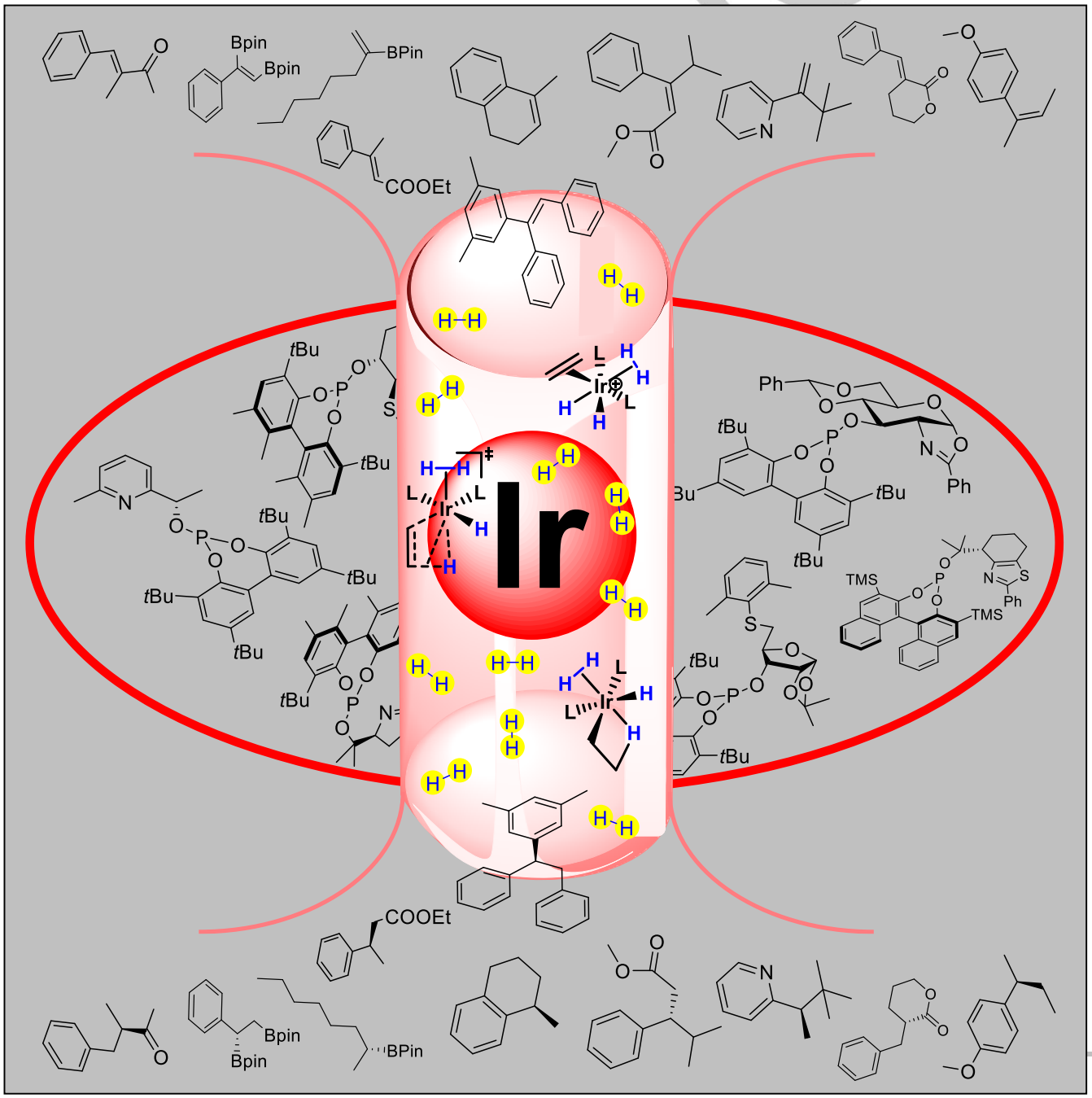
Extending the substrate scope for the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins by using biaryl phosphite-based modular ligand libraries

Oscar Pàmies,*[a] Marc Magre,[a] and Montserrat Diéguez*[a]

Dedication ((optional))



Abstract: The asymmetric hydrogenation is one of the most efficient and atom-economical tools to prepare chiral molecules. However, the enantiodiscrimination of simple, minimally functionalized olefins, is still challenging and requires more sophisticated ligand design. In this personal review we discuss our progress in the successful development in ligand design for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins.

1. Introduction

The increasing demand of enantiopure compounds for agrochemicals, pharmaceuticals, fine chemical, natural products and materials has stimulated the search for efficient strategies for their synthesis.[1] Asymmetric hydrogenation, the atom-economical addition of H_2 to a C=X (X = C, O or N) bond to construct chiral molecules is one of the most efficient, sustainable and straightforward chirality-generating process.[2] This field has been dominated by the Rh/Ru-catalyzed asymmetric reduction of substrates with a good coordinating group close to the C=X bond.[1-3] Today, a remarkable range of ligands are being applied to transform a broad range of functionalized substrates. In contrast, the asymmetric hydrogenation of olefins that do not have an adjacent coordinative polar group – minimally functionalized olefins – is still challenging and requires more sophisticated ligand design, despite the fact that it constitutes an easy way to create complex compounds from simple olefins.[4]

A breakthrough in the hydrogenation of minimally functionalized olefins came in 1997 when Pfaltz and coworkers used phosphine-oxazoline ligands **1** (Figure 1) to design [Ir(**1**)(cod)]PF_6 (cod = 1,5-cyclooctadiene),[5] a chiral analogue of Crabtree's catalyst.[6] Although this catalyst hydrogenated prochiral olefins highly enantioselectively, it was unstable to the reaction conditions. Pfaltz and co-workers overcame this limitation by changing the catalyst anion to [(3,5-$(F_3C)_2$-$C_6H_3)_4B]^-$ ($[BAr_F]^-$).[7] Since then researchers have mainly focused on Ir-catalysts based on a wide range of P-oxazoline ligands. Several successful phosphine/phosphinite-oxazoline ligands have been prepared by modifying the chiral backbone.[8] Carbene-oxazolines,[9] phosphine/phosphinite-oxazole/thiazole[10] and phosphinite-pyridine[11] are other type of ligands that have also been successfully applied in this process. Figure 2 shows a selection of the most successful ligands developed for 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.

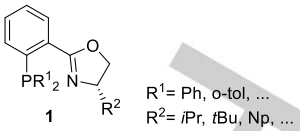


Figure 1. Phosphine-oxazoline PHOX-ligands **1**

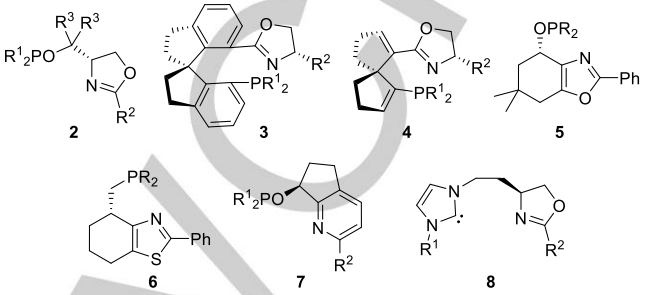


Figure 2. Presentation of the most successful ligands early developed for Ir-catalyzed hydrogenations.

Our group has contributed to the Ir-hydrogenation of minimally functionalized olefins with an improved series of ligands. We have shown that biaryl phosphite groups improve the ligand's efficiency. Mixed phosphite-oxazoline/thiazoline ligands have been shown to be exceptionally effective, providing better substrate versatility than earlier Ir-phosphinite/phosphine-oxazoline catalysts.[12-14] Then our research has progressed to heterodonor biaryl phosphite,X-ligands bearing more robust X-donor groups than oxazolines (thiazoles,[15] oxazoles,[15] pyridines[16,17] and thioethers[18-20]). We have also performed mechanistic studies to explain the origin of enantioselectivity, which allow rationalization of the modifications required into the ligand for improving selectivity.[14b,19,20]

Concerning mechanistic aspects, although the mechanism of olefin hydrogenation by Rh-catalysts is well understood, the mechanism when Ir-catalysts are used has not been fully determined until recently. In this context, computational and experimental research with P,N- and C,N- ligands have shown that the hydrogenation of minimally functionalized olefins proceeds via and Ir^{III}/Ir^{V} migratory-insertion/reductive-elimination catalytic cycle (Scheme 1).[14b,21] Very recently, Pfaltz's group, based on mechanistic studies under hydrogenation conditions, was able to detect the Ir(III) dihydride alkene intermediates responsible for the catalytic performance for the first time.[22] They found that, similarly to the classical Halpern-mechanism for asymmetric hydrogenation with Rh-catalysts, the minor intermediate, which is less stable, is converted to the major product enantiomer.

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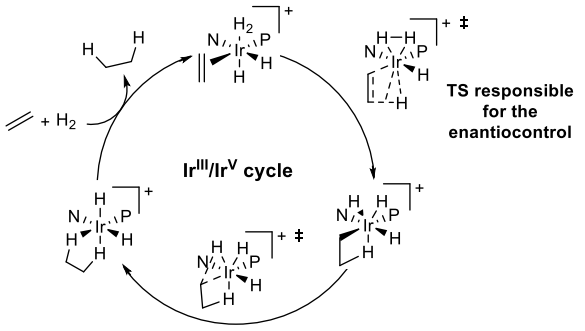
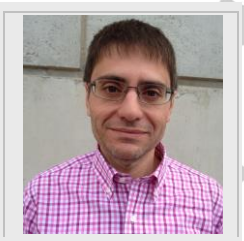


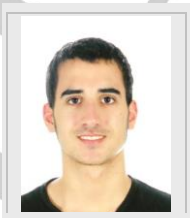
Scheme 1. Ir^{III}/Ir^{V} Migratory-insertion/reductive-elimination catalytic cycle for the hydrogenation of minimally functionalized olefins

This personal account, discusses our progress in the successful development in ligand design for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins, from biaryl phosphite-oxazoline/thiazolines to more recently emerged heterodonor biaryl phosphite-X ligands bearing more robust X-donor groups than oxazolines. Relevant mechanistic studies are also been discussed.

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. After she moved to Yale University as 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, steroselective synthesis and asymmetric catalysis. She is 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 industry. Her areas of interest include organometallic chemistry, steroselective synthesis and asymmetric catalysis using combinatorial and biotechnological approaches.



Oscar Pàmies obtained his Ph.D. in Prof. Carmen Claver's group in 1999 at the Rovira i Virgili University. After three years of post-doctoral 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. Recently he has been awarded the ICREA Academia Prize 2010 from the Catalan Institution for Research and Advanced Studies. His research interests are asymmetric catalysis, organometallic chemistry and combinatorial synthesis.



Marc Magre was born in Valls, Spain in 1989. He obtained the B.Sc in Chemistry at Universitat Rovira i Virgili in 2011 and the MSci in Homogeneous Catalysis at the same university in 2012. During his last year of the degree, he carried out the Degree Project at University of Nottingham, working under the supervision of Prof. Simon Woodward, working on the synthesis and application in homogeneous catalysis of organoaluminium compounds. In October of 2011, Marc was awarded a FPI grant from the Spanish Ministerio de Educación, Cultura y Deporte and he is currently pursuing a Ph. D at the Universitat Rovira i Virgili under the supervision of Prof. Montserrat Diéguez and Dr. Oscar Pàmies. His research is mainly focused on the development of new chiral ligands and their application in several asymmetric metal-catalyzed processes.

2. Application of phosphite-oxazoline/thiazoline ligands

Although phosphite containing ligands had been used in the Rh-catalyzed hydrogenation of functionalized substrates since the 90s,[23] it was not until 2008 that a publication reported their use in the reduction of minimally functionalized olefins This report described the application of a TADDOL-based phosphite–oxazoline ligand library in the Ir-hydrogenation of some model minimally functionalized substrates (Figure 3).[24] However, its substrate range limitation was higher and enantioselectivities and activities lower than their related phosphinite/phosphine–oxazoline ligands. They also required higher pressures (100 bars) and higher catalyst loadings (4 mol%) to obtain full conversions.

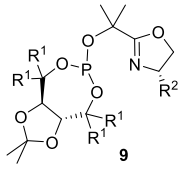


Figure 3. TADDOL-based phosphite–oxazoline ligands

Phosphite-containing ligands are particularly useful for asymmetric catalysis. They show a greater resistance to oxidation than phosphines and phosphinites, they are easily synthesized from readily available chiral alcohols, and their modular constructions are easy. Series of chiral ligands can therefore be synthesized and screened in the search for high

activities and selectivities for each type of substrate.[25] With the aim to find more versatile heterodonor phosphite–containing ligands for Ir-hydrogenation, our group in collaboration with Andersson's group took one of the most successful ligand families developed for this process, the phosphinite–oxazoline ligands **2** (Figure 2),[8f] and replaced the phosphinite group with biaryl phosphite moieties (Figure 4; ligands **10**-**25a**-**f**). With these ligands we investigated the effect on activity and enantioselectivity of several ligand parameters (the substituents in the oxazoline group, R^1, and in the alkyl backbone chain, R^2, the presence of a second stereogenic center in the heterocycle ring, H or Me, and its configuration and the substituents/configurations in the biaryl phosphite moiety, **a**-**f**).[12]

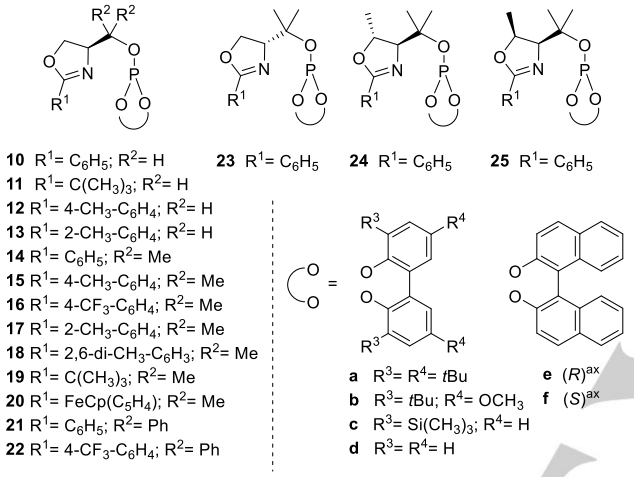


Figure 4. Phosphite-oxazoline ligands **10**-**25a**-**f**

By selecting these elements high catalytic performance was obtained in a wide range of minimally functionalized olefins (Figure 5). Ligand **14f** provided high enantioselectivities in the asymmetric hydrogenation of several trisubstituted minimally functionalized linear **S1**–**S3** and cyclic **S5** olefins, α,β-unsaturated ester **S6**, while for the allylic alcohol **S7** and acetate **S8**, the best ee's were obtained with ligand **14a** (Figure 5).[12a]

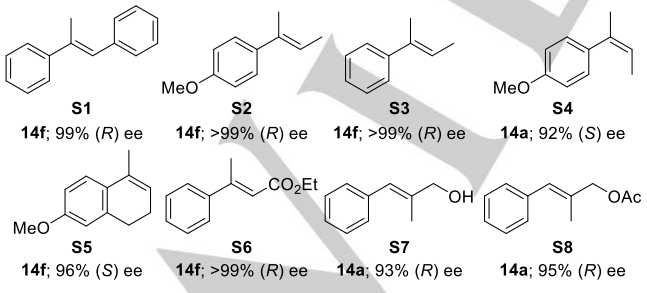


Figure 5. Summary of the catalytic results in the hydrogenation of several minimally functionalized trisubstituted olefins using [Ir(**10**-**25a**-**f**)(cod)]BAr_F catalyst precursors. Reaction conditions: 0.2 mol% catalyst, CH_2Cl_2 as solvent, 50 bar H_2, 2 h.

In addition, if the ligand is appropriately tuned, high enantioselectivity (92% ee with ligand **14a**) was also obtained for the more demanding *Z*-isomer **S4**, which usually reacts with a lower enantioselectivity than that of the corresponding *E*-isomer **S2**.[12a]

More remarkable were the excellent enantioselectivities obtained in reduction of a very broad range of the minimally functionalized 1,1-disubstituted olefins (29 examples; Figure 6).[12b] Unlike trisubstituted olefins, 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 face selectivity coordination (only two substituents compared with the three of trisubstituted olefins), but also the isomerization of the olefins to form the more stable *E*-trisubstituted substrates, which are hydrogenated to form the opposite enantiomer. In addition, in the hydrogenation of terminal alkenes the enantioselectivity is highly pressure dependent. In general, hydrogenation at atmospheric pressure of H_2 provides significantly higher ee's than at higher pressures. Enantioselectivities up to >99% and full conversions were obtained (Figure 6), including substrate classes that have never been asymmetrically hydrogenated before (i.e. trifluoromethyl-containing olefins **S17**, 1,1-hetereoraryl-alkyl olefins **S18**-**S21**, 1,1-diaryl olefins **S25**-**S27**, ...).

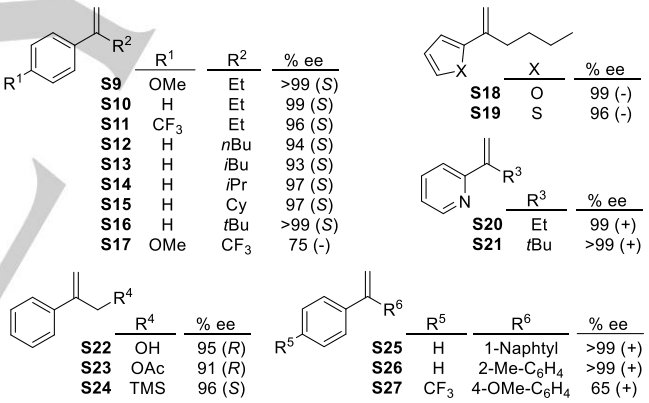


Figure 6. Summary of the catalytic results in the hydrogenation of several minimally functionalized disubstituted olefins using [Ir(**14f**)(cod)]BAr_F catalyst precursor. Reaction conditions: 0.5 mol% catalyst, CH_2Cl_2 as solvent, 1 bar H_2 for **S9**-**S21** or 50 bar of H_2 for **S22**-**S27**, 2 h.

Noteworthy, the high enantioselectivities obtained in the hydrogenation of diaryl terminal olefins **S25**-**S27**. Enantiopure diarylalkanes are important intermediates for the preparation of drugs and research materials.[26] To date chiral diarylalkanes are prepared through some rather laborious approaches.[26,27] Despite the asymmetric hydrogenation can provide a more efficient way to their preparation no enantioselective hydrogenation of this type of olefins was reported at the moment of our publication. It was also found that these catalytic systems have high tolerance to the steric and electronic requirements of the substrate and also to the presence of neighboring polar groups. High enantioselectivities were therefore obtained in the

hydrogenation of allylic alcohol derivatives, allylic silanes and trifluorometyl-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 organofluorine drugs.[28]

Catalyst library Ir/**10**-**25a**-**f** not only performed well in traditional organic solvents but also in propylene carbonate, an alternative environmentally friendly solvent, which allowed the catalyst to be reused while maintaining the excellent enantioselectivities.[12b] Therefore, the simple substitution of the phosphine by a biaryl phosphite group extended the range of olefins that could be successfully hydrogenated, and furnished enantioselectivities that surpass the best reported so far. Nevertheless, this catalysts library still underperformed on some important substrates such as α,β-unsaturated ketones and trifluoromethyl olefins. For this reason, we next designed a new family of ligands in which the oxazoline group in ligands **10**-**25** was replaced by a thiazoline moiety (ligands **26**-**27**, Figure 7).[13] As expected the subtle variation in the basicity of the N-donor group (the thiazoline group is more basic than the oxazoline) and the steric properties caused by the substituent at the N-heteroatom ring replacing the identity of the non-coordinating heteroatom allowed the catalysts to be fine-tuned for the most challenging substrates. The introduction of a thiazoline moiety have not only provided enantioselectivities up to >99% for a range of α,β-unsaturated ketones **S28**-**S32**, vinyl silane **S33** and trifluoromethyl olefins **S27**, but also have increased the enantioselectivities of simple *Z*-trisubstituted olefins, such as **S4**, up to 96% (Figure 8), while maintaining the excellent enantioselectivities for a range of *E*-trisubstituted and 1,1-disubstituted minimally functionalized olefins.[13]

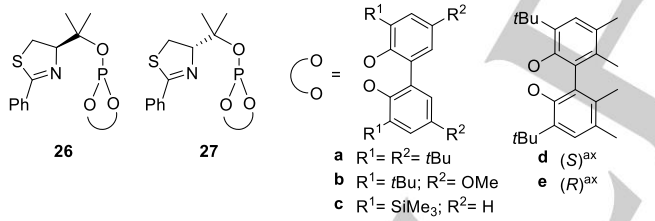


Figure 7. Phosphite-thiazoline ligands **26**-**27a**-**e**

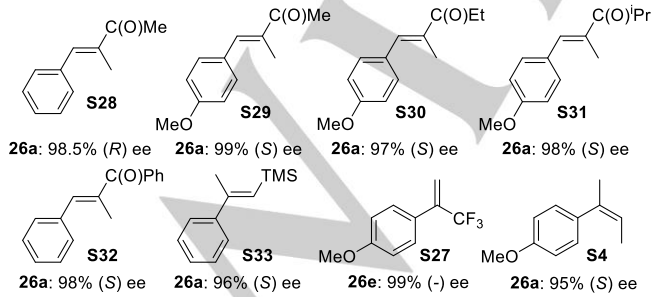


Figure 8. Application of Ir/**26**-**27a**-**e** in the hydrogenation of α,β-unsaturated ketones **S28**-**S32**, vinyl silane **S33**, trifluoromethyl olefin **S27** and *Z*-olefin **S4**. Reactions carried out using 0.5 mol% of catalyst, CH_2Cl_2 as solvent at 50 bar of H_2 (except for **S27** that were performed at 1 bar of H_2) for 2 h.

Taking advantage of our experience in the synthesis of sugar based ligands[29] we also prepared and screened a pyranoside phosphite-oxazoline ligand library (Figure 9; ligands **28**-**32a**-**k**) for the Ir-catalyzed hydrogenation of minimally functionalized olefins.[14] These ligands are derived from natural D-glucosamine so they also have the advantages of carbohydrates: that is to say, they are cheap and can be easily constructed in modules. With this family of ligands we were able to find highly selective ligands for each substrate and to identify two general ligands (**32c** and **32e**) with good performance in the reduction of 44 substrates, including challenging terminal disubstituted olefins (ee's up to 99% for a range of substrates; Figure 10 at low catalyst loadings (0.2 mol%) and under mild reaction conditions (1 bar of H_2). The results are comparable with the best ones reported in the literature, including previously Ir/phosphite-oxazoline/thiazolines **10**-**27a**-**f**, which are among the best catalysts for this process.

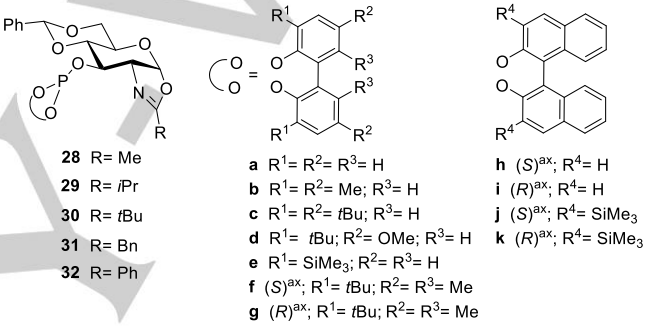


Figure 9. Pyranoside phosphite-oxazoline ligands **28**-**32a**-**k**

In collaboration with Profs. P-O. Norrby and P. G. Andersson we also performed a detailed computational study which allowed to identify the preferred reaction path, an Ir^{III}/Ir^{V} cycle with migratory insertion of a hydride as the selectivity-determining step (Scheme 1).[14b] The alternative metathesis mechanism[21d] was consistently higher in energy. DFT studies also allowed computational determination of the reached selectivities with high accuracy. Both the favored enantiomer and the effect of ligand modifications could be rationalized by using a simple quadrant model (Figure 11). In this quadrant model, the phenyl group of the oxazoline substituent blocks the upper left quadrant, and one of the aryls of the biaryl phosphite group partly occupies the lower right quadrant. The other two quadrants, which are free from bulky groups, are open (Figure 11). Therefore, the calculated structure clearly shows a chiral pocket that is well suited to olefins with large *trans*-substituents, like *E*-olefins. This quadrant model also explains that to obtain high enantioselectivity in the reduction of *Z*-olefins we have to switch from ligand **32e** to ligand **32c**. Ligand **32c** differs from the previous ligand **32e** in the presence of bulky substituents at the *para* position of the biphenyl group. These substituents increase the dihedral angle of the biaryl group, which results in lower occupancy of the lower right quadrant. So, the substituents of the biphenyl moieties can tune the steric hindrance of the lower right quadrant so that it can accommodate the phenyl

substituent of *Z*-substrates and lead to high enantioselectivity. The same explanation also account for the excellent enantioselectivities obtained with triarylsubstituted olefins **S37** and **S38**, for which very few catalysts have provided high enantioselectivities. The DFT studies verify that the flexibility of the biaryl phosphite groups seems to be crucial in expanding the substrate scope.

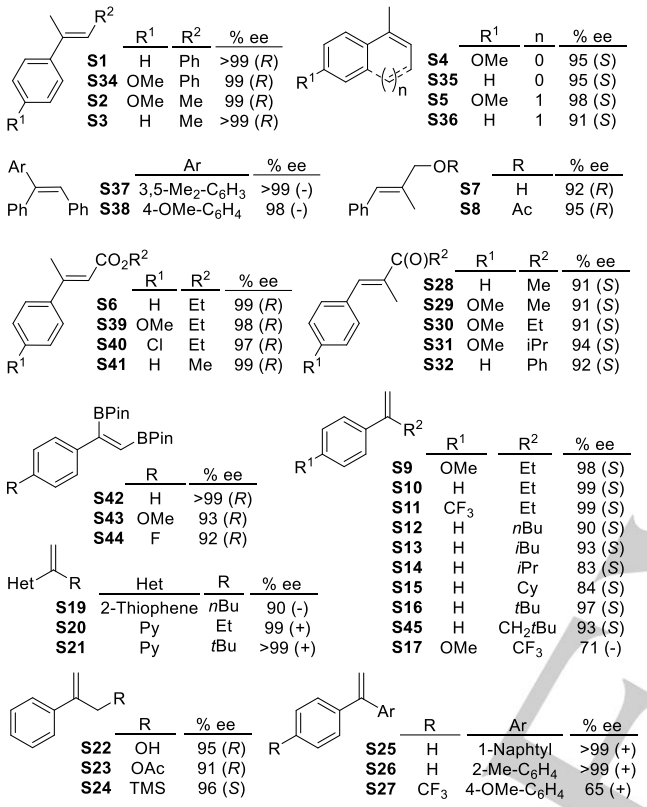


Figure 10. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using pyranoside ligands **28**-**32a**-**k**. Reactions carried out using 0.2-1 mol% of catalyst, CH_2Cl_2 as solvent at 50 bar of H_2 (except for **S9**-**S21** and **S45** that were performed at 1 bar of H_2) for 2 h.

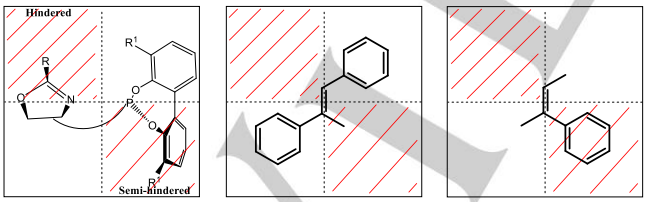


Figure 11. Quadrant diagram describing the enantioselective substrate-ligand interactions

Despite the advances in Ir-based phosphite-oxazoline/thiazoline catalysts, their activity and selectivity for reducing minimally functionalized olefins still needed to be improved, especially since the demand for new optically active chiral centers has moved researchers into the Ir-catalyzed asymmetric reduction of more "exotic" substrates. In this respect, our research progressed to heterodonor biaryl phosphite,X-ligands bearing more robust X-donor groups than oxazolines (thiazoles, oxazoles, pyridines and thioethers).

3. Application of phosphite-oxazole/thiazole ligands

In collaboration with Andersson's group we studied whether the biaryl phosphite moiety is still as effective when combined with oxazole and thiazole groups. For this purpose, we took two of the most successful ligand families (phosphinite/oxazole **5** and phosphine/thiazole **6**; Figure 2) used in Ir-hydrogenation[10a,l] and replaced their phosphinite or phosphine moieties with biaryl-phosphite groups to give ligands **33**-**39a**-**h** (Figure 12).[15]

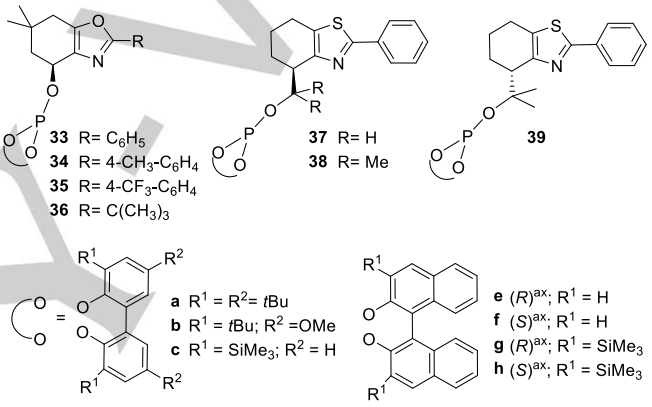


Figure 12. Phosphite-oxazole and phosphite-thiazole ligand library **33**-**39a**-**h**

We found 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. Enantioselectivities were therefore excellent (ee's up to >99%) in a wide range of *E*- and *Z*-trisubstituted and 1,1-disubstituted terminal alkenes (Figure 13).[15] 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 **S7** and **S22**, acetates **S8**, esters **S6**, silanes **S24** and **S33** and enol phosphinates **S46**-**S48** can be hydrogenated in high enantioselectivities (ee's up to 99%). Our results also showed that these Ir-phosphite-oxazole/thiazole catalytic systems provided higher enantioselectivities for a wider range of *E*- and *Z*-trisubstituted and 1,1-disubstituted substrates than their related phosphinite-oxazole (**5**) and phosphine-thiazole (**6**) counterparts (Figure 2).[10] For trisubstitued olefins the best enantioselectivities were in general obtained with ligands **37**-**39a**. In addition, both enantiomers of the hydrogenated product can be accessed in high enantioselectivity simply by changing the

configuration of the ligand backbone. For disubstitued olefins, the results indicated that the Ir-catalyst precursor containing phosphite-thiazole **37a** ligand provides high enantioselectivities in the reduction of a large series of α-alkylstyrenes, 1,1-heteroaromatic alkenes and silanes (Figure 13). For allylic alcohols, the enantioselectivities were best with catalyst precursor Ir/**38a** (ee's up to 90%). In addition the Ir-catalyst precursor containing phosphite-oxazole ligand **33a** provided better conversions and enantioselectivities in the hydrogenation of enol phosphinates **S46**-**S48** than those obtained with related phosphinite-oxazole ligands which constitute the state-of-art for this substrate class.[10e] The effective hydrogenation of this type of substrate opened up an appealing route for obtaining chiral organophosphinates, which can be easily transformed into high-value compounds such as alcohols and phosphines.[30]

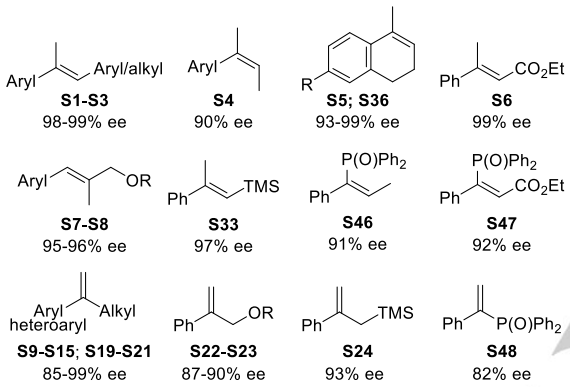


Figure 13. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphite-oxazole/thiazole **33**-**39a**-**h**. Reactions carried out using 0.2 mol% of catalyst, CH_2Cl_2 as solvent at 50 bar of H_2 (except for **S9**-**S15** and **S19**-**S21** that were performed at 1 bar of H_2 and for **S47** that was performed at 100 bars of H_2) for 2 h (except for **S46**-**S48** that were run for 12 h)

4. Application of phosphite-pyridine ligands

Researchers early thought in developing ligands containing more robust groups than oxazolines. In this respect, Pfaltz and coworkers synthesized phosphinite-pyridine ligands **40** (Figure 14),[11b] for Ir-hydrogenation which were successfully used in a limited range of alkenes.

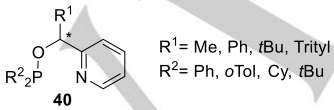


Figure 14. First generation of phosphinite-pyridine ligands **40** developed by Pfaltz and coworkers

The performance was subsequently further improved by introducing a more rigid chiral bicyclic ligand backbone (ligands **7**; Figure 1).[11c,d] Although the number of substrates that could be successfully reduced was increased with this second generation, high enantioselectivities were mainly limited to trisubstituted substrates. To benefit from the advantages of phosphite and pyridine moieties, we took the first generation of Pfaltz's phosphinite-pyridine ligands **40** and replaced the phosphinite moiety with a biaryl phosphite group to provide ligands **41**-**52a**-**g** (Figure 15).[16]

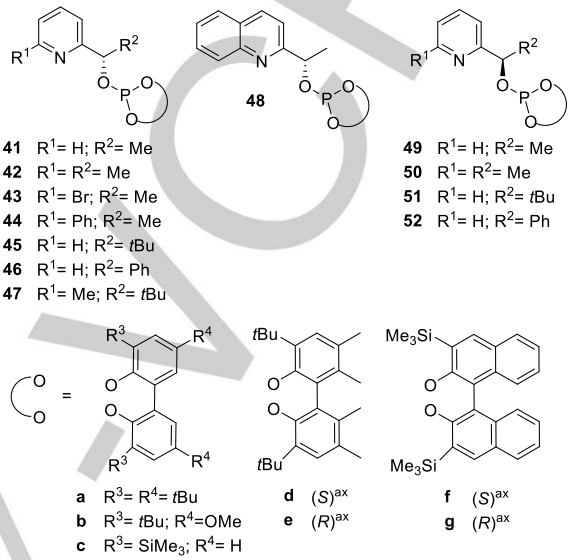


Figure 15. Phosphite-pyridine ligands **41**-**52a**-**g**

With Ir/**41**-**52a**-**g** catalysts, we could reach excellent enantioselectivities (ee's up to 99%) in a wide range of *E*- and *Z*-trisubstituted alkenes, including more demanding triaryl-substituted olefins, dihydronaphthalenes and disubstituted substrates (Figure 16). A range of allylic alcohols, acetates, α,β-unsaturated esters and ketones, allylic silanes, vinylboronates and trifluoromethyl olefins were also hydrogenated with high enantioselectivities. The hydrogenation of vinylboronates provides easy access to chiral borane compounds, which are useful building blocks in organic synthesis because the C-B can be readily converted to C-O, C-N and C-C bonds with retention of the chirality. In addition, both enantiomers of the reduction product were obtained in excellent enantioselectivities by simply changing the configuration of the carbon next to the phosphite moiety. The efficiency of this ligand design was also corroborated by the fact that these Ir/phosphite-pyridine catalysts provided higher enantioselectivity and broader substrate versatility than their phosphinite-pyridine analogues (ligands **40**; Figure 14).[11b] In addition the results of our phosphite-pyridine catalyst library compare very well with the ones achieved using the second generation of phosphinite-pyridine ligands (Figure 1; ligands **7**),[11c,d] 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.

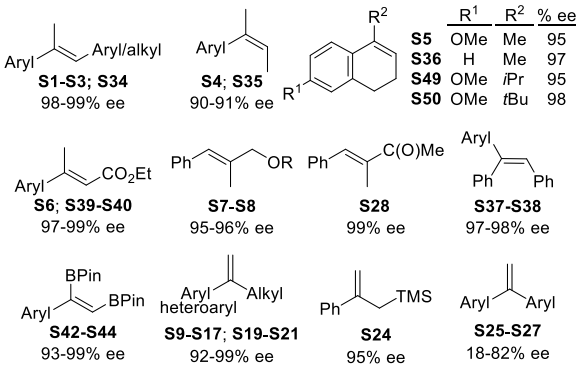


Figure 16. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphite-pyridine ligands **41**-**52a**-**g**. Reactions carried out using 0.25-1 mol% of catalyst, CH_2Cl_2 as solvent at 50 bar of H_2 (except for **S9**-**S17** and **S19**-**S21** that were performed at 1 bar of H_2) for 2 h

5. Application of P-thioether ligands

In contrast to other catalytic processes and to the Rh/Ru-hydrogenation, for the reduction of minimally functionalized olefins the possibility of changing the nature of the N-donor atom in the ligand design of heterodonor ligands was not contemplated until recently. In 2011 Pfaltz successfully reported the application of proline-based P,O ligands in the asymmetric hydrogenation of trisubstituted alkenes.[31] At the same time our group reported the application of a highly modular furanoside phosphite-thioether ligand library for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins (Figure 17).[18]

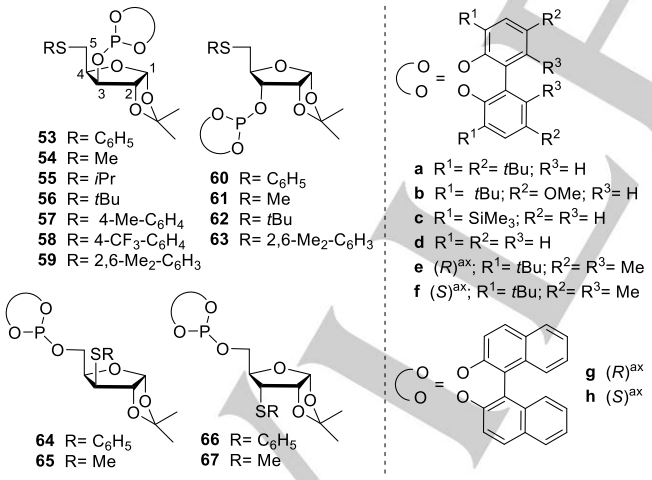


Figure 17. Furanoside phosphite-thioether ligands **53**-**67a**-**h**

The minor role of thioether-based ligands in this process can be due 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.[32] Nevertheless, if the ligand scaffold can control the S-coordination, this feature may be extremely beneficial because then the chirality moves closer to the metal.[32] In this respect, by carefully selecting the ligand components in furanoside-based ligand **53**-**65a**-**h** (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) we found that the best enantioselectivities were obtained using ligands with a 5-deoxy-ribofuranoside backbone (ligands **60**-**63**). We also studied the effect on catalytic performance of introducing either phosphinite or phosphine moieties (data not shown). The results indicated that replacing the phosphite moiety by a phosphinite or a phosphine group had a negative effect on enantioselectivity. Excellent enantioselectivities were obtained (ee's up to 99%) in the reduction of a very broad range of minimally functionalized alkenes (Figure 18), including relevant examples with poorly coordinative groups (such us, α,β-unsaturated esters and vinylboronates; Figure 18).[18] The results are comparable to the best ones reported in the literature except for the hydrogenation of terminal disubstituted aryl/alkyl olefins. For this substrate class, our results indicated that enantioselectivity is dependent on the nature of the alkyl substrate substituent and much less affected by the electronic nature of the aryl ring. This has been attributed to a isomerization process, that was 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's up to 98%), while the lowest enantioselectivities of the series were found for substrates which form the most stable isomerized tetrasubstituted olefins. Enantioselectivities were therefore best in the asymmetric reduction of aryl and heteroaryl/*tert*-butyl substrates (ee's up to 99%).

The asymmetric hydrogenation was also performed using propylene carbonate as solvent, which allowed the Ir-catalysts to be reused while maintaining the excellent enantioselectivities.

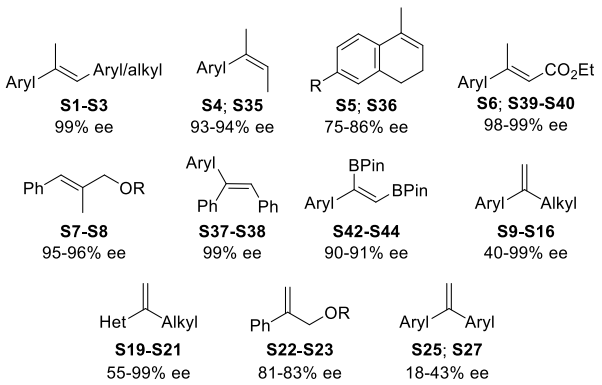


Figure 18. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphite-pyridine ligands **41**-**52a**-**g**. Reactions carried out using 0.5-2 mol% of catalyst, CH_2Cl_2 as solvent at 100 bar of H_2 (except for **S9**-**S16** and **S19**-**S21** that were performed at 1 bar of H_2 and for **S22**, **S23**, **S25** and **S27** that were performed at 50 bar of H_2) for 4 h

Next, in collaboration with the Pericas's group we applied a new family of highly modular phosphite/phosphinite-thioether ligand library (Figure 19; ligands **68**-**77a**-**g**).[19] In a simple 3 step procedure, several ligand parameters were easily tuned to maximize the enantioselectivities for each substrate.

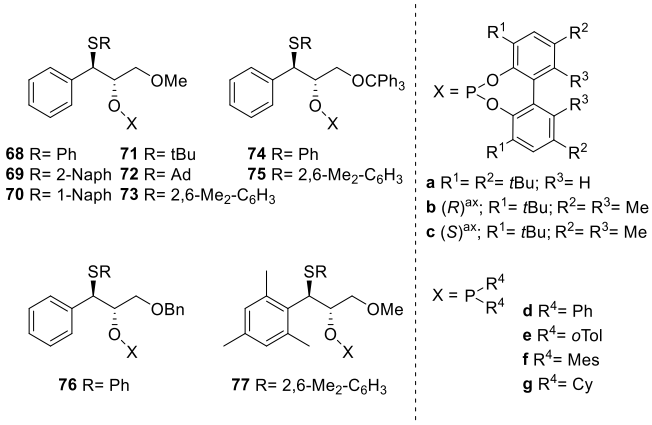


Figure 19. Modular phosphite/phosphinite-thioether ligands **68**-**77a**-**g**

Our results showed that the catalytic performance of these P-S ligands was excellent and comparable to the one achieved with previous furanoside P-S analogues,[18] which have appeared as some of the most successful ligands for this type of reduction reactions, with two added advantages. First, Ir/P-thioether catalysts **68**-**77a**-**g** are able to enlarge the number of olefins successfully hydrogenated, with α,β-unsaturated enones, tri- and disubstituted alkenylboronic esters and olefins with trifluoromethyl substituents (Figure 20). Second, as the starting enantiopure epoxides are prepared through a catalytic Sharpless epoxidation, both enantiomers of the P,S-ligands are therefore easily available. In contrast to previous furanoside-based thioether-P ligands (Figure 17), replacing the phosphite moiety by a bulky di-*o*-tolyl phosphinite group had a positive effect on enantioselectivity. These results clearly showed the importance of using modular scaffolds to build new ligand systems. This modular ligand design with help of DFT studies were crucial to find which ligand parameters should be modified in order to generate the most selective catalysts. In this respect they showed that the introduction of a bulky mesityl group (ligand **77**) instead of a phenyl group (ligand **73**) in the ligand backbone was necessary in order to obtain high enantioselectivity. DFT studies also confirmed that the preferred reaction path, is an Ir^{III}/Ir^{V} cycle with migratory insertion of a hydride as the selectivity-determining step. The calculations moreover indicated that the diastereoisomers resulting from coordination of the thioether to the metal centre interconvert rapidly under the reaction conditions through pyramidal inversion, thus allowing the use of the Curtin-Hammet principle in predicting the outcome of the reaction.

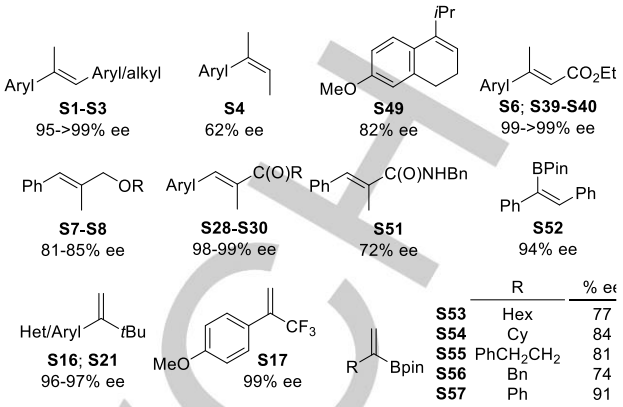


Figure 20. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphite/phosphinite-thioether ligands **68**-**77a**-**g**. Reactions carried out using 2 mol% of catalyst, CH_2Cl_2 as solvent at 100 bar of H_2 (except for **S16**, **S17**, **S21** and **S53**-**S57** that were performed at 1 bar of H_2) for 4 h

Despite these successes, the performance of this new class of ligands needed to be further studied by screening new readily accessible thioether-containing ligands and studying the species responsible for the catalytic performance under hydrogenation conditions. No experimental studies of the mechanism and the nature of the relevant catalytic intermediates under hydrogenation conditions were yet carried out with these type of ligands. We then designed and applied the use of a reduced but structurally valuable phosphite/phosphinite-thioether ligand library (Figure 21, ligands **78**-**79a**-**g**).[20] These phosphite/phosphinite-thioether ligands were synthesized in only two steps.

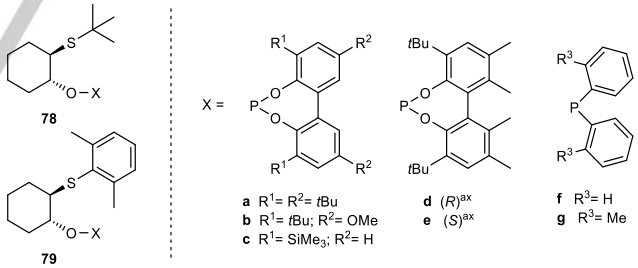
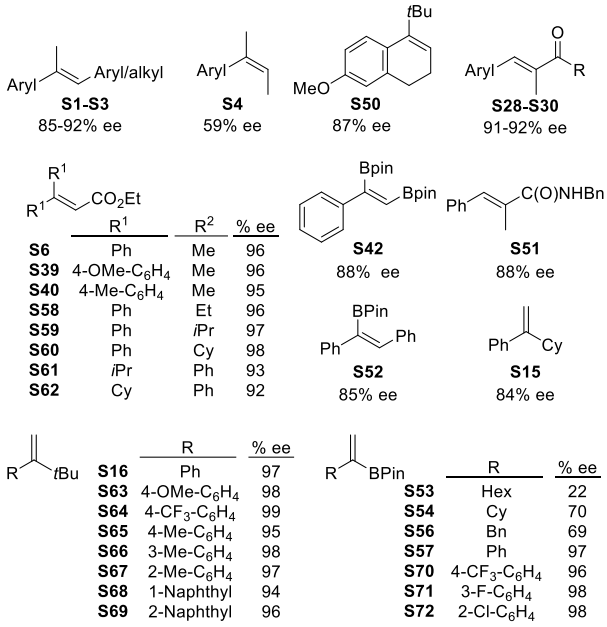


Figure 21. Phosphite/phosphinite-thioether ligands **78**-**79a**-**g**

We found that the ligand parameters must be selected specifically for each substrate with the aim of obtaining the highest enantioselectivity. Enantioselectivities up to 99% were achieved in the hydrogenation of 40 minimally functionalized olefins, including a variety of olefins that have recently caught 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 22).



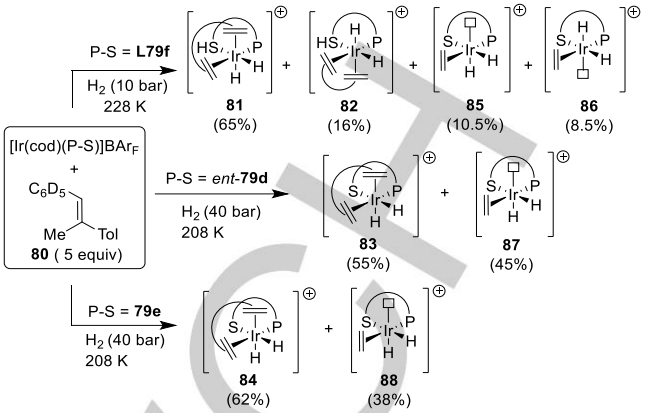
	R^1	R^2	% ee
S6	Ph	Me	96
S39	4-OMe-C_6H_4	Me	96
S40	4-Me-C_6H_4	Me	95
S58	Ph	Et	96
S59	Ph	*i*Pr	97
S60	Ph	Cy	98
S61	*i*Pr	Ph	93
S62	Cy	Ph	92

	R	% ee
S16	Ph	97
S63	4-OMe-C_6H_4	98
S64	4-CF_3-C_6H_4	99
S65	4-Me-C_6H_4	95
S66	3-Me-C_6H_4	98
S67	2-Me-C_6H_4	97
S68	1-Naphthyl	94
S69	2-Naphthyl	96

	R	% ee
S53	Hex	22
S54	Cy	70
S56	Bn	69
S57	Ph	97
S70	4-CF_3-C_6H_4	96
S71	3-F-C_6H_4	98
S72	2-Cl-C_6H_4	98

Figure 22. Summary of the catalytic results in the hydrogenation of several minimally functionalized olefins using phosphite/phosphinite-thioether ligands **78**-**79a**-**g**. Reactions carried out using 0.5-1 mol% of catalyst, CH_2Cl_2 as solvent at 100 bar of H_2 (except for **S15**, **S16**, **S63-S9**, **S53-S54**, **S56-S57** and **S70**-**S72** that were performed at 1 bar of H_2) for 4 h (except for **S51** that was run for 18 h)

In addition, these phosphite/phosphinite-thioether ligands have a simple backbone and thus their NMR spectra are simple, with reduced signal overlap, which facilitates the identification of relevant intermediates. Therefore, 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=**L79f**, *ent*-**79d** and **79e**) with H_2 in the presence of alkene **80** (Scheme 2). For each precatalysts the most abundant complexes were assigned to the dihydride species **81**-**84** and the minor isomers were assigned to the dihydride intermediate species [Ir$(H)_2$(**80**)(P-S)]BAr_F **85**-**88**, in which the alkene is coordinated. Then, the screening of precatalyst [Ir(cod)(**L79f**)]BAr_F with the same alkene, under the reaction conditions used for HP-NMR, showed that the configuration of the product obtained from hydrogenation requires coordination of the substrate as determined for the minor isomer **86**. This result therefore indicates that the hydrogenation of substrate with the Ir/**L79f** catalytic system follows the Halpern-type mechanism in which the less stable isomer **86** reacts faster than the major intermediate **85**, and it is converted into the major product enantiomer. The same behavior was obtained using the other precatalysts. Accordingly, the lowest enantioselectivities obtained with precatalysts [Ir(cod)(*ent*-**79d**)]BAr_F and [Ir(cod)(**79e**)]BAr_F in comparison with [Ir(cod)(**79f**)]BAr_F could be explained by the lower population of the faster reacting olefinic dihydride isomer.



Scheme 2. Reactivity of [Ir(cod)(P-S)]BAr_F complexes with olefin **80** under hydrogenation conditions

Conclusions

Compared to the Rh/Ru-catalyzed hydrogenation of substrates with a good coordinative group close to the C=C bond, the enantiodiscrimination in the hydrogenation of minimally functionalized olefins is still challenging and requires more sophisticated ligand design. Ligands with wide substrate scope are desirable in order to limit time-consuming ligand design and preparation. The discovery of "privileged ligands" easy to handle (solid, robust and air stable), modular and prepared from simple starting materials and good for a broad range of substrates is still a relevant topic. Our group has contributed to this field with an improved series of ligands which are easy to handle and prepared in few steps from readily available sources. The use of modular ligand scaffolds has been crucial in building new effective ligand systems for each substrate. We have shown that the introduction of biaryl phosphite groups into the ligand design improve the ligand's efficiency. Modular, mixed phosphite-oxazoline/thiazoline ligands have been shown to be exceptionally effective, providing better substrate versatility than earlier Ir-phosphinite/phosphine-oxazoline catalysts. Our DFT studies showed that the flexibility of the biaryl phosphite groups was crucial in expanding the substrate scope. Both the favored enantiomer and the effect of ligand modifications could be rationalized by using a simple quadrant model. With the aim of improving even further the substrate versatility, our research has successfully progressed to heterodonor P,X-ligands bearing more robust X-donor groups than oxazolines/thiazolines. Families of P-pyridine/thiazole/oxazole/thioether ligands have been developed and screened in the search of suitable Ir/catalysts.

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Keywords: Ir-hydrogenation • phosphite • P-N ligands • P-S ligands • ligand design

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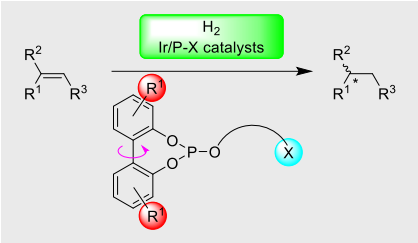
PERSONAL ACCOUNT

This personal review discuss the progress in the successful design of biaryl phosphite-based ligand libraries for the Ir-catalyzed asymmetric hydrogenation of minimally functionalized olefins.



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Extending the substrate scope for the asymmetric Ir-catalyzed hydrogenation of minimally functionalized olefins by using biaryl phosphite-based modular ligand libraries