselectivity for a broader range of substrates than their phosphinite–pyridine analogues (ligands **2**; Figure 21).[40a] Moreover, the results of our Ir/**L36**–**L47c**–**g**,**j**,**k** catalyst library compare very well with those achieved using the second generation of phosphinite–pyridine ligands (Figure 21; ligands **3**),[40b,c] which can be considered as the state of the art for this transformation, with the added advantage that our Ir–phosphite–pyridine systems are able to expand the scope to a broad range of disubstituted substrates.



	R^1	R^2	L*	% ee
S19	Ph	Ph	**L66f**	99 (*R*)
S21	4-OMe-C_6H_4	Me	**L66f**	99 (*R*)
S22	Ph	Me	**L66f**	99 (*R*)

	R^1	n	R^2	L*	% ee
S23	OMe	0	Me	**L66f**	94 (*S*)
S24	H	0	Me	**L66f**	93 (*S*)
S25	OMe	1	Me	**L66f**	86 (*S*)
S26	H	1	Me	**L66f**	75 (*S*)

	R^1	R^2	L*	% ee
S29	Ph	Et	**L66f**	99 (*R*)
S30	4-OMe-C_6H_4	Et	**L66f**	99 (*R*)
S31	4-Cl-C_6H_4	Et	**L66f**	98 (*R*)

	R	L*	% ee
S27	OH	**L66f**	90 (*R*)
S28	OAc	**L66f**	92 (*R*)

	R^1	R^2	L*	% ee
S44	4-OMe-C_6H_4	Et	**L66f**	73 (*S*)
S45	Ph	Et	**L66f**	80 (*S*)
S46	4-CF_3-C_6H_4	Et	**L66f**	81 (*S*)
S47	Ph	*n*Bu	**L66f**	62 (*S*)
S49	Ph	*i*Pr	**L66f**	28 (*S*)
S51	Ph	*t*Bu	**L66f**	92 (*S*)
S55	Py	Et	**L66f**	61 (+)
S56	Py	*t*Bu	**L66f**	99 (+)
S57	2-Naph	Ph	**L66f**	43 (+)
S60	CH_2OH	Ph	**L66f**	83 (*S*)

	Ar	L*	% ee
S33	3,5-Me_2-C_6H_3	**L66f**	99 (-)
S34	4-OMe-C_6H_4	**L66f**	99 (-)

	R^1	L*	% ee
S41	Ph	**L66f**	91 (*R*)
S42	4-OMe-C_6H_4	**L66f**	90 (*R*)

Fig. 23. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphite–thioether ligands **L56**–**L70a**–**i**. Reactions carried out using 0.5–2 mol% of catalyst, CH_2Cl_2 as solvent at 100 bar of H_2 (except for **S44**–**S56**, which were performed at 1 bar of H_2, and for **S57** and **S60**, which were performed at 50 bar of H_2) for 4 h.

5.2.2. *Application of P-Thioether Ligands*

In contrast to Rh/Ru hydrogenation, for the hydrogenation of minimally functionalized alkenes, research centered on developing heterodonor P,N-containing ligands.[2d,e,33] Changing the N-donor group was not contemplated until recently. In 2011, our group reported the application of the first P-thioether ligand family for the reduction of minimally functionalized olefins.[18a,b] At the same time, Pfaltz et al. successfully reported the application of proline-based P,O ligands in the asymmetric hydrogenation of trisubstituted alkenes.[41]

Initially, we applied a highly modular furanoside phosphite–thioether ligand library **L56**–**L70a**–**i** (Figure 2).[18a,b] These ligands, which are prepared from readily available xylose, include the benefits of the high stability of the thioether group and the additional control of sulfur inversion by the help of both the flexibility of the biaryl phosphite moieties and the highly modular ligand scaffold. By carefully selecting the ligand parameters, we found that ligands **L63**–**L66**, with a 5-deoxyribofuranoside backbone, provided the best enantioselectivities. Excellent enantioselectivities, comparable to the best ones reported in the literature, were obtained (*ee* values up to 99%) for the reduction of a very broad range of minimally functionalized alkenes (Figure 23), including relevant examples with poorly coordinative groups (such as α,β-unsaturated esters and vinylboronates; Figure 23).[18a,b]

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For the reduction of terminal disubstituted aryl/alkyl olefins, the enantioselectivities are affected by the nature of the alkyl substrate substituent, while the electronic nature of the aryl ring had little effect. This is due to an isomerization process, as supported by the fact that the hydrogenation of substrates bearing a *tert*-butyl group, for which isomerization cannot occur, provides high levels of enantioselectivity (*ee* values up to 98%), whereas the lowest enantioselectivities of the series are found for substrates that form the most stable isomerized tetrasubstituted olefins. Enantioselectivities were therefore best in the asymmetric reduction of aryl and heteroaryl/*tert*-butyl substrates (*ee* values up to 99%). Asymmetric hydrogenation was also performed using propylene carbonate as the solvent, which allowed the Ir catalysts to be reused up to five times with excellent enantioselectivities.

Finally, we also studied the effect on catalytic performance of introducing either phosphinite or phosphine moieties (data not shown).[18b] The results showed that replacing the phosphite moiety with several phosphine or phosphinite moieties had a negative effect on the catalytic performance.

We then moved our research to find new P-thioether ligand libraries that should be prepared in fewer steps than previous furanoside P,S ligands, but still maintaining a highly modular scaffold. In collaboration with Pericas's group, we therefore next applied a library of a family of phosphite–thioether ligands (Figure 2; ligands **L71**–**L80a**,**f**,**g**) in the Ir hydrogenation of minimally functionalized olefins.[19] In only three steps, several ligand parameters were easily varied to maximize the enantioselectivities for each substrate. The modular ligand design, with help of DFT studies, was crucial to find which ligand parameters should be modified to generate the most selective catalysts. DFT studies showed that the introduction of a bulky mesityl group (ligand **L80**) instead of a phenyl group (ligand **L76**) in the ligand backbone was required for high enantioselectivity.

In contrast to previous sugar-based thioether-P compounds **L56**–**L70**, changing the phosphite moiety for a bulky di-*o*-tolyl phosphinite group had a positive effect on enantioselectivity, which confirmed the relevance of using modular scaffolds to construct new ligand families. Excellent enantioselectivities comparable to those achieved with previous furanoside P–S analogues were obtained,[18a,b] with two added advantages. First, Ir/P-thioether catalysts **L71**–**L80** were able to expand the number of substrates effectively hydrogenated, including α,β-unsaturated enones, tri- and disubstituted alkenylboronic esters, and olefins with trifluoromethyl substituents (Figure 24). Second, because the starting enantiopure epoxides are obtained through a catalytic Sharpless epoxidation, both enantiomers of the P,S-ligands are therefore easily available.

With the aim of further studying the performance of P-thioether compounds as a new class of ligands for this process, we decided to perform a study of the species responsible

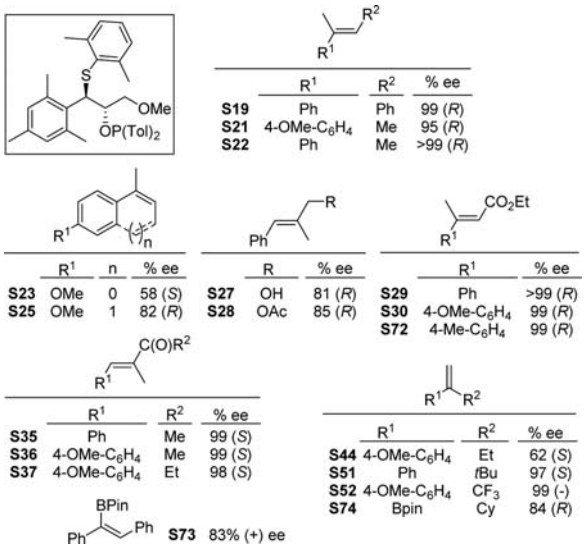

Fig. 24. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphinite–thioether ligand. Reactions carried out using 0.5–2 mol% of catalyst, CH_2Cl_2 as solvent at 100 bar of H_2 (except for **S44**, **S51**, **S52,** and **S74**, which were performed at 1 bar of H_2) for 4 h.

for the catalytic performance under hydrogenation conditions. No experimental studies of the mechanism and nature of the relevant catalytic intermediates under hydrogenation conditions were yet carried out with these type of ligands. For this purpose, we need to design P,S ligands with a simple ligand backbone, and thus, their NMR spectra are simple, with reduced signal overlap, which facilitates the identification of relevant intermediates. We therefore used a reduced but structurally valuable phosphite–thioether ligand library (Figure 2; ligands **L81**,**L82c**–**g**).[20] These phosphite–thioether ligands were synthesized in only two steps. Enantioselectivities up to 99% were reached in the hydrogenation of 40 minimally unfunctionalized alkenes, including a variety of olefins that have recently attracted attention because their hydrogenated compounds can lead to high-value chemicals. Moreover, these catalysts extended the state-of-the-art with the successful reduction, for the first time, of terminal aryl-substituted boronic esters (Figure 25).

By combining HP-NMR spectroscopy and theoretical studies, we were able to identify the catalytically competent Ir–dihydride alkene species, which made it possible to explain the enantioselectivity obtained. In this respect, we investigated the reactivity of iridium precatalysts [Ir(cod)(P–S)]BAr_F (P–S=*ent*-**L82f** and **L82g**) with H_2 in the presence of alkene **4** (Scheme 7).[20] For each precatalyst, the most abundant complexes were assigned to the dihydride species **5** and **7** and the minor isomers were assigned to the dihydride intermediate species [Ir$(H)_2$(**4**)(P–S)]BAr_F **6** and **8**, in which the alkene is coordinated. Then, the screening of precatalysts [Ir(cod)(*ent*-**L82f**)]BAr_F and [Ir(cod)(**L82g**)]BAr_F with the same alkene,

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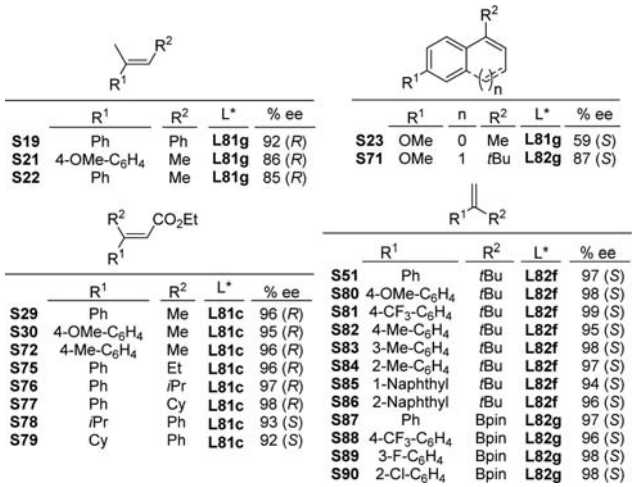


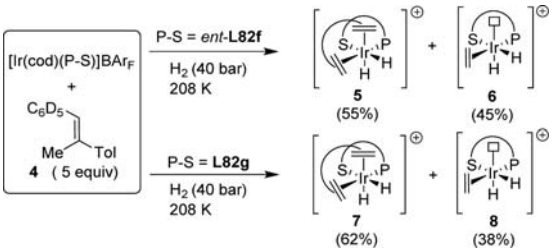
	R^1	R^2	L*	% ee
S19	Ph	Ph	L81g	92 (*R*)
S21	4-OMe-C_6H_4	Me	L81g	86 (*R*)
S22	Ph	Me	L81g	85 (*R*)

	R^1	n	R^2	L*	% ee
S23	OMe	0	Me	L81g	59 (*S*)
S71	OMe	1	*t*Bu	L82g	87 (*S*)

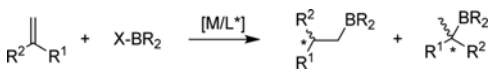
	R^1	R^2	L*	% ee
S29	Ph	Me	L81c	96 (*R*)
S30	4-OMe-C_6H_4	Me	L81c	95 (*R*)
S72	4-Me-C_6H_4	Me	L81c	96 (*R*)
S75	Ph	Et	L81c	96 (*R*)
S76	Ph	*i*Pr	L81c	97 (*R*)
S77	Ph	Cy	L81c	98 (*R*)
S78	*i*Pr	Ph	L81c	93 (*S*)
S79	Cy	Ph	L81c	92 (*S*)

	R^1	R^2	L*	% ee
S51	Ph	*t*Bu	L82f	97 (*S*)
S80	4-OMe-C_6H_4	*t*Bu	L82f	98 (*S*)
S81	4-CF_3-C_6H_4	*t*Bu	L82f	99 (*S*)
S82	4-Me-C_6H_4	*t*Bu	L82f	95 (*S*)
S83	3-Me-C_6H_4	*t*Bu	L82f	98 (*S*)
S84	2-Me-C_6H_4	*t*Bu	L82f	97 (*S*)
S85	1-Naphthyl	*t*Bu	L82f	94 (*S*)
S86	2-Naphthyl	*t*Bu	L82f	96 (*S*)
S87	Ph	Bpin	L82g	97 (*S*)
S88	4-CF_3-C_6H_4	Bpin	L82g	96 (*S*)
S89	3-F-C_6H_4	Bpin	L82g	98 (*S*)
S90	2-Cl-C_6H_4	Bpin	L82g	98 (*S*)

Fig. 25. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphite–thioether ligands **L81** and **L82c–g**. Reactions carried out using 0.5–2 mol% of catalyst, CH_2Cl_2 as solvent at 100 bar of H_2 (except for **S51**, and **S80** and **S90**, which were performed at 1 bar of H_2) for 4 h.



Scheme 7. Reactivity of [Ir(cod)(P–S)]BAr_F complexes with olefin **4** under hydrogenation conditions.



Scheme 8. Asymmetric hydroboration of 1,1-disusbstituted olefins.

under the reaction conditions used for HP-NMR spectroscopy, showed that the configuration of the product obtained from hydrogenation was opposite to that determined for intermediate dihydride species **6** and **8**. These results therefore indicate that the hydrogenation of **4** with the Ir/*ent*-**L82f** and Ir/**L82g** catalytic systems follow the Halpern-type mechanism, in which the less stable intermediate species (not detected in our case) react faster than major intermediates **6** and **8**, and they are converted into the major product enantiomer.[19]

6. Application of Phosphite-Based Ligands in Ir-Catalyzed Hydroboration of 1,1-Disubstituted Alkenes

All results obtained so far more recently encouraged us to move our research to a more challenging asymmetric catalytic transformation: the Ir hydroboration of 1,1-disubstituted olefins. The transition-metal-catalyzed asymmetric hydroboration has attracted considerable interest for synthesizing chiral organoboron compounds, which are valuable organic intermediates because the C–B bond can be readily transformed into chiral C–N, C–O, and C–C bonds (Scheme 8).[42] However, whereas the asymmetric hydroboration of monosubstituted and internal 1,2-disubstituted olefins has been well studied, the hydroboration of 1,1-disubstituted olefins remains a challenge.[43] This is because the chiral transition-metal catalyst has difficulty in controlling not only the specific boration at the desired terminal β position, rather than at the more substituted α-position (most catalysts favor Markovnikov regioselectivity),[44] but also the face selectivity coordination (due to the presence of two relatively similar substituents at the geminal position).

To date, high regio- and enantioselectivities, using M-catalyzed hydroboration, have been reported in only two publications, with limited substrate scope.[45] One of them showed that Cu–carbene catalysts could hydroborate α-methylstyrenes, and some aryl olefins with alkyl substituents other than the typical methyl unit and exocyclic alkenes, with high regio- and enantioselectivities in the range 61–92% *ee*. However, high catalyst loading (7.5%), long reaction times (48 h), low temperature (−50 °C), and the presence of an almost equimolar amount of base were required.[45a] The other report showed that Ir–phosphine–oxazoline PHOX catalysts could hydroborate 1,1-disubstituted olefins.[45b] However, the enantioselectivity was only high for α-methylstyrene. Although fewer substrates were successfully hydroborated than those for the Cu–carbene catalysts, the Ir–PHOX catalysts allow this transformation to take place under milder reaction conditions and with lower catalyst loading. With the aim of increasing the substrate versatility and having into account the similarities of the elementary steps involved in hydroboration and hydrogenation, we decided, as a first approach, to apply the phosphite–oxazoline **L1–L4c**,**f**,**g** analogues (Figure 2). We were glad to see that the new phosphite–oxazoline PHOX-based ligands could efficiently hydroborate (enantioselectivity up to 94%, excellent yields, and perfect regioselectivity) a broader range of olefins than previous phosphine–oxazoline PHOX ligands (Figure 26).[5b] Particularly, we were able to successfully hydroborate a wide range of α-*tert*-butylstyrenes, with aryl substituents that had different electronic and steric properties; thus complementing the results of Cu–carbene catalysts, which was the only other system reported to date that attempted these reactions. In addition, the introduction of a biaryl phosphite moiety allows, for the first time, the highly regioselective hydroboration of aryl/trifluoromethyl olefins (Figure 26).[5b]

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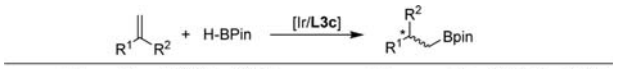

	R^1	R^2	% Yield	% ee		R^1	R^2	% Yield	% ee
S91	Ph	Me	93	50 (*S*)	**S96**	4-Me-C_6H_4	*t*Bu	93	50 (*S*)
S92	Ph	Et	90	56 (*S*)	**S97**	4-OMe-C_6H_4	*t*Bu	90	56 (*S*)
S93	Ph	*i*Bu	89	58 (*S*)	**S98**	4-CF_3-C_6H_4	*t*Bu	89	58 (*S*)
S94	Ph	*i*Pr	88	58 (*S*)	**S99**	3-Me-C_6H_4	*t*Bu	88	58 (*S*)
S95	Ph	*t*Bu	91	92 (*S*)	**S100**	Ph	CF_3	91	92 (*S*)

Fig. 26. Summary of the catalytic results in the hydroboration of several 1,1-disubstituted olefins using Ir/**L3c** catalyst. Reactions carried out using 1.25 mol% of $[Ir(\mu\text{-Cl})(cod)]_2$, 2.5 mol% of ligand, hexane (2 mL), 18 h. In all cases, regioselectivities were >99%.

7. Conclusions

Despite the early success of phosphites in transition-metal-catalyzed reactions, such as Rh hydroformylation, Cu conjugate additions, and Rh hydrogenation of functionalized olefins, their high potential for other relevant M-catalyzed reactions was not discovered until recently, as shown herein. With ligands that contain phosphite/phosphoroamidite groups, important breakthroughs have been achieved in the asymmetric hydrogenation of minimally functionalized olefins, asymmetric allylic substitution and Mizoroki–Heck reactions, and the hydroboration of 1,1-disubstituted alkenes. Our NMR spectroscopy and DFT studies confirmed that the exceptionally broad substrate scope of ligands containing phosphites was due to the flexibility of the biaryl phosphite moieties, which helped the ligands to adapt the size of the substrate-binding pocket to the reaction substrate. This also explains their excellent performance in several catalytic processes. We also found that the π-accepting character of the phosphite/phosphoroamidite moiety had a positive effect on the activity and favored regioselectivity. The structural diversity of phosphites/phosphoroamidite moieties and the variety of ligand backbones generate many combinations for derivatization and tailoring of synthetic tools in the search for the right ligand for each reaction. Another advantage of phosphite/phosphoroamidite ligands is that they are less sensitive to air and other oxidizing agents than phosphines and they are amenable to parallel synthesis. Although they are prone to decomposition (hydrolysis, alcoholysis, and the Arbuzov reaction), these side reactions can be suppressed when bulky aryl phosphites are used. Other advantages of the ligands presented herein, in addition to being stable in air, include that they are solid, and hence, easy to manipulate and can be stored in air. Therefore, biaryl phosphite/phosphoramidite-containing ligands have undoubtedly become very versatile ligands for enantioselective metal-catalyzed reactions. Because of their excellent performance and facile synthesis, these ligands are foreseen to lead to new designs of phosphite/phosphoroamidite ligands and to expand even further the range of substrates and catalytic reactions in the forthcoming years.

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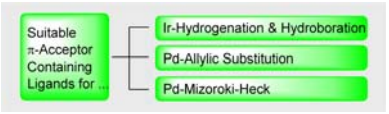

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