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The Evolution of Phosphite-Oxazoline Ligands for the Pd-Allylic Substitution and Their Application in Building Chiral Molecules

Maria Biosca,*[a] Daniel Tarr,[a] Oscar Pàmies,[a] and Montserrat Diéguez[a]

Pd-catalyzed asymmetric allylic substitution (AAS) is a highly effective method for producing chiral molecules with alkene-substituted frameworks which can be further derivatized. However, its stereochemical outcome is affected by the steric requirements of the substrate and only a narrow set of nucleophiles yield excellent enantioselectivities. In this regard, phosphite-oxazolines have emerged as strong candidates to be privileged ligands for this process, providing results that surpass most of the previously published studies. They have provided high enantiocontrol when used in the Pd-AAS of several hindered and unhindered substrates, using a wide range of C-, O-, and N-nucleophiles. In this concept, we review and discuss the current progress made in the design of tailor-made phosphite-oxazoline ligand libraries for the Pd-AAS of a broad range of substrates and nucleophiles and its application in the construction of chiral complex molecules.

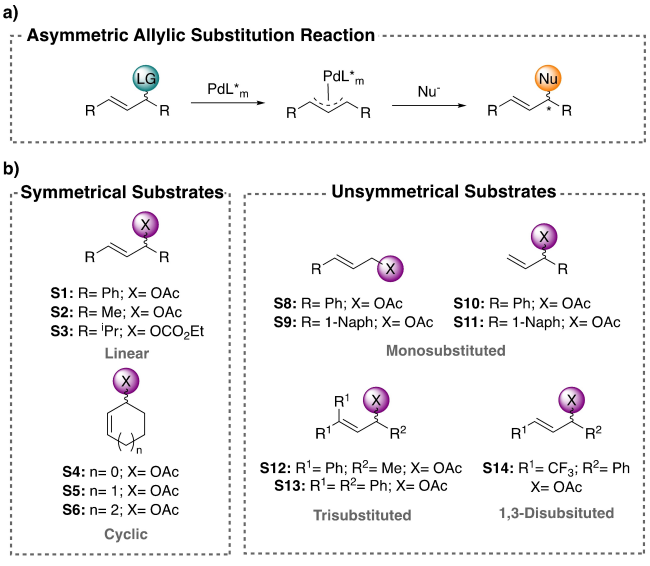
1. Introduction

Optically active alkene-substituted frameworks are important building blocks in enantioselective synthetic chemistry. The presence of a double bond makes these molecules highly versatile for the construction of more complex natural and biologically relevant products.[1] In this sense, Pd-AAS reactions offer a simple and efficient approach to forming chiral C–X bonds (where X = C, N, O, Scheme 1a), and therefore is considered a valuable method for synthesizing these compounds.[2]

This reaction has been tested on a wide range of allylic substrates, with activated allylic substrates being the most common (Scheme 1). Among them, 1,3-diphenylprop-2-enyl acetate (**S1**, Scheme 1b) is broadly employed as a benchmark substrate for testing new catalytic systems.[2]

When the benchmark substrate or other racemic disubstituted substrates with identical substituents at the allylic termini, also so-called symmetrical substrates (e.g. **S2**–**S6**, Scheme 1b), are used, the reaction proceeds via a symmetrical π-allyl intermediate that primarily interconverts via the well-stablished π-o-π isomerization mechanism between the two most stable *syn*/*syn* isomers. Therefore, the stereochemical outcome is determined by the regioselectivity of the nucleophilic attack, which relies on the ability of the chiral ligand to differentiate between the two allylic termini and the two *syn*/*syn* isomers.[2]

In contrast, when racemic or prochiral substrates with different substituents at the two allyl termini are used, not only does the enantioselectivity need to be controlled, but also the regioselectivity. In that instance, for monosubstituted substrates (e.g. **S8**–**S11**, Scheme 1b) the vast majority of the Pd-catalytic systems developed to date favor the nucleophilic attack towards the less substituted carbon, leading to the undesired achiral linear product. This is in direct contrast to other transition metal complexes, mainly Ir ones, which provide very high selectivity towards the chiral branched product.[2,3] Similarly, when trisubstituted substrates with two identical substituents at one of the allyl termini (e.g. **S12**–**S13**, Scheme 1b) are used, steric constraints mainly control the regioselectivity and favor a nucleophilic attack at the less substituted allylic



Scheme 1. a) A general example of Pd-AAS of an activated allylic substrate. b) Commonly used activated allylic substrates in the Pd-AAS.

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carbon terminus.[2] However, when 1,3-disubstituted unsymmetrical substrates (e.g. **S14**, Scheme 1b) are used an additional issue arises as the two isomeric allyl intermediates cannot interconvert via the π-σ-π isomerization mechanism.[2] Although Pd(0)-catalyzed allyl exchange can occur,[4] it is rarely observed, and most of the catalytic systems proceed via a kinetic resolution.[5] Otherwise, in some cases, the catalyst is able to epimerize the Pd-allyl intermediates, enabling the conversion of racemic substrates to a single enantiomer.[6]

Due to this diverse scenario, each type of substrate requires a different catalyst for the desired optimal outcome. Despite a large number of ligands being successfully applied in the Pd-AAS, the challenge of finding a catalyst with a wide adaptability to a vast substrate-nucleophile combination still persists.[2,7]

The ligand design in the Pd-AAS has been mainly based on two strategies. The first strategy involves the creation of a chiral pocket between the metal center and the chiral ligand where the π-allyl complex is perfectly embedded, the first successful example being the diphosphine ligand **1** developed by Trost et al. (Figure 1a).[8] The observed enantioselectivity results from the interplay between the steric hindrance imposed by the chiral cavity and the electrostatic interaction between the nucleophile and the ligand.[9]

The second strategy is based on the use of heterodonor ligands, which creates electronic differentiation between the two allylic carbon terminal atoms due to the different *trans* influences of the donor groups. The first ligands which employ this strategy are the phosphine-oxazoline PHOX ligands (Figure 1b, R= Me, Ph, ^{i}Pr, ^{t}Bu), reported by the groups of Helmchen, Pfaltz and Williams.[10] Unfortunately, whilst these pioneering ligands provided excellent enantioselectivities (ee's up to 99%) when benchmark substrate (**S1**) was used, the enantioselectivities decreased up to 71% or even to racemic mixtures when less sterically hindered linear or cyclic substrates were tested.[10] Moreover, these ligands are susceptible to oxidation in the presence of air.

Rewardingly, our group and others have demonstrated that the ligand's oxidation can be avoided using robust biaryl

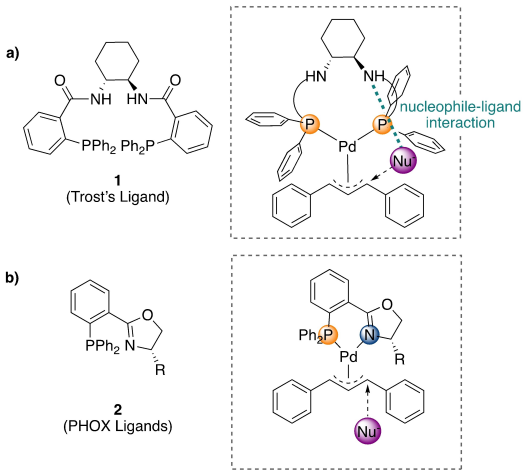

Figure 1. Two of the main strategies for the ligand design in the Pd-catalyzed enantioselective allylic substitution; a) based on (*R*,*R*)-Ph-DACH Trost's ligand, **1**. b) based on phosphine-oxazoline PHOX ligands, **2**.

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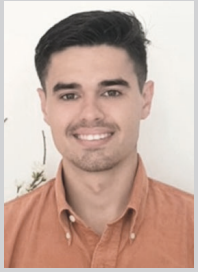

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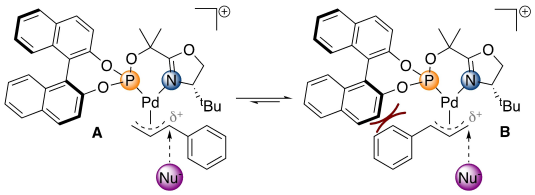
phosphite-containing ligands which are easy to synthesize from readily available alcohols.[11] Furthermore, their application overcomes most of the common limitations associated with Pd-AAS. Thus, the introduction of the biaryl phosphite moiety in the ligand scaffold provides a larger flexibility, allowing the catalyst chiral pocket to adapt to both hindered and unhindered substrates whilst providing for the first time, high enantioselectivities for both types of substrates. Additionally, the large π-acceptor ability of the biaryl phosphite group enhances reaction rates.

In recent years, the design and application of biaryl phosphite-oxazoline ligands in Pd-AAS has significantly advanced, leading to a broad substrate and nucleophile scope. Furthermore, the resulting chiral products have been applied for synthesizing relevant chiral bi- and tricyclic complex molecules. Therefore, herein, we discuss the progress made in the use of biaryl phosphite-oxazoline ligand libraries in Pd-AAS and their use in the synthesis of complex chiral molecules.



Scheme 2. Main Pd-allyl intermediates with monosubstituted substrates using the best ligand developed by Pfaltz and Prêtot.

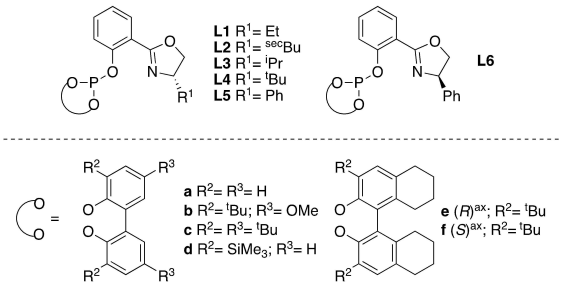


Figure 2. PHOX-based phosphite-oxazoline ligands **L1**–**L6a**–**f**.

2. Phosphite-Oxazoline Ligands in Pd-Catalyzed Asymmetric Allylic Substitution

The efficiency of phosphite containing ligands in several transition metal catalyzed reactions has been discovered in the 1990s, however their application in Pd-AAS was not explored until much more recently.[11] In this sense, our group and others successfully applied several biaryl diphosphite ligands in the Pd-AAS[12] of hindered and unhindered linear and cyclic substrates with excellent activities (TOF's up to >22000 mol substrate x (mol Pd x h)$^{-1}$) and enantioselectivities (ee's up to 99% for **S1**–**S6**, Scheme 1). However, for monosubstituted substrates (**S10**–**S11**, Scheme 1), their effectiveness could not be maintained, reaching only regioselectivities of up to 34% for the desired branched product.[12a,e]

With the aim to solve the regioselectivity issue of diphosphite ligands whilst maintaining the activities and versatility with symmetrical substrates, our group decided to investigate the introduction of a biaryl phosphite group in mixed P,N-heterodonor ligands. This approach was inspired by the work of Pfaltz and Prêtot,[13] who found that such types of ligands overcome the problem of regioselectivity towards the branched product in the AAS of monosubstituted linear substrates. This is achieved by taking advantage of the combination of two ligand properties; (i) the π-acceptor ability of the phosphite moiety which makes the Pd center more electrophilic, enhancing the S_N1 character of the nucleophilic attack, (ii) the bulkiness of the biaryl phosphine group which switches the equilibrium towards the desired Pd-π-allyl intermediate (A, Scheme 2), favoring nucleophilic attack to the most substituted carbon.

Thus, in 2005, we synthesized a new family of phosphite-oxazoline ligands **L1**–**L6a**–**f** (Figure 2)[14] by replacing the phosphine moiety within the PHOX ligands (Figure 1b) with a flexible and bulky biphenyl phosphite group. The idea behind this design was that although the new ligand modification provided a larger chelate ring upon coordination to Pd, the chiral pocket created is smaller than that of PHOX ligands, but thanks to the flexibility offered by the biphenyl moiety, it is flexible enough to be adapted to the steric hindrance of the substrate. This enables the ligands to overcome the substrate specificity of PHOX ligands (Figure 1b).

The application of these novel phosphite-oxazoline ligands provided extremely promising results, exhibiting high activities (TOF's up to >2400 mol substrate x (mol Pd x h)$^{-1}$), as well as high enantioselectivities (ee's up to >99%) for hindered and unhindered disubstituted linear and cyclic substrates (Figure 3a–c). In addition, high levels of regioselectivity (up to >99%) and enantioselectivity (ee's up to 92%) were obtained for monosubstituted substrates (Figure 3d).

The results indicate that the enantioselectivity is affected by the substituents/configuration of the biphenyl phosphite moiety and the configuration of the oxazoline group, whereas the substituent in the oxazoline moiety does not have an important effect.[14] This behavior contrasts with the oxazoline-substituent effect observed for related PHOX ligands. For all substrates, the best enantioselectivities were obtained with ligand **L3c**, containing a bulky tetra-*tert*-butyl-biphenyl phosphite moiety (**c**).

The authors expanded the nucleophile scope to O-nucleophiles and C-nucleophiles others than dimethylmalonate, testing a total of 46 combinations of substrate-nucleophile (Figure 3). Regarding the C-nucleophiles, their catalytic system showed a broad tolerance to the variation of the steric properties of the ester moiety and the substituents of the malonate nucleophile, obtaining ee's up to >99% for allyl-, butenyl-, pentenyl-, and propargyl-substituted malonates using the benchmark substrate (**S1**, Figure 3a). These chiral products are of high value since they are key intermediates in the synthesis of more complex molecules (see section below). Also, high enantioselectivities (ee's up to 99%) were obtained when

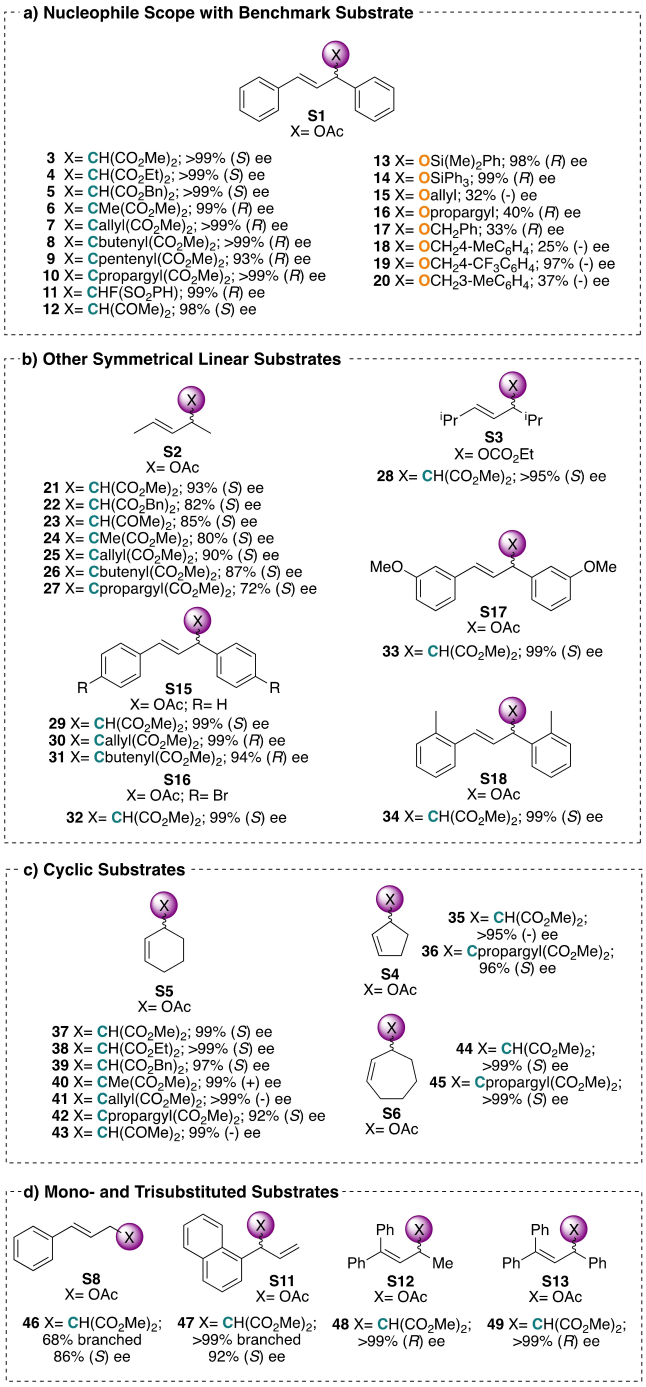


Figure 3. Summary of the catalytic results obtained in the Pd-AAS with **L3c**.

acetylacetone and ((fluoromethyl)sulfonyl)benzene were used as nucleophiles, the latter being of special interest for its potential use in medicinal chemistry for synthesizing monofluoromethylated compounds.[15] Referring to the scope of O-nucleophiles, excellent values of enantioselectivity were obtained in the esterification with silanols (ee's up to 99%), however when aliphatic alcohols were used, the enantioselectivity drastically decreases and in the case of benzylic alcohols, it is considerably affected by the electronic nature of the nucleophile (Figure 3a).

Furthermore, excellent results were obtained in the AAS of several unhindered cyclic substrates (**S4**–**S6**, Figure 3c) using malonates with different steric properties and even in the more challenging monosubstituted (**S8** and **S11**, Figure 3d) and trisubstituted substrates (**S12**–**S13**, Figure 3d).

Therefore, the ability of the phosphite moiety to adapt its conformation to each substrate provided a broader substrate tolerance than their phosphine-oxazoline analogues. This ability has been further confirmed by DFT calculations and NMR studies using **L3c** and their rigid analogues, **L3e**–**f**.[14c] The explanation is found in the different energy gaps between the most stable transition states leading to opposite enantiomers for both hindered and unhindered substrates.

Following this significant contribution, four new libraries of biaryl phosphite-oxazoline ligands have been developed and applied in Pd-AAS with the aim of further increasing the substrate and nucleophile scope. Another modification of the PHOX backbone was the introduction of a methylene spacer between the oxazoline and the phenyl ring to previous ligands **L1**–**L6** (new ligands **L7**–**L9c**, **g**–**h**, Figure 4).[16] Positively, the ligands **L7**–**L9** were synthesized in just two steps using readily available starting materials.

Good-to-high enantioselectivities and activities (TOF's up to >4000 mol substrate x $(\text{mol Pd x h})^{-1}$) were accomplished for hindered and unhindered linear and cyclic substrates (Figure 4) by skillfully combining the oxazoline substituent and the biaryl phosphite group. However, in contrast to previous phosphite-oxazoline ligand families, the impact of both the ligand's parameters on the enantioselectivity varies depending on the substrate employed. Thus, in contrast with previous ligand families, for both substrates, an (*S*)-biaryl phosphite group is needed to obtain the highest enantioselectivities. Nevertheless, the effect of the oxazoline substituent depends on the substrate used. For linear substrates, it has little effect, proving slightly better with ligand **L8h** with an ^{i}Pr substituent, whilst for cyclic substrates, **L9h** with a ^{t}Bu substituent provided the best results.

According to DFT calculations and NMR spectroscopy, the wide substrate scope is due to the ligands' ability to adjust its ligand parameters to the reacting substrate. In this regard, whilst the biaryl phosphite functionality mainly affects the enantioselectivity for hindered linear substrate **S1**, for cyclic

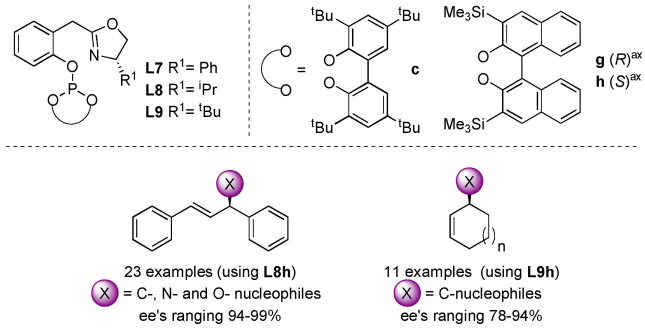


Figure 4. Phosphite-oxazoline ligands **L7**–**L9c, g**–**h** and summary of their catalytic results obtained in the Pd-AAS of hindered and unhindered cyclic and linear substrates.

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substrate **S2**, the oxazoline group also plays a critical role. Therefore, in the latter case, the introduction of a methylene spacer in the ligand backbone made the biaryl phosphite group, alone, uncapable of adapting the size of the chiral pocket to the substrate's steric demands. Hence, a bulky oxazoline group is necessary to adjust the ligand pocket's size for the narrow substrate. Moreover, the higher effect of the configuration of the biaryl phosphite moiety on the catalytic performance in **S2** can be explained by the relative disposition of the trimethylsilyl groups of the biaryl phosphite moiety and their interactions with the substrate.

Although these newly developed phosphite-oxazoline ligands yielded promising outcomes in Pd-AAS, they were unable to outperform the results achieved by the initial phosphite-oxazoline ligands **L1**–**L6** (Figure 2). Thus, to investigate the effectiveness of the biaryl phosphite group when combined with other types of ligand backbones, we applied a pyranoside phosphite-oxazoline ligand library **L10**–**L13a-d**, **g**–**k** (Figure 5), which derives from a natural source, D-glucosamine.[17] Unlike previous PHOX-based ligands, the phosphite moiety is bonded to the stereogenic center next to the oxazoline and a sugar-backbone is present. The use of carbohydrates for the construction of the ligand backbone is highly advantageous due to their low price and high modularity.[18] Moreover, diphosphite furanoside-based ligands have demonstrated promising performance in their application in Pd-AAS.[12d]

High enantioselectivities (ee's up to 99%) in a broad range of mono-, di- and trisubstituted hindered and unhindered linear and cyclic substrates with regioselectivities up to 85% for monosubstituted linear substrates were reached (Figure 5). These phosphite-oxazoline ligands provided better results than their phosphinite-oxazoline counterparts in several substrate classes.[19] Therefore, once again, the incorporation of biaryl phosphite moiety in the ligand design provides higher substrate versatility.

Later on, the development and application of a new set of phosphite-oxazoline ligands **L14**–**L25, L27, L29a–d, g–h, j–k** (Figure 6) was reported.[20] Again, as in the previous ligands **L10**–**L13** (Figure 5), and in contrast to PHOX-based ligand libraries, the biaryl phosphite group is connected to the chiral center adjacent to the oxazoline through a chiral alkyl chain, which provide a higher level of modularity compared with the previous ligand libraries.

Again, high regio- and enantioselectivities (up to 99% ee) across a wide range of mono-, tri- and disubstituted hindered and unhindered linear substrates were reached, with results comparable with the previous pyranoside ligands (Figure 5).[20–21] For cyclic substrates, only moderate ee's (up to 83%) were attained. Note, that ee's could be increased up to 94% by replacing the oxazoline moiety by a thiazoline group (**L26** and **L28**, Figure 6), which also coordinates through the N atom. The latter creates a smaller chiral pocket more suitable for

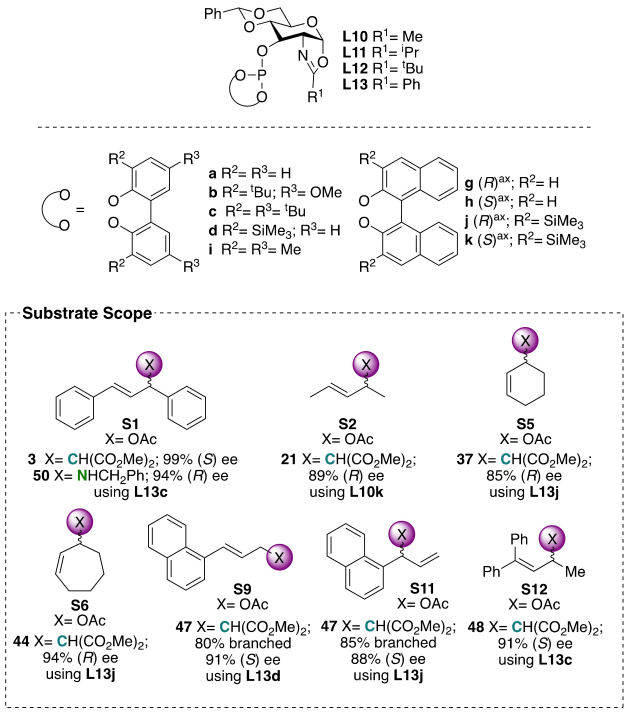


Figure 5. Pyranoside-based phosphite-oxazoline ligands **L10**–**L13** and summary of their catalytic results obtained in the Pd-AAS of hindered and unhindered mono-, di- and trisubstituted cyclic and linear substrates.

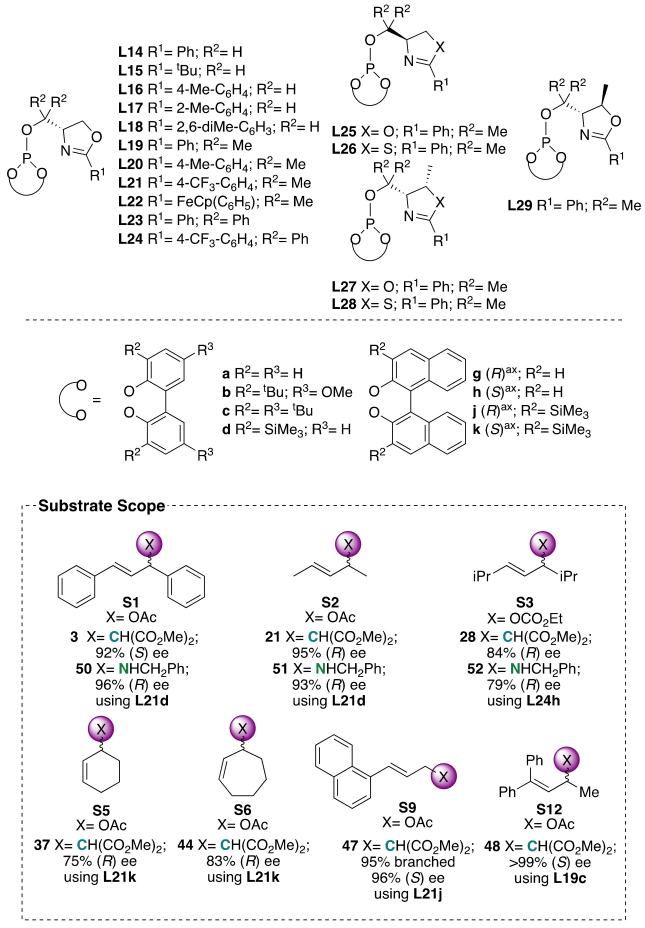


Figure 6. Phosphite-oxazoline ligands **L14**–**L29** and summary of their catalytic results obtained in the Pd-AAS of hindered and unhindered mono- and disubstituted cyclic and linear substrates.

unhindered cyclic substrates while maintaining the flexibility conferred by the biaryl phosphite group.[21]

Despite the two latter families of phosphite-oxazoline ligands (**L10**–**L13** and **L14**–**L25**, **L27** and **L29**, Figure 5 and 6, respectively) provide promising results in Pd-AAS, they were not able to surpass the results obtained with the first PHOX-based phosphite-oxazoline ligands (**L1**–**L6**, Figure 2). Thus, the presence of chirality closer to the metal center (oxazoline substituent) seems to favor the control of the stereochemical outcome.

Based on these results, our group focused on the further modification of PHOX-based ligands **L1**–**L6**, maintaining the chirality on the oxazoline substituent but replacing the flat *ortho*-phenylene with a chiral alkyl chain, in order to extend the number of ligand parameters that can be studied to enhance the catalyst performance (Ligands **L30**–**L36c**, **j**–**k** Figure 7).[22]

With these ligands, high activities (TOF's up to >8000 mol substrate x (mol Pd x h)$^{-1}$) and enantioselectivities (ee's up to $>99\%$) were achieved for many hindered and unhindered substrates with a large variety of C-, O- and N-nucleophiles, with a total of 73 tested combinations of substrate-nucleophile (Figure 8 and 9), surpassing phosphite-oxazoline ligands **L1**–**L6a**–**f** (Figure 2). To obtain the highest enantioselectivities, the ligand must contain an (*S*)-configuration on the biaryl phosphite moiety and a phenyl substituent on the oxazoline group, however, the substituent of the chiral alkyl chain differs between each substrate class.

Ligand **L34k** yielded the best results for a broad range of disubstituted linear substrates with a large variety of C-, N- and O-nucleophiles (Figure 8). It is noteworthy that the AAS of **S1** provided high enantioselectivities for functionalized malonates, β-diketones, 2-cyanoacetates, amines, pyrroles, and aliphatic alcohols, leading to chiral products that are appealing from a synthetic perspective. It should also be noted, that compared to the previous generation of PHOX-based phosphite-oxazoline ligands (Figure 2), these new ligands exhibit high enantioselectivities not only for silanols but also for allylic alcohols and several benzylic alcohols. Additionally, the scope of N-nucleophiles has been expanded to include primary, secondary, benzylic, aromatic, and sulfonamide nucleophiles, whereas the previous generation only showed high enantioselectivities with benzylamine.[14a] Remarkably, this catalytic system also displayed

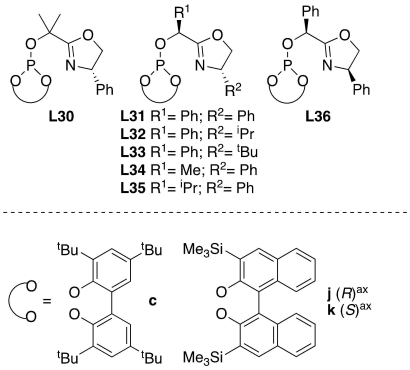


Figure 7. Phosphite-oxazoline compounds **L30**–**L36c**, **j**–**k**.

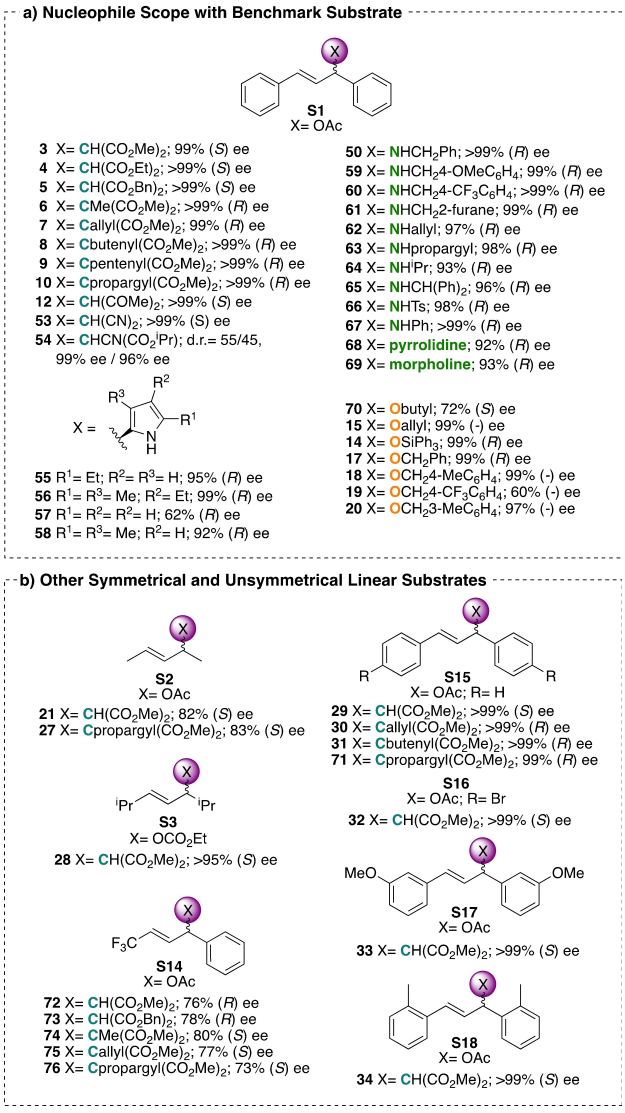


Figure 8. Summary of the catalytic results obtained in the Pd-AAS of linear substrates using **L34k**. a) C-, O- and N-nucleophile scope with benchmark substrate S1. b) Substrate scope of symmetrical and unsymmetrical linear substrates.

adaptability towards linear substrates with different steric and electronic properties (Figure 8b). Outstandingly, the study was also extended to the AAS of unsymmetrically 1,3-disubstituted substrate **S14**, for which excellent regioselectivities and promising enantioselectivities (up to 80% ee) were achieved. Therefore, this catalytic system was capable of facilitating a dynamic kinetic asymmetric transformation (DYKAT) under mild reaction conditions.

Regarding cyclic substrates, the best results were obtained using ligand **L30k** with an achiral alkyl backbone chain. High enantioselectivities were obtained with cyclic substrates with different ring sizes and using a wide range of C- and N-nucleophiles (**S4**–**S7**, Figure 9). Similar ligands with less bulky *ortho*-substituents in the phosphite moiety were previously tested in the pioneering work of Pfaltz and Prêtot (see previous Scheme 2).[13] However, in their study, moderate results were

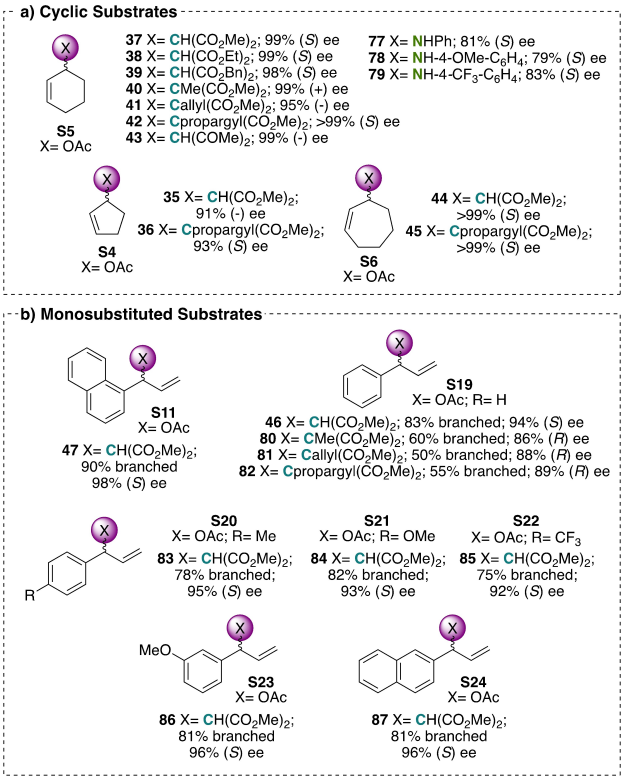


Figure 9. Summary of the catalytic results obtained in the Pd-AAS of cyclic and monosubstituted substrates using **L30k** and **L35k**.

obtained for unhindered cyclic substrates (ee's up to 70% for **S4**). Therefore, the increment of the steric hinderance in the *ortho*-substituents of the phosphite moiety creates a more suitable chiral pocket for these less hindered substrates.

Finally, using **L35k**, excellent regioselectivities were observed independently of the substituent pattern of the aryl group of the substrate with different C-nucleophiles (**S11**, **S19**–**S24**, Figure 9).

Furthermore, in this study, mechanistic investigations using DFT calculations in conjunction with NMR studies were performed to identify the species and factors responsible for the enantioselectivity. These studies disclosed that the *endo*/*exo* isomer ratio of the Pd-allyl intermediates is the primary factor responsible for enantioselectivity. However, whilst the configuration of the phosphite moiety and the substituents of the chiral alkyl chain primarily control the *endo*/*exo* isomer ratio for cyclic substrates, for linear substrates, the oxazoline substituent also plays a crucial role.

3. Application of the Best Phosphite-Oxazoline Ligand Family in the Synthesis of Complex Chiral Molecules

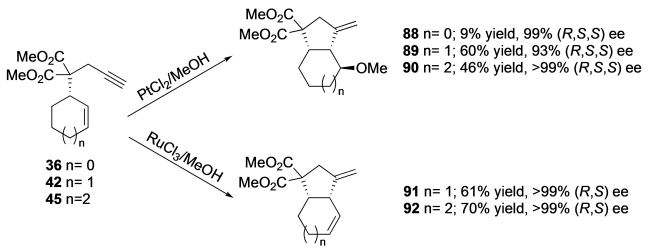
Chiral bi- and tricyclic structures are commonly found in natural products,[23] and therefore are highly desirable in industries such as pharmaceuticals, agrochemicals, and fragrances. Significant efforts have been made towards synthesizing these complex frameworks,[24] however, there is still a high demand for easy and effective methods to synthesize them. In this regard, the combination of Pd-AAS with other sequential reactions could be a good methodology, since it offers a straightforward route to synthesize strained polycyclic compounds, in which the enantioselectivity is induced during the allylic alkylation step. The previously demonstrated unique ability of phosphite-oxazoline ligands to tolerate steric hindrance from the substrate and a wide nucleophile variability allows for an extended scope, thereby enabling the synthesis of a wide range of complex chiral molecules.

Acknowledging this, in 2019, Diéguez et al. make use of the excellent outcomes observed in Pd-AAS with our best family of phosphite-oxazoline ligands developed for this process (**L30–L36c, j–k**, Figure 7) to synthesize chiral bicycles with various stereocenters by employing sequential reactions.[22]

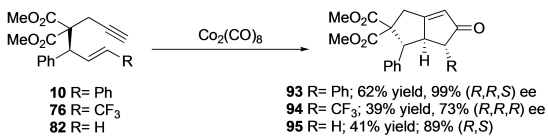
As shown in scheme 3, the propargylated products with different cycloalkane ring sizes of the Pd-AAS (**36**, **42**, **45**, Figure 9) were derivatized using a 1,6-enyne cyclization to afford the corresponding chiral carbobicycles. By altering the catalyst, two different derivatives could be obtained (Scheme 3). Good yields were obtained with both systems while maintaining high enantioselectivities, except for the most sterically hindered constrained compound **88** that provided high enantioselectivity but low yield.

The second method, which involves a Pauson-Khand enyne cyclization, also maintained the enantioselectivity obtained in the Pd-AAS while producing chiral bicyclopentenones (Scheme 4). The derivatization was tested with different substituents on the initial linear allylic substrate with no adverse effect observed, acknowledging the great potential of this sequential reaction.

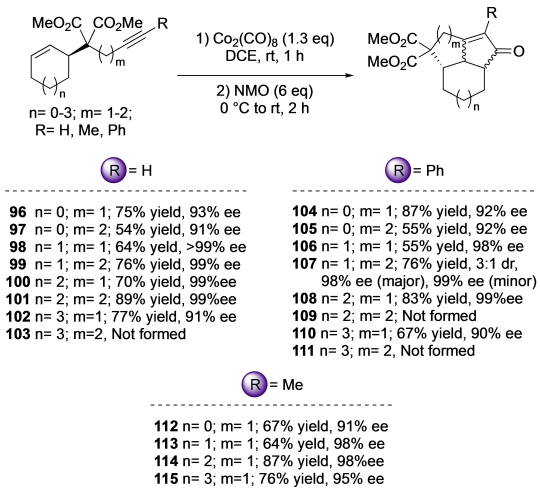
Following on from this, with the same family of ligands, the authors also used two-step sequential reactions to obtain a set of chiral complex fused-tricyclic compounds containing several functional groups and multiple stereogenic centers (Scheme 5



Scheme 3. Formation of chiral carbobicycle compounds **88**–**92** via 1,6-enyne cyclization of propargylated derivatives.

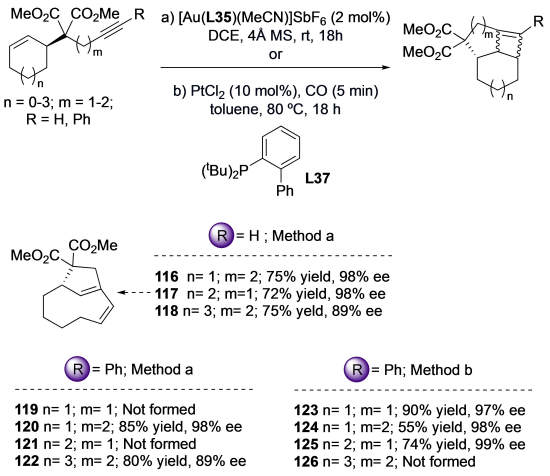


Scheme 4. Pauson-Khand enyne cyclization of propargylated derivatives to from chiral bicyclopentenone compounds **93**–**95**.



Scheme 5. Preparation of chiral fused tricyclic pentenones via Pauson-Khand enyne cyclisation.

and 6).[25] In this case, they combined the Pd-AAS of 5- to 8-membered cyclic allylic substrates with a diastereoselective transformation to synthesize a range of cyclopentenone- and cyclobutene-based tricyclic compounds. Again, a Pauson-Khand transformation is used to form cyclopentenone containing compounds (Scheme 5). The transformations of 1,6- and 1,7-enynes with 5- to 7-membered cycles, were in general carried out with good yields (up to 89%, **96–101**, Scheme 5) without compromising the enantiopurity of the starting enyne. However, attempts to carry out reactions of 1,8-enynes did not yield any product. Substituents on the α-position of the enyne (**104–109** R= Ph and **112–114** R=Me, Scheme 5) were greatly tolerated, regardless of the ring size of the starting enyne cycle (5- to 7-membered cycles), with the exception of a Ph group on a 1,7-enyne containing a 7-membered ring (**109**, Scheme 5). Furthermore, only 1,6-enynes provided the desired tricyclic compounds when 8-membered ring enynes were used (**102**, **110** and **115**, Scheme 5). Notably, a one-pot strategy, running the Pd-AAS with the Pauson-Khand transformation in tandem,



Scheme 6. Metal-catalyzed cyclization of chiral 1,6- and 1,7-enynes.

resulted to produce the tricyclic compounds in excellent enantioselectivity with only slightly lower yields.

To further explore the potential of building tricyclic molecules, the authors also applied [2+2] cycloisomerization reactions (Scheme 6), making use of previously developed methodologies in Echavarren[26] and Fürstner's[27] groups for achiral enynes. Firstly, unsubstituted chiral 6- and 8-membered ring 1,7-enynes were treated with a Au catalyst to obtain the target tricyclic compound, as a single diastereomer, in good yield and high enantioselectivities (ee's up to 98%). However, the desired product was not formed for the 5- and 7-membered ring enynes. While 1,6- and 1,8-enynes did not react, an interesting bicyclic product was identified when a 7-membered ring 1,6-enyne was reacted (**117**, Scheme 6).

Enynes with a phenyl substituent on the α-position were also tested using both Au- and a Pt-approaches (Scheme 6), which provided complementary results. Whilst the Au methodology found success with 6- and 8-membered ringed 1,7-enynes, the Pt approach worked better with 6- and 7-membered ringed 1,6-enynes.

4. Summary and Outlook

This concept outlines the advances made in Pd-AAS through the development of new families of highly modular and air-stable phosphite-oxazoline ligands that can be easily accessed from readily available starting materials. Notably, these phosphite-oxazoline ligands have been particularly successful, with the design being iteratively improved based on systematic studies of the ligand parameters thanks to DFT and NMR studies. The excellent results, when considering the substrate and nucleophile scope, can be largely attributed to the flexibility of the bulky biaryl phosphite moiety, which allows the chiral pocket to adapt to different substrate types and are also the result of an evolutionary ligand design. The resulting ligands have provided unprecedented results for a wide range of hindered and unhindered, symmetric and unsymmetric, mono-, di- and trisubstituted linear and cyclic substrates with a wide range of C-, N- and O-nucleophiles. In addition, the ability of phosphite-oxazoline ligands to tolerate sterically challenging substrates in Pd-AAS consequently enables the synthesis of increasingly complex chiral molecules, in particular compounds containing bi- and tricyclic structures. In summary, the substrate and nucleophile scope of Pd-AAS reaction has been drastically increased with the application of phosphite-oxazoline ligands, and the further potential of the resulting chiral products has been demonstrated by sequential derivatization, paving the way for the synthesis of chiral natural compounds using this strategy.

Successful ligand design is a complex and usually an iterative task. Ligand design serendipity can be minimized by incorporating into the design what is already mechanistically known for a given transformation. Another important key aspect is the use of affordable and highly modular ligand backbones, which can be adequately tuned. In order to speed up the process and diminishing the combinatorial ligand space,

it is desirable that the ligand design could be guided by combining experimental and theoretical approaches. Thus, for instance, we have shown herein how crucial it is to understand the ligand-substrate interactions to help to predict the ligand performance, and ultimately to guide the ligand selection. Theoretical calculations at all levels of complexity are becoming more and more powerful and affordable. This has allowed the development of predictive models for AAS based on QMM calculations.[28] Advances in computer science should, in the near future, facilitate a fully in silico ligand DFT design and/or the application of machine learning techniques.

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Conflict of Interests

The authors declare no conflict of interest.

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