An improved class of phosphite-oxazoline ligands for Pd-catalyzed allylic substitution reactions

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ABSTRACT: A generation of Pd/phosphite-oxazoline catalysts containing an alkyl backbone chain has been successfully applied to Pd-catalyzed allylic substitution reactions. By carefully selecting the substituents at both oxazoline and the alkyl backbone chain of the ligand, as well as the configuration of the biaryl phosphite group, high activities (TOF > 8000 mol substrate×(mol Pd×h)$^{-1}$) and excellent enantioselectivities (ee's up to 99%) have been achieved for a broad range of hindered and unhindered substrates with a wide range of C-, N- and O-nucleophiles (73 compounds in total). Moreover, DFT calculations and NMR studies of the key Pd-intermediates allowed us to better understand the origin of the excellent enantioselectivities observed experimentally. The synthetic application of the new Pd/phosphite-oxazoline catalysts was demonstrated by the synthesis of a range of chiral carbobicyles, with multiples stereocenters, by simple sequential reactions involving Pd-allylic substitution an either 1,6-enyne cyclization or Pauson-Khand enyne cyclization.

KEYWORDS: *Palladium, allylic substitution, DFT study, NMR study, P,N-ligands.*

INTRODUCTION

Many pharmaceutical, fragrance and crop protection industries rely on enantiomerically pure compounds. The discovery of synthetic routes for their preparation is a recurrent research in chemistry[1] and the Pd-catalyzed asymmetric allylic substitution (AAS) has been shown to be one of the most powerful approaches. AAS works under mild reaction conditions, has a high functional group tolerance and the versatility of the alkene functionality allows further functionalization.[1,2] Given its advantages, it is understandable the constant aim to expand the range of nucleophiles and substrates to reach more complex chiral compounds. Its main limitation is still that asymmetric induction is highly dependent on the steric demands of the substrate.[2] Each type of substrate requires a particular ligand for optimal enantiopurity so most of the best-performing ligands rarely tolerate a broad range of substrates. Consequently, the discovery of the best performing ligands is time consuming and expensive. This is facilitated with the identification of ligands with a wide substrate and nucleophile scope. Our group early found that biaryl diphosphite-based ligands favor substrate versatility.[2i,3] From a common skeleton, the right combination of ligand parameters gives ligands that are suitable for both linear and cyclic substrates using dimethylmalonate as nucleophile.[3] The study of Pd-intermediates showed that the adaptability of the biaryl phosphite groups enables the catalyst to appropriately fit its chiral pocket to accommodate substrates with different steric requirements. In addition, the π-acceptor capacity of the phosphite moiety has an extremely positive effect on activities, providing higher TOF than the most common ligands.[2i,3,4] Encouraged by the excellent enantioselectivities achieved with heterodonor ligands in AAS we then started the development of heterodonor ligands containing a biaryl phosphite moiety.[5] In this respect, our group took one of the most successful ligand families developed for this process, the phosphine-oxazoline PHOX ligands **1**,[2e,6] and replaced the phosphine moiety with a biaryl phosphite group (Figure 1, ligands **2**).[5a] Whereas Pd-PHOX catalyst gave excellent results with the model substrate *rac*-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene, modest-to-good results with 1,3-dialkyl-2-propenyl substrates and racemic results for cyclic substrates,[2e] the Pd-phosphite-oxazoline analogues **2** were very successful in all of them.[5a,7] Pd/**2** turned out to be an unprecedented catalytic system to generate C–C, C–N, and C–O bonds with high enantiocontrol for a number of hindered and unhindered substrates using a wide range of C-, N-, and O-nucleophiles. In addition, the improvement in activity achieved with diphosphite ligands was maintained. NMR and DFT studies confirmed that the broad substrate scope of Pd/**2** system is due to the ability of the ligand to adapt the size of the substrate-binding pocket to the reacting substrate.[7] This ability also explains its high performance in other types of catalytic processes.[8]

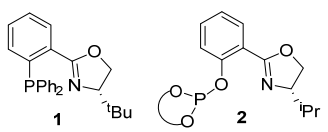


Figure 1. PHOX-based ligand **1** and the related phosphite-oxazoline ligands **2**.

Despite the wide scope of ligands **2**, there is still room for improvement in terms of both substrate and nucleophile scope. For instance, the efficiency disclosed for non-symmetrical substrates has to be further enhanced and the nucleophile scope has to be expanded

to cover a wider range of amines and alcohols. To continue the improvement of Pd-catalysts with air stable and readily available ligands, we replaced the *ortho*-phenylene tether in privileged ligands **2** by an alkyl backbone chain (Figure 2, ligands **L1**–**L7a**–**c**). With this simple modification, we have extended the number of ligand parameters than can be modified to maximize the catalyst performance. Therefore, in addition of studying different substituents and configurations in the oxazoline and phosphite groups we also studied the effect of a new stereogenic center in the alkyl backbone chain and the effect of varying the substituent in this alkyl backbone chain. In this respect, we here report the application of ligands **L1**–**L7a**–**c** in the Pd-catalyzed AAS of linear substrates (including unsymmetrical 1,3-disubstituted and monosubstituted substrates) and cyclic substrates with many C-, N- and O-nucleophiles (73 compounds in total). We also used DFT calculations and the study of the key Pd-π-allyl intermediates to explain the origin of enantioselectivity. Finally, we showed that these new Pd-catalytic systems can be used in the synthesis of chiral carbobicyclic compounds by simple sequential allylic substitution/1,6-enyne cyclization or allylic substitution/Pauson-Khand reactions.

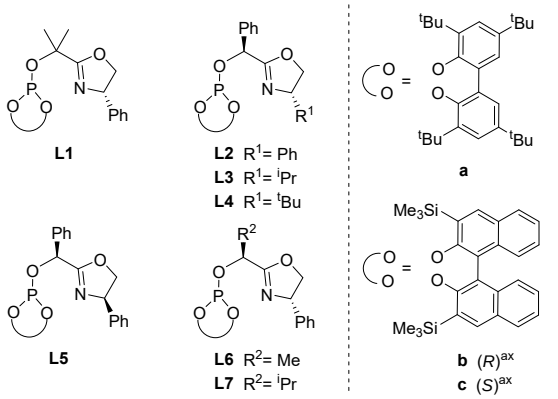
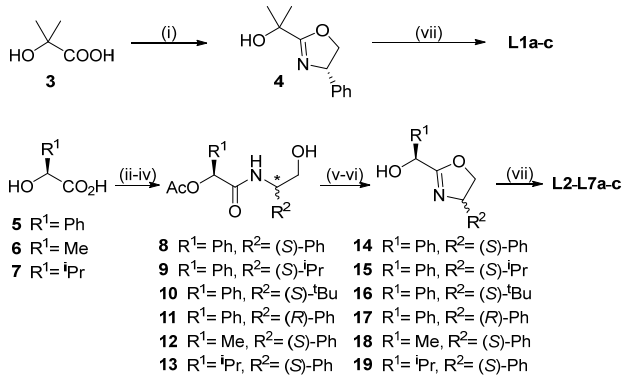


Figure 2. Phosphite-oxazoline ligands **L1**–**L7a**–**c**.

RESULTS AND DISCUSSION

Synthesis of ligands. Phosphite-oxazoline ligands **L1**–**L7a**–**c** were synthesized in a simple two or five step procedure, starting from commercially available materials (Scheme 1). Therefore, ligands **L1a**–**c**, with two methyl groups in the alkyl backbone chain, were synthesized in only two steps from cheap α-hydroxyisobutyric acid **3**. Condensation of **3** with (*S*)-phenylglycinol afforded hydroxyl-oxazoline **4** in a multigram scale (step *i*).[9] Then, compound **4** react with the corresponding *in situ* formed phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**–**c**; step *vii*) to yield phosphite-oxazoline ligands **L1a**–**c**, with different biaryl phosphite moieties. Phosphite-oxazolines **L2**–**L7a**–**c**, which differ from previous ligands in a stereogenic center in the alkyl backbone chain, were prepared following the procedure previously reported in our group from commercially available α-hydroxy acids **5**–**7**.[10] Therefore, compounds **5**–**7** were first converted to amides **8**–**13** and subsequent reaction with diethylaminosulfur trifluoride (DAST) followed by standard deprotection yielded hydroxyl-oxazolines **14**–**19** (steps *v*–*vi*).[11,12] Finally, compounds **14**–**19** react with the desired phosphorochloridite ($ClP(OR)_2$; $(OR)_2$ = **a**–**c**; step *vii*) to afford ligands **L2**–**L7a**–**c**.

Advantageously, all ligands were isolated as white solids stable in air. They were therefore further manipulated and stored in air. The formation of the ligands was confirmed by HRMS-ESI and ^{1}H, ^{13}C and ^{31}P NMR spectroscopy (see experimental and SI sections for detail).



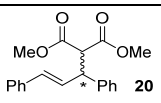
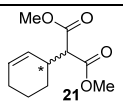
Scheme 1. Synthetic route for the preparation of the phosphite-oxazoline ligand library **L1**–**L7a**–**c**. (i) (*S*)-phenylglycinol, xylene, reflux, 16 h;[9] (ii) acetylchloride, rt, 2 h;[11] (iii) $SOCl_2$, CH_2Cl_2, reflux, 3 h;[11] (iv) aminoalcohol, NEt_3, CH_2Cl_2, rt, 5 h;[11] (v) DAST, K_2CO_3, CH_2Cl_2, -78 °C to rt for 3 h;[11,12] (vi) NaOH (aq), EtOH, 0 °C, 3 h;[11,12] (vii) $ClP(OR)_2$; $(OR)_2$ = a–c, Py, toluene, 16 h.

Allylic substitution of disubstituted substrates S1–S2 using dimethyl malonate as nucleophile. The effectiveness of the phosphite-oxazoline ligands **L1**–**L7a**–**c** was first studied in the Pd-allylic alkylation of two benchmark substrates with different steric properties, *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** and *rac*-3-acetoxycyclohexene **S2**. For comparison, we use the same optimal reaction conditions found in our previous study with related Pd/PHOX-based phosphite-oxazoline catalysts **2**.[5a] The reactions were therefore performed at room temperature, using 0.5 mol% of *in situ* generated catalyst from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand, and using dimethyl malonate as nucleophile. It should be noted, that the enantioselectivity for cyclic **S2** is more difficult to control than for **S1** due to the presence of less bulky anti substituents. However, by carefully selecting the ligand components we have been able to identify two particular ligands **L1c** and **L6c**, that performs exceptionally well for both substrate types, with enantioselectivities up to 99% ee and TOF's up to 8640 mol substrate×(mol Pd×h)$^{-1}$. The results (Table 1) indicated that enantioselectivities are affected by the substituents at both the oxazoline and at the alkyl backbone chain as well as by the biaryl phosphite groups. However, the effect of these parameters on enantioselectivity is different for both substrates. While for substrate **S1** the best enantioselectivity was achieved with ligand **L6c** (ee's up to 99%), for substrate **S2** ligand **L1c** provided the best selectivity (ee's up to 99%).

The results with ligands **L1a**–**c**, with an achiral alkyl backbone chain (entries 1-3), indicated that the ligand backbone is only able to control the tropoisomerization of the biphenyl phosphite moiety (**a**) for substrate **S1**. While high enantioselectivities are achieved with ligands **L1a** and **L1c** for substrate **S1** (96% ee, entries 1 and 3), the use of ligand **L1c** with an enantiopure (*S*)-biaryl phosphite group is necessary to maximize enantioselectivities for substrate **S2** (99% ee, entry 3 vs 1 and 2). The same behavior is found with ligands **L2**–**L7** that differ from **L1** in that they contain a substituent at the alkyl backbone chain that generates a new chiral center.

The results with ligands **L2**–**L4a** also indicated that enantioselectivities are dependent on the oxazoline substituent. In contrast to the phosphine-oxazoline PHOX ligands **1** the presence of bulky substituents has a negative effect on enantioselectivity (see for e.g., entries 4, 7 and 8). Thus, the highest enantioselectivities for both substrates were achieved using ligands **L2**, containing a phenyl oxazoline substituent (entry 4). This represents an advantage over the traditional phosphine-oxazoline PHOX ligands **1** because enantiopure phenylglycinol (used for the synthesis of **L2**) is much cheaper than *tert*-leucinol used for the synthesis of **1**.

Table 1. Pd-catalyzed asymmetric allylic alkylation of substrates S1 and S2 using phosphite-oxazoline ligands L1–L7a–c [a]

		 **20**		 **21**	
Entry	L	% Conv[b]	%ee[c]	% Conv[d]	%ee[e]
1	**L1a**	100	96 (*S*)	100	60 (*S*)
2	**L1b**	100	86 (*S*)	100	78 (*R*)
3	**L1c**	100	96 (*S*)	100	99 (*S*)
4	**L2a**	100	93 (*S*)	100	40 (*S*)
5	**L2b**	100	40 (*S*)	100	74 (*R*)
6	**L2c**	100	90 (*S*)	100	90 (*S*)
7	**L3a**	100	92 (*S*)	100	7 (*S*)
8	**L4a**	100	73 (*S*)	100	4 (*S*)
9	**L5a**	100	90 (*R*)	100	20 (*R*)
10	**L5b**	100	94 (*R*)	100	81 (*R*)
11	**L5c**	100	55 (*R*)	100	77 (*S*)
12	**L6a**	100	97 (*S*)	100	44 (*S*)
13	**L6b**	100	89 (*S*)	100	65 (*R*)
14	**L6c**	100	99 (*S*)	100	96 (*S*)
15	**L7a**	100	84 (*S*)	100	33 (*S*)
16	**L7b**	100	91 (*S*)	100	60 (*R*)
17	**L7c**	100	90 (*S*)	100	97 (*S*)
18[f]	**L6c**	72	99 (*S*)	41	96 (*S*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), dimethyl malonate (3 equiv), KOAc (3 mol%) at 23 °C. [b] Conversion percentage determined by ^{1}H-NMR after 10 min. [c] Enantiomeric excesses determined by HPLC. Absolute configuration drawn in parentheses. [d] Conversion percentage determined by GC after 30 min. [e] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses. [f] Reactions carried for 5 min using 0.1 mol% of catalyst precursor.

The results comparing the use of diasteriomeric ligands **L2b**–**c** and **L5b**–**c** indicated that there is a cooperative between the configuration of the biaryl phosphite group and the configuration of the oxazoline substituent. This resulted in a matched combination for ligands **L2c** and **L5b** (entries 6 and 10). In addition, while for linear substrate **S1** the sense of enantioselectivity is controlled by the configuration of the oxazoline substituent (ligands **L2** provide the opposite enantiomer of alkylated products than ligands **L5**; entries 4–6 vs 9–11), for the cyclic substrate **S2** it is controlled by the configuration of the biaryl phosphite (ligands **L2b** and **L5b** provides the opposite enantiomers than ligands **L2c** and **L5c**). Both enantiomers of the products can be therefore obtained by simple selecting the correct combination of ligand parameters.

Finally, the effect of the substituent at the alkyl chain was studied using ligands **L1**, **L2**, **L6** and **L7**. The best enantioselectivities were achieved with ligands **L1** (for **S2**) and **L6** (for **S1**) containing two or one methyl group at the alkyl backbone chain, respectively.

In summary, the enantioselectivities with Pd/**L1c** and Pd/**L6c** are excellent and similar to those with previous Pd/PHOX-based phosphite-oxazoline catalysts **2**, which have recently emerged as one of the most successful catalysts designed for this process, with the added advantage that the activity with Pd/**L1c** and Pd/**L6c** is much higher[13].

Allylic substitution of other disubstituted linear and cyclic substrates with other nucleophiles. We further studied the performance of **L1**–**L7a**–**c** in the allylic substitution of other linear substrates, including unsymmetrical 1,3-disubstituted ones and cyclic disubstituted substrates with different electronic and steric properties. The range of nucleophiles was also extended with special attention to some more challenging and appealing from a synthetic point of view, namely functionalized malonates, β-diketones, 2-cyanoacetates, amines, pyrroles and aliphatic alcohols.

Initially we used the Pd-catalyzed allylic substitution of **S1** to study the nucleophile scope using ligand **L6c**, which had provided the best results in the allylic alkylation of **S1** with dimethyl malonate. The results, which are summarized in Figure 3, indicated that a wide range of C-, N- and O-nucleophiles could be efficiently used for this transformation.

In this respect, a broad range of malonates, including those with allyl-, butenyl, pentenyl- and propargyl- substituents, reacted with **S1** to give the alkylated products **22**–**28** in excellent yields and enantioselectivities (ee's ≥99%). These results are important because the resulting products (**22**–**28**) are crucial intermediates for preparing more complex chiral compounds (for some of their applications see synthetic applications section, vide infra).[14] The use of malononitrile (compound **29**) and acetylacetone (compound **31**) also gave the desired alkylated products in excellent enantioselectivities (>99% ee). Similarly to previous reports, the use of isopropyl cyanoacetate as nucleophile (compound **30**) resulted in the formation of two diastereoisomers,[15] albeit both diastereoisomers were obtained almost enantiopure (ee's up to 99%).

The nucleophile scope was extended to use pyrroles as C-nucleophiles (Figure 3, compounds **32**–**35**). Pyrroles are present in many relevant compounds with biological and synthetic applications.[16] Despite their relevance only two successful examples can be found in the literature[17] and one of them required low temperature (-20 °C) to achieve high enantioselectivities[17a]. The difficulty of using pyrroles as C-nucleophiles is also evident if we consider that, even the two most successful ligands developed for Pd allylic alkylation (Trost diphosphine and PHOX **1**) did not work well with pyrroles.[17a] By improving the Pd/**2** catalysts, we were pleased to see that we could reach for substituted pyrroles ee's up to 99% and high yields working at room temperature.

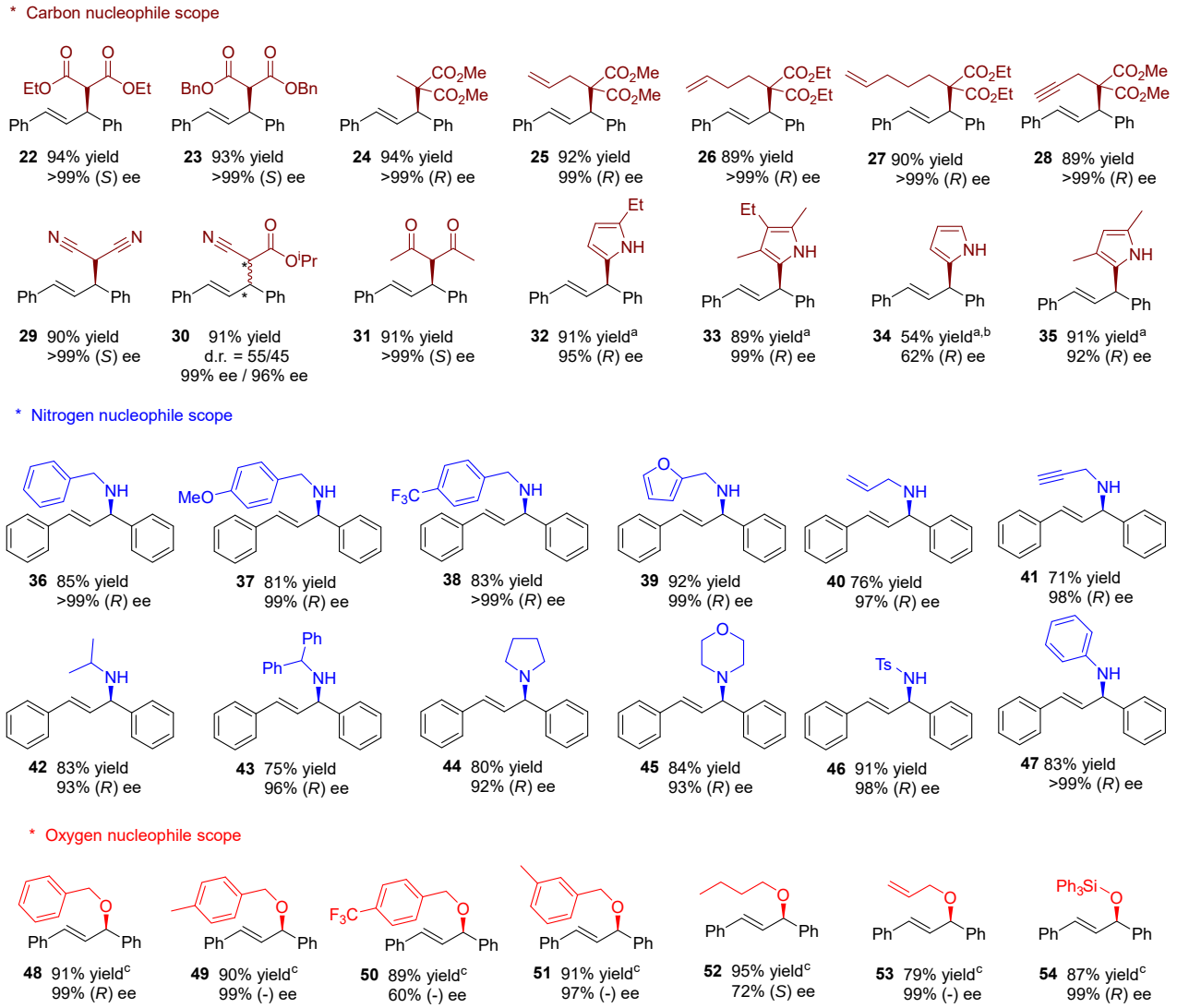


Figure 3. Allylic substitution of **S1** with other several C-, N- and O-nucleophiles with Pd/**L6c** catalytic system. Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), CH_2Cl_2 as solvent, ligand (1.1 mol%), BSA (3 equiv), and KOAc (3 mol%). Full conversions were achieved after 2 h. [a] Reactions carried out using KOAc (3 equiv). [b] Reaction carried out at -20 °C for 48 h. [c] Reactions carried out using 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol% ligand, and Cs_2CO_3 (3 equiv). Full conversions were achieved after 18 h.

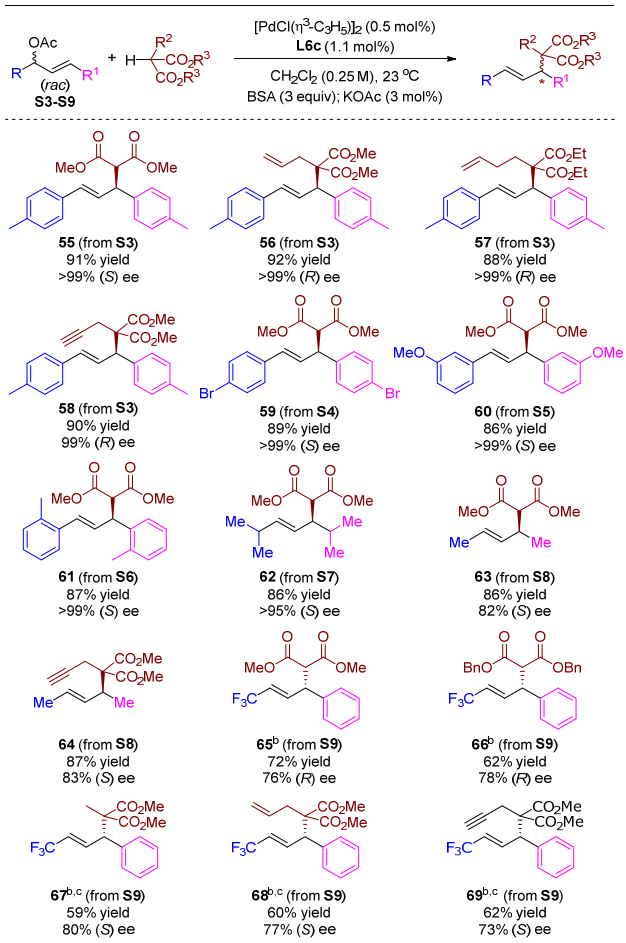
The reaction also worked well when the nucleophiles were amines. High yields and enantioselectivities in products **36**–**47**, comparable to those achieved with C-nucleophiles, were obtained with a broad range of primary and secondary amines (aryl-, alkyl-, allyl- and propargyl-substituted amines). Among them, several benzylic amines, including furfurylamine, afforded the substitution products **36**–**39** in excellent enantioselectivity (>99% ee). Enantiocontrol was also excellent in the addition of alkyl primary amines (products **42**–**43**) and cyclic secondary amines (products **44**–**45**). Gratifyingly, Pd/**L6c** was also successfully applied in the addition of sulfonamide and aromatic amines (products **46** and **47**, ee's up to >99%). Finally, enantioselectivities up to 98% ee with high yields were also found with allyl- and propargyl-substituted amines (compounds **40** and **41**, respectively). These results represent a significant improvement compared to those obtained with the Pd/**2** catalytic system, for which a high enantioselectivity has been only reported for benzylamine.[5a]

The excellent enantioselectivities also extend to the addition of O-nucleophiles (Figure 3, compounds **48**–**54**) with enantioselectivities as high as those obtained with dimethyl malonate. Aliphatic alcohols are another relevant set of nucleophiles whose resulting chiral ethers are found in biologically active targets.[18] Despite the fact that addition of aliphatic alcohols has been well studied, only a few successful examples have been reported.[19] In addition, the type of aliphatic alcohol highly influences the enantioselectivity, whose value largely depends on the electronic properties of the alcohol. In this respect, for previous Pd/phosphite-oxazoline PHOX systems **2** the highest enantioselectivity was only obtained when the benzylic alcohol contained an electron-deficient *para* substituent (ee's up to 97%), and the selectivity diminished dramatically if the substituent was more electron rich.[20] Improving these previous results with Pd/**L6c** catalyst, high enantioselectivity was achieved for the addition of a broader range of benzylic alcohols (compounds **48**–**51**, ee's up to 99%). The only exception was compound **50** with a *para*-CF_3 substituent that led to a lower enantioselectivity. Similarly, the use of

butanol afforded the corresponding product **52** in 72% ee. Excellent enantioselectivities (up to 99%) were also achieved for the addition of the much less studied allylic alcohol (compound **53**) and the triphenylsilanol (compound **54**).[21]

We then used the Pd/**L6c** catalytic system to study other symmetrical disubstituted linear substrates **S3**–**S8** (Table 2) with electronic and steric requirements different from those of **S1**. The results indicated that Pd/**L6c** can also be used for the alkylation of substrates **S3**–**S5** (compounds **55**–**60**), with different substituents in the aryl groups, even with highly appealing nucleophiles such as those substituted with allyl, pentenyl and propargyl groups, with yields and enantioselectivities comparable to those of **S1** (compounds **55**–**60**, ee's ≥99%).

Table 2. Allylic substitution of substrates S3-S9 with several C-nucleophiles with Pd/L6c.[a]



[a] Full conversions were achieved after 2 h (except for reactions using substrates **S6** and **S7** that were run for 12 h; and for **S9** that were run for 18 h). [b] Complete regioselectivity towards the nucleophilic attack at carbon next to the aryl group was obtained. [c] Reactions carried out at 40 °C.

The scope of Pd/**L6c** was also studied to other linear substrates with different steric requirements, which usually react with much lower enantioselectivity than the model **S1** (substrates **S6**–**S8**).[2] Thus, comparable high enantioselectivities were still achieved in the alkylation of those more sterically demanding substrates (compounds **61** and **62**). Pd/**L6c** could also successfully adapt its chiral pocket in the alkylation of the much less sterically demanding substrate **S8** (compounds **63** and **64**), even using propargyl malonate as nucleophile for which only very few catalytic systems have provided high enantioselectivity.[2]

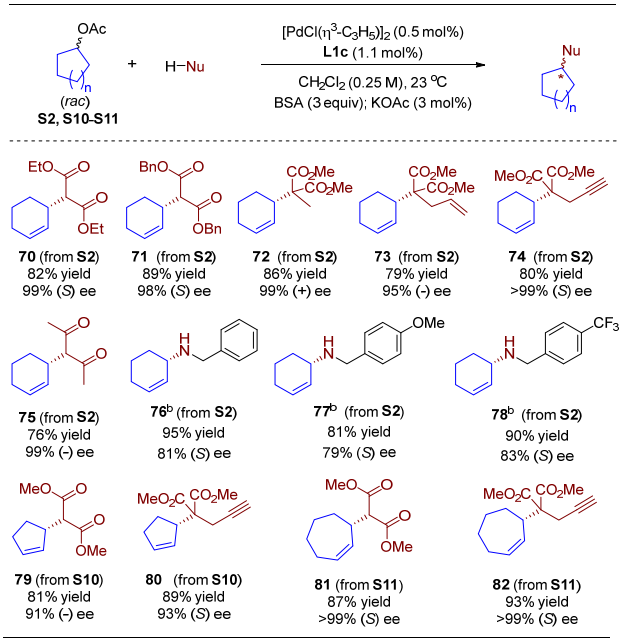
Encouraged by the previous results, we further extended our work to a more challenging class of linear disubstituted substrates, the unsymmetrical 1,3-disubstituted ones. For this substrate class not only regioselectivity has to be controlled, but also most of the catalytic systems tend to proceed via kinetic resolution, which limits the maximum yield to 50%.[22] There are, however, few successful examples in which the catalyst is able to epimerize the Pd-allyl intermediates under reaction conditions and therefore they are able to overcome the 50% maximum yield limitation via a dynamic kinetic asymmetric transformation (DYKAT).[23] Due to the importance of chiral organofluorine compounds we focused on the Pd-catalyzed allylic alkylation of the CF_3-group-substituted linear substrate **S9** with several C-nucleophiles (Table 2). For this substrate only one catalytic system, the Pd/(*S*)-tol-BINAP, has been successfully applied but it required high catalyst loading (10 mol% Pd) and high temperature (60 °C) using dioxane as solvent.[23h] Interestingly, Pd/**L6c** catalytic system is able to promote a DYKAT process of *rac*-**S9** under mild reaction conditions (see Supporting Information for details). Thus, excellent regioselectivities and promising enantioselectivities (up to 80% ee) were achieved with our Pd/**L6c** system using several C-nucleophiles (Table 2, compounds **65**–**69**). The results obtained using propargyl malonate as nucleophile is of special interest due to the fact that the alkylated product **69** is a relevant intermediate in the synthesis of more complex compounds such as a chiral bicyclopentenone derivative by a Pauson-Khand reaction (vide infra).

Based on the successful results described above for the cyclic substrate **S2**, we expanded the substrate scope to other cyclic substrates with different ring sizes (**S2**, **S10** and **S11**) and with nucleophiles other than the dimethyl malonate. These studies were carried out with ligand **L1c** which had provided the best result in the alkylation of **S2** (see Table 1 above). The results are summarized in Table 3. For the allylic alkylation of **S2**, high yields and excellent enantioselectivities (ee's to >99%) were achieved with a wide range of C-nucleophiles (compounds **70**–**75**), including the propargyl-substituted malonate (compound **74**) whose alkylation gave a lower enantioselectivity with Pd/**2**. Excellent enantioselectivities were also obtained for the seven-membered cyclic substrate **S11** with dimethyl and propargyl malonates as nucleophiles (ee's up to >99%; compounds **81**–**82**). The good performance could be also extended to the more challenging five-membered cyclic substrate **S10** (compounds **79**–**80**). Note that the resulting propargylated compounds **74**, **80** and **82** are key intermediates for the synthesis of more complex molecules such as chiral carbobicycles by a subsequent simple 1,6-enyne cyclization reaction (vide infra).

The allylic amination of cyclic substrates turned to be more challenging than the amination of linear substrates described above.[2c,m,5k,24] The reactions with cyclic substrates are less studied and in general provide low enantioselectivity. Improving on Pd/**2** catalysts, Pd/**L1c** were also found to be well suited for the allylic amination of **S2** (Table 3, compounds **76**–**78**), albeit the enantioselectivities where somewhat lower than in the allylic alkylation. The results also indicated that the enantioselectivity is not affected by the

electronic nature of the group at the *para* position of the aromatic ring.

Table 3. Allylic substitution of cyclic substrates S2, S10 and S11 with several C- and N-nucleophiles with Pd/L1c.[a]

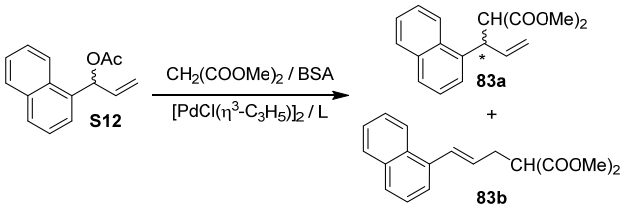


[a] Full conversions were achieved after 2 h. [b] Reactions carried out using cyclohex-2-en-1-yl ethyl carbonate as substrate and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1 mol%) for 18 h.

Allylic substitution of monosubstituted substrates S12–S18. Finally, we tested whether the good catalytic results obtained in the allylic substitution of disubstituted substrates could be retained for the monosubstituted ones. In these substrates the catalyst must control not only the enantioselectivity but also the regioselectivity and most Pd-catalysts tend to produce the undesired achiral linear product. For these substrates, the development of highly regio- and enantioselective Pd-catalysts is still quite an unsolved issue.[25]

Table 4 shows the results of using ligands **L1**–**L7a–c** in the allylic alkylation of benchmark monosubstituted subtrate **S12** under the same optimal reaction conditions as in our previous study with related Pd/PHOX-based phosphite-oxazoline catalysts **2**. Pd/**L7c** provided the desired branched product in high regioselectivity (up to 90%) with an enantioselectivity (up to 98% ee) that was somewhat higher than those obtained with the Pd/**2** systems. It was also found that the ligand structure hardly affected regioselectivity but did affect enantioselectivity substantially. More precisely, while the configuration/substituent at both the oxazoline and the biaryl phosphite groups affected the enantioselectivity like in the alkylation of disubstituted **S1**, the effect of the substituent at the alkyl backbone chain was different and the best enantioselectivities were obtained with **L7c**, that contains an isopropyl group at the alkyl backbone chain (ee's up to 98%; entry 11). Like for **S1**, the sense of enantioselectivity was dictated by the configuration of the oxazoline substituent (entries 4–6 vs 7–9) while its value depended on a cooperative effect between the configurations of the biaryl phosphite group and of the oxazoline substituent (compare e.g., ligand **L2c**, entry 6 and ligand **L5b**, entry 8). The control on the ligand structure allowed us to obtain both configurations of the alkylated product in high enantioselectivities.

Table 4. Regio- and enantioselective Pd-catalyzed allylic substitution of monosubstituted substrate S12.[a]

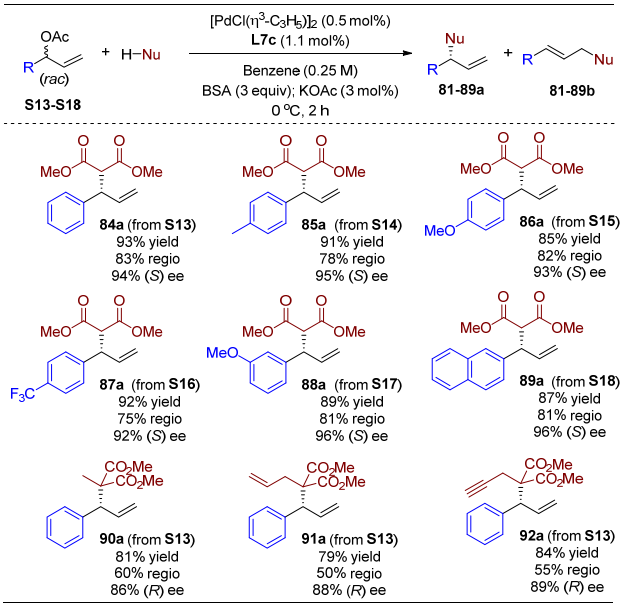


Entry	Ligand	% Conv[b] (% yield)	% branched[c]	% ee[d]
1	**L1a**	100 (88)	80	64 (*S*)
2	**L1b**	100 (89)	80	37 (*S*)
3	**L1c**	100 (88)	75	88 (*S*)
4	**L2a**	100 (91)	75	64 (*S*)
5	**L2b**	100 (89)	80	34 (*S*)
6	**L2c**	100 (90)	75	91 (*S*)
7	**L5a**	100 (89)	80	45 (*R*)
8	**L5b**	100 (88)	85	87 (*R*)
9	**L5c**	100 (91)	70	45 (*R*)
10	**L6c**	100 (90)	70	93 (*S*)
11	**L7c**	100 (91)	90	98 (*S*)

[a] 1 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.2 mol% ligand, benzene as solvent, BSA/KOAc as base, 0 °C. [b] % Conversion measured after 1 h. Isolated yield shown in parenthesis. [c] Regioselectivity measured by ^{1}H NMR. [d] Enantiomeric excesses determined by chiral HPLC.

With the optimal ligand **L7c**, we next studied the Pd-AAS of other challenging monosubstituted substrates with different steric and electronic properties, using dimethyl malonate as nucleophile (Table 5). In previous studies with Pd/**2**, it has been observed that the enantioselectivity and the regioselectivity to the desired branched isomer were reduced when the 1-naphthyl group was replaced by a phenyl (**S13**).[7] This effect was also observed with the Pd/**1** catalyst. In addition, the decrease in regioselectivity was more pronounced or even reversed to the achiral linear product when the substrates had electron-withdrawing groups on the aryl group.[25a] This was overcome with ligand Pd/**L7c**. Thus, enantioselectivities and regioselectivities (Table 5) were quite independent on the substitution pattern of the substituent of the aryl group, and high enantioselectivities (up to 96%) and regioselectivities up to 84% were obtained in substrates bearing either an electron-donating group and even an electron-withdrawing group on the aromatic ring (**84a**–**89a**). Finally, we studied the use of other nucleophiles. Although the good performance in terms of regioselectivity was not retained, promising high enantioselectivities were achieved (compounds **90a**–**92a**).

Table 5. Pd-catalyzed allylic substitution of monosubstituted substrates S13–S18 with ligand L7c.[a]



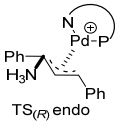
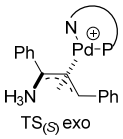
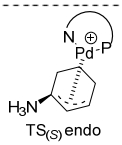
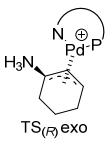
[a] Regioselectivities measured by ^{1}H NMR and enantiomeric excesses determined by chiral HPLC.

Origin of enantioselectivity

DFT computational studies. Previous mechanistic studies with related Pd/phosphite-oxazoline **2** showed that the nucleophilic attack, that is the step that determines enantioselectivity, occurs via an early transition state (TS).[7] Thus, the stereochemistry of the reaction was governed by the relative electrophilicity of the allylic carbon atoms, with the allyl terminus *trans* to P being more reactive than the one *trans* to the oxazoline group, in agreement with the stronger *trans* influence of the phosphorus.[26] With the aim of identifying what properties of ligands **L1**–**L7a**–**c** are responsible for the catalytic performance, we performed a DFT computational study of the early TSs involved in the enantiocontrol of the hindered substrate **S1** and the unhindered substrate **S2** with ligands **L1b**, **L1c** and **L6c**.[27] The selected ligands allowed us to study the effect on enantioselectivity of varying the configuration of the biaryl phosphite moiety (ligands **L1b** and **L1c**) as well as the effect of having a chiral center in the alkyl backbone chain (ligand **L6c**). To accelerate DFT calculations, NH_3 was used as the nucleophile instead of dimethyl malonate.[28,29] Moreover, and in agreement with that already described in the literature, only the two *syn-syn* allyl complexes were calculated (TS_{endo} and TS_{exo}), neglecting the contribution of other allylic species of higher energy (*anti-anti* and *syn-anti*).[2d]

Table 6 collects the results of the most stable TSs, leading to the formation of both product enantiomers ($TS_{(S)}$ and $TS_{(R)}$), with the three ligands. The full set of calculated TSs can be found in the Supporting Information. The energy differences of the calculated TSs for both substrates **S1** and **S2** agree with the catalytic results. They correctly identify the Pd/**L1c** and Pd/**L6c** catalytic systems as more enantioselective than Pd/**L1b**. Similarly, in the reaction of both substrates with ligands **L1b** and **L1c**, the energy difference between the TSs with **L1b** is lower than with **L1c**, which agrees with the higher enantioselectivities obtained with **L1c** (Table 1; for **S1**, 96% (*S*) ee for **L1c** vs. 86% (*S*) ee for **L1b** and for **S2**, 99% (*S*) ee for **L1c** vs. 78% (*R*) ee for **L1b**). With **S2** the calculations also correctly predict the formation of the opposite product enantiomers with **L1b** and **L1c**.

Table 6. Calculated energies for the most stable TSs using S1 and S2 and NH_3 as nucleophile.[a]

Structure	L1b	L1c	L6c
 $TS_{(R)}$ endo	16.6[b]	21	14.2
 $TS_{(S)}$ exo	5.4[b]	0	0
 $TS_{(S)}$ endo	5[c]	0	0
 $TS_{(R)}$ exo	4[c]	15.6	13.6

[a] Relative energies in kJ/mol. [b] Energies relative to that of $TS_{(R)}$ *exo*-**L1c**. [c] Energies relative to that of $TS_{(S)}$ *endo*-**L1c**.

Of all the TSs evaluated in reactions of **S1** and **S2** with ligands **L1b** and **L1c**, Figure 4 shows the two most stable for each substrate. The analysis of these structures allows us to explain the impact of the configuration of biaryl phosphite group on enantioselectivity. Interestingly, for both catalytic systems (Pd/**L1b**–**c**) with substrate **S1** the *endo* TSs are destabilized due to a steric repulsion between one of the phenyl substituents of the substrate and the oxazoline substituent. This repulsion is not observed with substrate **S2**. This unfavorable interaction is reflected in a larger dihedral angle ω (C^1-N-C^2-C^3) for *exo* TSs than in *endo* TSs of **S1**. In the *endo* TSs of **S1** the steric interaction pushes the oxazoline moiety away leading to a lower dihedral angle. These destabilized interactions explain why the same configuration of the alkylated product was achieved with both ligands.

In **S1**, it is also interesting to note that for Pd/**L1c** the *exo* $TS_{(S)}$ presents a CH/π interaction between one of the phenyl rings of the substrate and the biaryl phosphite moiety (see the non-covalent interaction (NCI) plots in Figure 5(b)) that further stabilize this TS. This increases the energy gap between the *endo* and *exo* TSs and could explain the preference for one of the pathways and, consequently, the higher enantiomeric excess achieved with Pd/**L1c** compared with Pd/**L1b**. In the Pd/**L1b** catalyst, there is also a CH/π interaction but in this case in the *endo* $TS_{(R)}$. Therefore the energy of the two TSs are more similar among them than for the Pd/**L1c** (see NCI plot in Figure 5(a)).

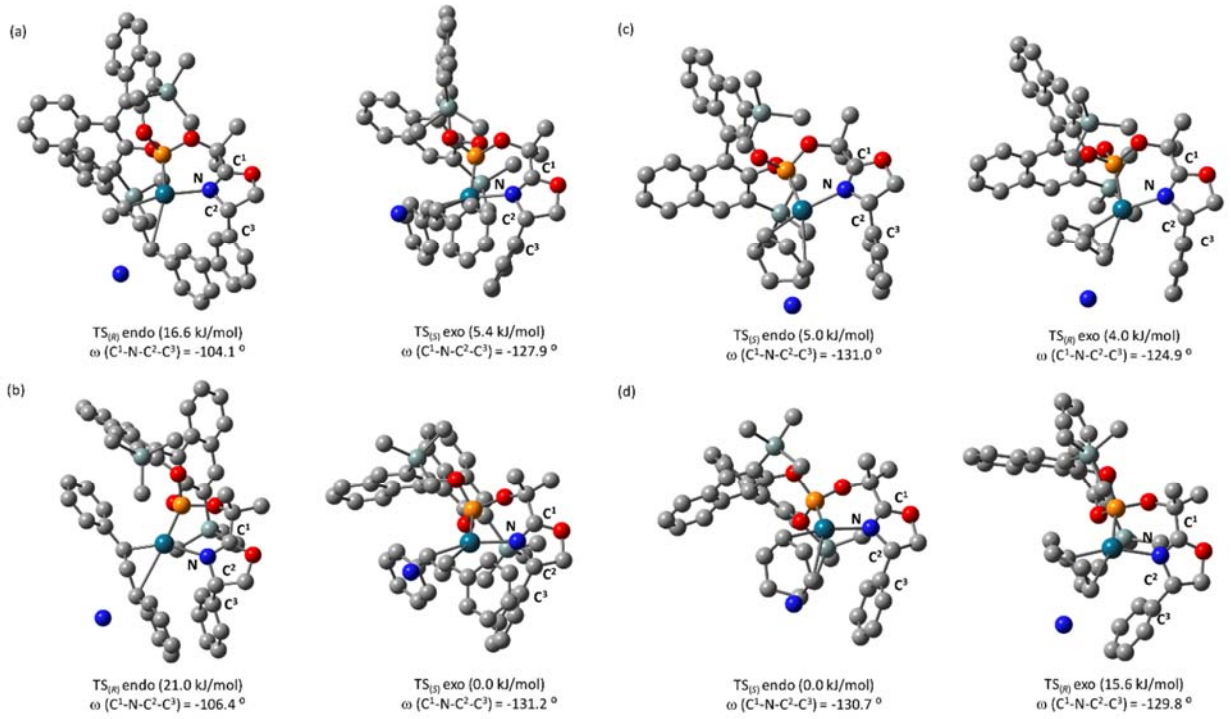


Figure 4. Most stable calculated TSs ($TS_{(R)}$ *endo* and $TS_{(S)}$ *exo*) from **S1** using ligands (a) **L1b** and (b) **L1c**; and from **S2** using ligands (c) **L1b** and (d) **L1c**. All hydrogens atoms have been omitted for clarity. Relative free energies in solution and in kJ/mol respect to the corresponding lowest energy transition state.

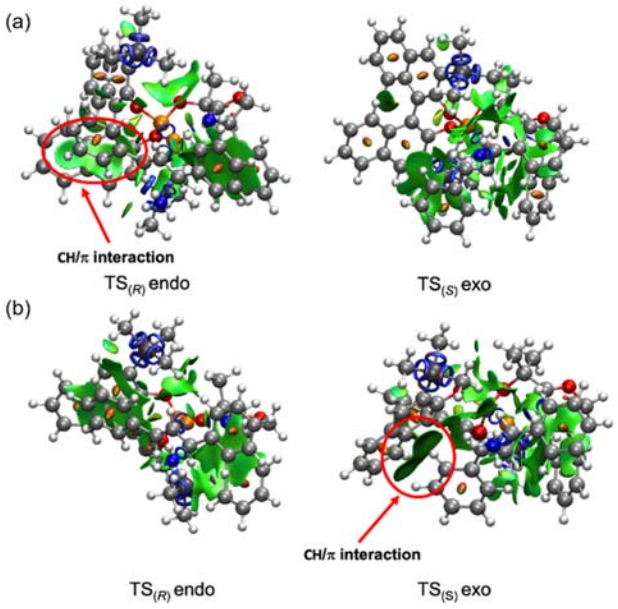


Figure 5. NCI plots of the most stable calculated TSs ($TS_{(R)}$ *endo* and $TS_{(S)}$ *exo*) from **S1** using ligands (a) **L1b** and (b) **L1c**. Strong and attractive interactions are blue, weak interactions are green and strong and repulsive interactions are red.

For substrate **S2** the NCI plots of the two most stable TSs of ligands **L1b** and **L1c** showed weak stabilizing attractive interactions between the substrate and one of the aryls of the biaryl phosphite moiety (Figure 6). However, while with ligand **L1b** with an *R*-biaryl phosphite moiety this favorable interaction is found in the *exo* $TS_{(R)}$ leading to the *R*-product, with ligand **L1c** (whose phosphite group has the opposite configuration) this is found in *endo* $TS_{(S)}$ responsible of the *S*-product. This explains the formation of opposite enantiomers when using both ligands. Moreover, these weak attractive interactions are larger in the *endo* $TS_{(S)}$ of ligand **L1c** than in *exo* $TS_{(R)}$ of ligand **L1b**, which agrees with the highest enantioselectivity obtained with ligand **L1c**.

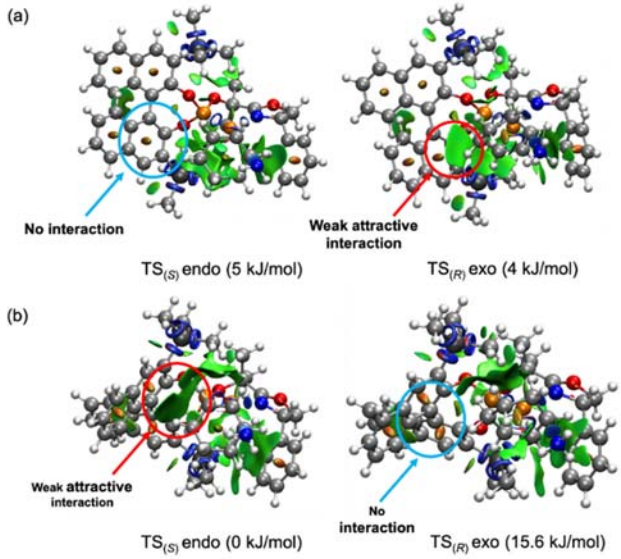
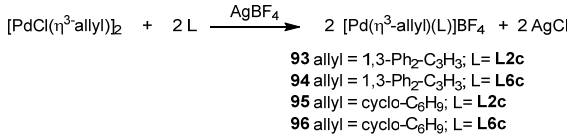


Figure 6. NCI plots of the most stable calculated TSs ($TS_{(R)}$ *endo* and $TS_{(S)}$ *exo*) from **S2** using ligands (a) **L1b** and (b) **L1c**. Strong and attractive interactions are blue, weak interactions are green and strong and repulsive interactions are red.

In summary, the DFT calculations showed that while for cyclic substrates the enantioselectivity is mainly controlled by the biaryl phosphite groups, for linear substrates the oxazoline substituent also has a crucial role.

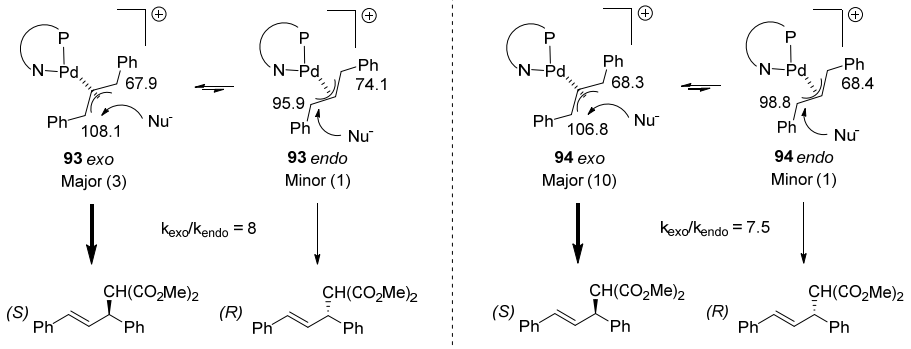
Preparation and NMR study of Pd-allyl intermediates. DFT calculations pointed out that enantiocontrol occurs during the nucleophilic attack through an early transition state. Consequently, the study of the Pd-allyl intermediates and their reactivity with the nucleophile will provide a further insight into how ligand parameters affect catalytic performance. For this purpose, we prepared the Pd-π-allyl compounds **93**–**96** $[Pd(\eta^3\text{-allyl})(L)]BF_4$ (L= **L2c** and **L6c**) containing 1,3-diphenyl or cyclohexenyl allyl groups (Scheme 2).[30] Ligands **L2c** and **L6c** were chosen to complete the study of the effect on the catalytic performance of different substituents in the alkyl backbone chain.[31]



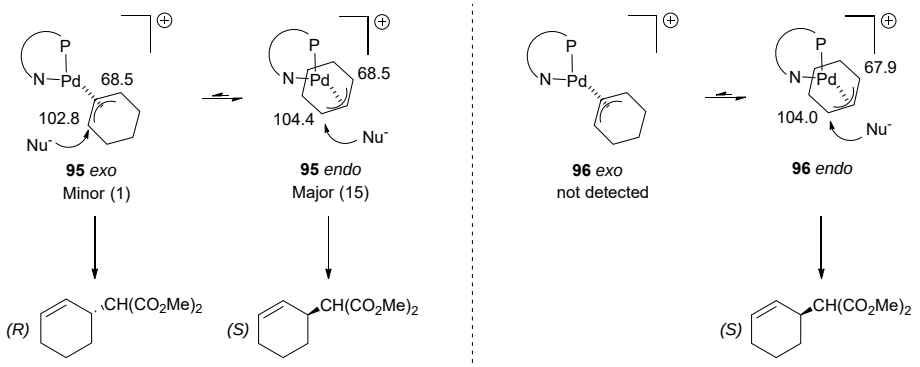
Scheme 2. Preparation of $[Pd(\eta^3\text{-allyl})(L)]BF_4$ complexes **93**–**96**.

The VT-NMR study (30 °C to -80 °C) of Pd-1,3-diphenyl allyl intermediates **93** and **94** showed a mixture of two isomers in equilibrium at 3:1 and 10:1 ratios respectively (Scheme 3). No changes in the signals have been observed during these VT-experiments, which agree with a fast equilibrium between both isomers even at low temperature. These isomers were assigned to be *syn*/*syn* according to the NOE interaction between the two terminal protons of the allyl group. The NOE interactions also confirmed an *exo* disposition for the major isomers and an *endo* for the minor isomers (see Supporting Information for NOE details). The carbon chemical shifts of compounds **93** and **94** indicated that the most electrophilic allylic terminal carbons are located *trans* to the phosphite moiety in the major isomers. Assuming that the nucleophilic attack takes place at the more electron deficient allylic carbon terminus and since the diastereomeric excesses differ from the enantiomeric excesses, the major isomers should react faster than the minor ones. If we take into account that the electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers **93** ($\Delta\delta(^{13}C) \approx$ 12.4 ppm) is higher than for **94** ($\Delta\delta(^{13}C) \approx$ 8 ppm), then the major isomer of **93** should react faster than the major isomer of **94**. However, the study of the reactivity of the Pd-1,3-diphenyl allyl intermediates **93** and **94** with sodium dimethyl malonate at low temperature by *in situ* NMR indicated that both isomers react at a similar rate: the major isomer of **93** reacts 8 times faster than the minor isomer while the relative reaction rate of **94** is of 7.5 times faster than the minor isomer (see Figure S20 in the Supporting Information). Since the speeds are similar, the higher enantioselectivity with Pd/**L6c** is explained by the much higher relative population of the faster reacting isomer in Pd/**L6c** catalytic system than that of Pd/**L2c**. This indicates that the ability of Pd/**L6c** to effectively control both the population and the relative electrophilicity in the Pd-allyl intermediates is crucial for achieving excellent enantiocontrol.

The VT-NMR study (30 °C to -80 °C) of the Pd-1,3-cyclohexenyl allyl intermediate **95** showed a mixture of two isomers in fast equilibrium in a 15:1 ratio, while for intermediate **96** only one isomer was detected (Scheme 4).



Scheme 3. Diastereoisomeric Pd-allyl intermediates for **S1** with ligands **L2c** (isomers **93**) and **L6c** (isomers **94**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

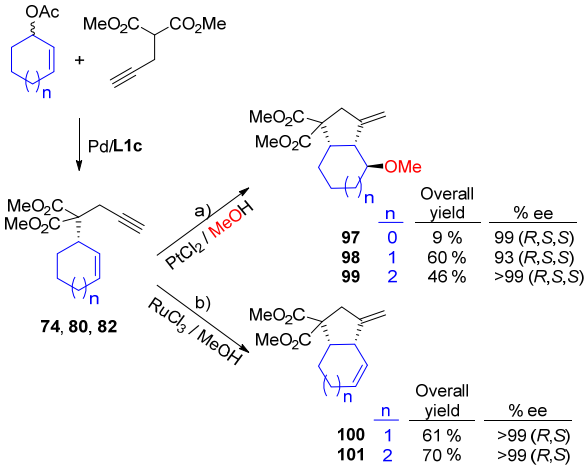


Scheme 4. Diastereoisomeric Pd-allyl intermediates for **S2** with ligands **L2c** (isomers **95**) and **L6c** (isomers **96**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

The major isomers of intermediates **92** and **93** were characterized by NOE as *endo* isomers (see Supporting Information for NOE details). The ^{13}C-NMR chemical shifts indicated again that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. For intermediate **95**, the fact that the electrophilicity of the allylic terminal carbon atom *trans* to the phosphite is rather similar in *endo* and *exo* isomers ($\Delta\delta(^{13}C) \approx 1.6$ ppm) suggests that both isomers react at a similar rate. Therefore, the study of the Pd-allyl intermediates confirms that changing the substituent in the alkyl backbone chain lead to changes in the ratio of the species that provide both enantiomers. The enantioselectivity is therefore mainly governed by the relative population of the *endo* and *exo* isomers. The higher enantioselectivity obtained using Pd/**L6c** can therefore be attributed to the fact that only the *endo* isomer is detected.

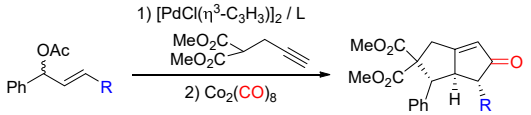
Synthetic applications of the allylic alkylated compounds. Preparation of chiral carbobicycles. In this section we show a further application of the propargylated compounds **28**, **69**, **74**, **80**, **82** and **92**, prepared in previous section by Pd-AAS, to produce a range of chiral carbobicycles (**97**-**104**) with multiple stereocentres. These carbobicycles have been synthesized by simple sequential reactions involving allylic substitution of the appropriate substrates followed by either 1,6-enyne cyclization (Scheme 5) or Pauson–Khand enyne cyclization (Scheme 6).

The first studied derivatization was a 1,6-enyne cyclization of the propargylated derivatives **74**, **80** and **82**, which differ only in the size of the cycloalkane ring (Scheme 5). By changing the catalyst source we were able to prepare two types of carbobicycles: $PtCl_2$/MeOH lead to bicycles with insertion of methanol into the double bond (Scheme 5a),[32] and $RuCl_3$/MeOH gave unsaturated bicycles maintaining the endocyclic double bond (Scheme 5b)[33]. With these strategies, the alkylated derivatives **74**, **80** and **82**, undergo the cyclization with no loss of enantioselectivity, providing carbobicycles **97**–**101** in good yields, except for the most sterically constrained compound **97**, and excellent-to-high enantioselectivities (Scheme 5).



Scheme 5. Preparation of chiral carbobicycles compounds **97**–**101.**

The second derivatization consisted of a Pauson-Khand reaction of three linear alkylated derivatives **28**, **69** and **92**, which differ in the substituents of the allylic substrate (Scheme 6). In the three cases the corresponding bicyclopentenones **102**–**104** were obtained in good yields and with no loss in enantiomeric excess. This derivatization was not affected by the substituents of the substrate (**102**–**104**).



	R	L	Overall yield	% ee
102	Ph	**L6c**	62 %	99 (*R*,*R*,*S*)
103	CF_3	**L6c**	39 %	73 (*R*,*R*,*R*)
104	H	**L7c**	41 %	89 (*R*,*S*)

Scheme 6. Preparation of chiral bicyclopentenone compounds **102**–**104**.

CONCLUSIONS

We report a new generation of air stable and readily available Pd/phosphite-oxazoline catalysts for the Pd-AAS of a broad range of linear substrates (including unsymmetrical di- and monosubsti-

tuted) and cyclic substrates with different electronic and steric properties, using many C-, N- and O- nucleophiles. A total of 73 combinations of substrate-nucleophile have been studied. These catalysts derive from the successful Pd/phosphite-oxazoline PHOX catalysts **2** by replacing the *ortho*-phenylene tether by an alkyl backbone chain. With this simple modification, we have increased the number of ligand parameters than can be modified to maximize the catalyst performance for a major number of substrates and nucleophiles. We have been able to identify three ligands with high performance for a broad range of linear disubstituted substrates (ligand **L6c**) and monosubstituted substrates (ligand **L7c**) and cyclic substrates (ligand **L1c**), with many nucleophiles (73 compounds in total). The three ligands have in common a chiral biaryl phosphite moiety with an *S*-configuration, the same substituent and configuration at the oxazoline moiety but differ on the substituent in the alkyl backbone chain; while **L6c** has a methyl, **L7c** has isopropyl and **L1c** has two methyl groups. In comparison with Pd/**2** the new Pd-catalysts provided a better activity and a wider substrate and nucleophile scope.

Mechanistic studies based on DFT calculations and NMR spectroscopy let us identify the species responsible for the catalytic performance and the impact of the ligand parameters on the origin of enantioselectivity. Thus, these studies confirm that changing the ligand parameters lead to changes in the ratio of the species that provide both enantiomers. The enantioselectivity is therefore mainly governed by the relative population of the *endo* and *exo* isomers. However, while the ratios of *endo* and *exo* isomers for cyclic substrates is mainly controlled by the configuration of the biaryl phosphite group and the substituent in the alkyl backbone chain, for linear substrates the oxazoline substituent also has a crucial role.

Finally, to evaluate the potential impact of this new generation of Pd-catalysts in synthesis, some alkylated products have been applied in subsequent sequential derivatizations, such as Pauson-Khand or 1,6-enyne cyclizations, to produce a range of chiral carbobicycles with multiple stereocentres with faithful transmission of the chirality.

EXPERIMENTAL SECTION

General considerations. All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded using a Varian Mercury-400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and $^{13}C\{^{1}H\}$) or H_3PO_4 ($^{31}P\{^{1}H\}$) as internal standard. Racemic substrates **S1**–**S12**[34] and **S13**–**S18**[35] were prepared as previously described. Compounds **4**,[9] **8**–**13**[7,11] and **14**–**19**[7,11], phosphorochloridite[36] and ligands **L1a**[8a] and **L2**–**L7a**–**c**[7] were synthesized following already reported procedures.

Computational details. The geometries of all intermediates were optimized using the Gaussian 09 program,[37] employing the B3LYP-D3[38] density functional and the LANL2DZ[39] basis set for palladium and the 6-31G* basis set for all other elements.[40] Solvation correction was applied in the course of the optimizations using the PCM model with the default parameters for dichloromethane.[41] The complexes were treated with charge +1 and in the singlet state. No symmetry constraints were applied. The energies were further refined by performing single point calculations using the above-mentioned parameters, with the exception that the 6-311+G**[42] basis set was used for all elements except palladium for which SDD basis set was employed. All energies reported are Gibbs free energies at 298.15 K and calculated as $G_{reported} = G_{6\text{-}31G^*} + (E_{6\text{-}311+G^{**}} - E_{6\text{-}31G^*})$.

We used the NCI method[43] to study the non-covalent interactions. The method is capable of mapping real-space regions where non-covalent interactions are important and is based exclusively on the electron density and its gradient. The information provided by NCI plots is essentially qualitative. To perform these calculations, we used promolecular approximation using xyz files.

Typical procedure for the preparation of phosphite-oxazoline ligands. To a solution of in situ generated phosphochloridite (1.1 mmol) in dry toluene (6 mL), pyridine (0.16 mL, 2.0 mmol) was added. Then, this solution was placed in a -78 ºC bath. After 2 min at that temperature, a solution of the alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C. The mixture was left to warm to room temperature and stirred overnight at this temperature. The precipitate formed was filtered under argon and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (under argon, using neutral alumina and dry toluene as eluent system) to afford the corresponding phosphite-oxazoline **L1**–**L7a**–**c** as white solids.

L1b: Yield: 398.3 mg (60%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 153.9 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.52 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.57 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.76 (pt, 1H, CH-O, $J_{H\text{-}H}$= 8.4 Hz), 4.07 (dd, 1H, CH-O, $^{2}J_{H\text{-}H}$= 10.0 Hz; $^{3}J_{H\text{-}H}$= 8.4 Hz), 4.92 (dd, 1H, CH-N, $^{2}J_{H\text{-}H}$= 10.0 Hz, $^{3}J_{H\text{-}H}$= 8.4 Hz), 6.82 (m, 2H, CH=), 6.96-7.13 (m, 7H, CH=), 7.26 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.4 Hz), 7.27 (d, 1H, CH=, $^{3}J_{H\text{-}H}$= 8.4 Hz), 7.66 (m, 2H, CH=), 8.09 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ = -0.3 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$= 4.5 Hz), 0.4 (CH_3, $SiMe_3$), 28.2 (d, CH_3, $^{3}J_{C\text{-}P}$= 3.8 Hz), 28.7 (d, CH_3, $^{3}J_{C\text{-}P}$= 7.7 Hz), 69.8 (CH-N), 74.9 (CH_2-O), 76.2 (d, C, CMe_2, $^{3}J_{C\text{-}P}$= 5.3 Hz), 122.6-152.4 (aromatic carbons), 169.1 (C=N). TOF-MS (ESI+): m/z = 686.2285, calcd. for $C_{38}H_{42}NNaO_4PSi_2$ $[M+Na]^+$: 686.2282.

L1c: Yield: 331.9 mg (50%); ^{31}P NMR (161.9 MHz, C_6D_6): δ = 153.6 (s); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.53 (s, 9H, CH_3, $SiMe_3$), 0.59 (s, 9H, CH_3, $SiMe_3$), 1.62 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.55 (pt, 1H, CH-O, $J_{H\text{-}H}$ = 8.0 Hz), 4.06 (dd, 1H, CH-O, $^{2}J_{H\text{-}H}$= 10.8 Hz, $^{3}J_{H\text{-}H}$= 8.8 Hz), 4.92 (dd, 1H, CH-N, $^{2}J_{H\text{-}H}$= 10.0 Hz, $^{3}J_{H\text{-}H}$= 8.0 Hz), 6.81 (m, 2H, CH=), 6.95-7.11 (m, 7H, CH=), 7.26 (m, 2H, CH=), 7.67 (m, 2H, CH=), 8.11 (s, 1H, CH=), 8.15 (s, 1H, CH=). ^{13}C (100.6 MHz, C_6D_6): δ = -0.3 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$= 4.6 Hz), 0.4 (CH_3, $SiMe_3$), 28.0 (d, CH_3, $^{3}J_{C\text{-}P}$= 3.9 Hz), 28.7 (d, CH_3, $^{3}J_{C\text{-}P}$= 6.9 Hz), 69.5 (CH-N), 74.8 (CH_2-O), 75.9 (d, C, CMe_2, $^{3}J_{C\text{-}P}$= 5.3 Hz), 122.5-152.4 (aromatic carbons), 169.0 (C=N). TOF-MS (ESI+): m/z = 686.2280, calcd. for $C_{38}H_{42}NNaO_4PSi_2$ $[M+Na]^+$: 686.2282.

General procedure for the preparation of [Pd(η³-allyl)(P-N)]BF_4 complexes 93–96. The corresponding ligand (0.05 mmol) and the complex $[Pd(\mu\text{-}Cl)(\eta^3\text{-}1,3\text{-}allyl)]_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite

under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale yellow solids by adding hexane.

[Pd(η³-1,3-diphenylallyl)(L2c)]BF₄ (93): Major isomer (75%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 139.5 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.30 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 4.38 (m, 1H, CH_2), 4.47 (m, 1H, CH= *trans* to N), 5.01 (m, 2H, CH_2, CH-N), 5.96 (m, 1H, CH_c=), 6.15 (m, 2H, CH-O, CH= *trans* to P), 7.10-8.21 (m, 30H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.6 (CH_3, $SiMe_3$), 67.7 (CH-N), 67.9 (d, CH= *trans* to N, $J_{C\text{-}P}$= 10.7 Hz), 76.3 (CH-OP), 78.0 (CH_2), 108.1 (d, CH= *trans* to P, $J_{C\text{-}P}$= 29.8 Hz), 112.6 (d, CH_c=, $J_{C\text{-}P}$= 9.9 Hz), 120.0-150.0 (aromatic carbons), 169.5 (C=N). Minor isomer (25%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 140.2 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.20 (s, 9H, CH_3, $SiMe_3$), 0.39 (s, 9H, CH_3, $SiMe_3$), 4.35 (m, 1H, CH_2), 4.74 (m, 1H, CH-N), 5.01 (m, 1H, CH_2), 5.23 (m, 1H, CH= *trans* to N), 5.27 (m, 1H, CH= *trans* to P), 5.60 (m, 1H, CH_c=), 6.15 (m, 1H, CH-OP), 7.1-8.2 (m, 25H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.5 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), 68.9 (CH-N), 74.1 (d, CH= *trans* to N, $J_{C\text{-}P}$= 10.7 Hz), 75.9 (CH-OP), 77.6 (CH_2), 95.9 (d, CH= *trans* to P, $J_{C\text{-}P}$= 42 Hz), 109.2 (d, CH_c=, $J_{C\text{-}P}$= 13.0 Hz), 120.0-150.0 (aromatic carbons), 170.2 (C=N).

[Pd(η³-1,3-diphenylallyl)(L6c)]BF₄ (94): Major isomer (91%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 140.3 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.46 (s, 9H, CH_3, $SiMe_3$), 0.74 (s, 9H, CH_3, $SiMe_3$), 1.96 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 4.33 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 8.8 Hz, $^3J_{H\text{-}H}$= 4.8 Hz), 4.51 (m, 1H, CH= *trans* to N), 4.88 (m, 1H, CH-N), 5.00 (m, 1H, CH_2), 5.12 (m, 1H, CH-OP), 6.02 (m, 2H, CH_c=, CH= *trans* to P), 6.3-8.4 (m, 25H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.8 (CH_3, $SiMe_3$), 22.6 (b, CH_3), 67.3 (CH-N), 68.3 (d, CH= *trans* to N, $J_{C\text{-}P}$= 9.9 Hz), 71.5 (CH-OP), 78.2 (CH_2), 106.8 (d, CH= *trans* to P, $J_{C\text{-}P}$= 30.4 Hz), 112.2 (d, CH_c=, $J_{C\text{-}P}$= 9.8 Hz), 121.0-150.0 (aromatic carbons), 172.1 (C=N). Minor isomer (9%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 142.9 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.41 (s, 9H, CH_3, $SiMe_3$), 0.62 (s, 9H, CH_3, $SiMe_3$), 1.75 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 4.39 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 8.8 Hz, $^3J_{H\text{-}H}$= 4.4 Hz), 4.53 (m, 1H, CH= *trans* to N), 4.71 (m, 1H, CH_2), 4.88 (m, 1H, CH-N), 5.12 (m, 1H, CH-OP), 5.98 (m, 1H, CH= *trans* to P), 6.09 (m, 1H, CH_c=), 6.3-8.4 (m, 25H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= 0.1 (CH_3, $SiMe_3$), 0.3 (CH_3, $SiMe_3$), 22.4 (b, CH_3), 68.1 (CH-N), 68.4 (d, CH= *trans* to N, $J_{C\text{-}P}$= 9.2 Hz), 70.9 (CH-OP), 78.0 (CH_2), 98.8 (d, CH= *trans* to P, $J_{C\text{-}P}$= 32.4 Hz), 112.7 (d, CH_c=, $J_{C\text{-}P}$= 9.2 Hz), 121.0-150.0 (aromatic carbons), 172.3 (C=N).

[Pd(η³-1,3-cyclohexenyl)(L2c)]BF₄ (95): Major isomer (95%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 143.3 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.03 (s, 9H, CH_3, $SiMe_3$), 0.10 (m, 1H, CH_2), 0.61 (s, 9H, CH_3, $SiMe_3$), 0.81 (m, 1H, CH_2), 1.0-1.3 (m, 4H, CH_2), 4.05 (b, 1H, CH= *trans* to N), 4.53 (m, 1H, CH_2), 5.18 (m, 1H, CH_2), 5.33 (m, 1H, CH_c=), 5.95 (m, 1H, CH-N), 6.09 (m, 1H, CH= *trans* to P) 6.36 (d, 1H, CH-OP, $J_{C\text{-}P}$= 26.0 Hz), 7.10 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz) , 7.11-7.30 (m, 2H, CH=), 7.42-7.60 (m, 14H, CH=), 8.02 (d, 2H, CH=, $^3J_{H\text{-}H}$= 8.4 Hz), 8.24 (s, 1H, CH=). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.4 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 19.9 (CH_2), 27.0 (b, CH_2), 68.5 (d, CH= *trans* to N, $J_{C\text{-}P}$= 9.1 Hz), 74.5 (CH-OP), 76.4 (CH-N), 78.2 (CH_2), 104.4 (d, CH= *trans* to P, $J_{C\text{-}P}$= 39.5 Hz), 111.6 (d, CHc=, $J_{C\text{-}P}$= 10.7 Hz), 122.7-151.0 (aromatic carbons), 169.4 (C=N). Minor isomer (5%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 139.5 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.08 (s, 9H, CH_3, $SiMe_3$), 0.10 (m, 1H, CH_2), 0.61 (s, 9H, CH_3, $SiMe_3$), 0.81 (m, 1H, CH_2), 1.0-1.3 (m, 4H, CH_2), 3.94 (b, 1H, CH= *trans* to N), 4.53 (m, 1H, CH_2), 5.21 (m, 2H, CH_2, CH_c=), 5.95 (m, 2H, CH= *trans* to P, CH-N), 6.34 (d, 1H, CH-OP, $J_{C\text{-}P}$= 21.0 Hz), 7.0-8.2 (m, 20H, CH=).

[Pd(η³-1,3-cyclohexenyl)(L6c)]BF₄ (96): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 143.7 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ= 0.11 (m, 1H, CH_2), 0.47 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 0.68 (m, 1H, CH_2), 1.0-1.3 (m, 4H, CH_2), 1.89 (d, 1H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 4.04 (b, 1H, CH= *trans* to N), 4.51 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 9.2 Hz, $^3J_{H\text{-}H}$= 8 Hz), 5.15 (dd, 1H, CH_2, $^2J_{H\text{-}H}$= 9.2 Hz, $^3J_{H\text{-}H}$= 10.8 Hz), 5.33 (m, 1H, CHc=), 5.36 (q, 1H, CH, $^3J_{H\text{-}H}$= 6.8 Hz), 5.71 (dd, 1H, CH-N, $^3J_{H\text{-}H}$= 8.0 Hz, $^3J_{H\text{-}H}$= 10.8 Hz), 5.95 (m, 1H, CH= *trans* to P), 6.99 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz), 7.12 (d, 1H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz), 7.28 (m, 2H, CH=), 7.41-7.50 (m, 7H, CH=), 8.02 (t, 1H, CH=, $^3J_{H\text{-}H}$= 8.8 Hz), 8.23 (d, 1H, CH=, $^3J_{H\text{-}H}$= 7.2 Hz). ^{13}C (100.6 MHz, CD_2Cl_2): δ= -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 19.5 (CH_2), 22.9 (d, CH_3, $J_{C\text{-}P}$= 4.5 Hz), 27.1 (b, CH_2), 67.9 (d, CH= *trans* to N, $J_{C\text{-}P}$= 9.2 Hz), 71.6 (CH-OP), 74.3 (CH-N), 78.2 (CH_2), 104.0 (d, CH= *trans* to P, $J_{C\text{-}P}$= 40 Hz), 111.7 (d, CHc=, $J_{C\text{-}P}$= 10.7 Hz), 121.0-151.0 (aromatic carbons), 171.8 (C=N).

Typical procedure for the allylic alkylation of linear (S1, S3–S9, S12–S18) and cyclic (S2, S10 and S11) substrates. A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL), nucleophile (3 mmol), *N,O*-bis(trimethylsilyl)-acetamide (3 mmol) and KOAc (3 mg, 0.03 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **20**, **22**–**35**, **55**–**61**, **64**–**69**, **72**–**73** and **82**–**92**, the solvent was removed, conversions were measured by ^{1}H NMR and enantiomeric excesses were determined by HPLC. For compounds **21**, **63**, **70**–**71**, **74**–**75** and **80**–**81**, conversion and enantiomeric excesses were determined by GC.[5g] For compounds **62** and **79**, conversion was measured by ^{1}H NMR and ees were determined by ^{1}H NMR using $[Eu(hfc)_3]$. See Supporting Information for characterization and enantiomeric excess determination details.

Typical procedure for the allylic amination of S1 and S2. A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. After this time, a solution of substrate (1 mmol) in dichloromethane (1.5 mL) and the corresponding amine (3 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^{1}H NMR. HPLC was used to determine enantiomeric excesses of compounds **36**–**47** and **76**–**78**. See Supporting Information for characterization and enantiomeric excess determination details.

Typical procedure for the allylic etherification and silylation of S1. A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the desired phosphite-oxazoline ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 min, Cs_2CO_3 (122 mg, 0.375 mmol) and the corresponding alkyl alcohol or silanol (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^1H NMR. HPLC was used to determine enantiomeric excesses of substrates **48**–**54**. See Supporting Information for characterization and enantiomeric excess determination details.

Typical procedure for the preparation of carbobicycles 97–101. A mixture of the enyne (1 mmol) and $PdCl_2$ or $RuCl_3$ (0.05 mmol) in MeOH (5 mL) was heated at reflux for 24 h. Then, the solution was cooled down to room temperature, the solvent was evaporated and the residue was purified by column chromatography (hexane: EtOAc mixtures) to give the desired carbobicycle. See Supporting Information for characterization and enantiomeric excess determination details.

Typical procedure for the preparation of bicyclopentenones 102–104. Under an atmosphere of argon a solution of the enyne (1.0 mmol.) and $Co_2(CO)_8$ (359 mg, 1.05 mmol) in dry CH_2Cl_2 (0.06 M) was stirred at room temperature until TLC monitoring indicated full conversion. Then $Me_3NO{\cdot}2H_2O$ (3–10 mmol) was added in one portion. Stirring was continued until TLC monitoring showed complete consumption of the cobalt-alkyne complex. The solvent was then removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate) to give the desired bicyclopentenone. See Supporting Information for characterization and enantiomeric excess determination details.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Copies of NMR spectra of the new ligands **L1b**–**c** and Pd-allyl intermediates **93**–**96**. Reactivity studies of Pd-intermediates. NMR and ee determination details of substitution products and chiral functionalized bicyclic compounds.

Calculated energies and coordinates for all computational structures.

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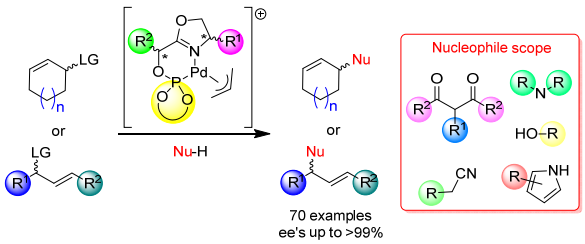
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