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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 the alkyl backbone chain and the oxazoline 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 many hindered and unhindered substrates with a wide range of C-, O- and N-nucleophiles (73 substitution products in total). Moreover, DFT and NMR studies of the key Pd-allyl complexes allowed us to better understand the origin of the excellent enantioselectivities observed experimentally. The synthetic application of the Pd/phosphite-oxazoline catalysts was demonstrated by the synthesis of many 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, asymmetric allylic substitution, DFT calculations, NMR study, mixed P,N-ligands.*

INTRODUCTION

Many pharmaceutical, fragrance and crop protection industries depend on chiral compounds. The finding of synthetic methods for their preparation is a recurrent research in chemistry[1] and the Pd-catalyzed asymmetric allylic substitution (AAS) has been proved to be one of the most powerful approaches. AAS works with mild reaction conditions and has a high functional group tolerance. Moreover the substitution products can be further derivatized due to the presence of the alkene group.[1,2] Given its advantages, it is understandable the constant aim to increase the substrate and nucleophile scope to reach compounds with more complexity. Its main limitation is still enantioselectivity is extremely affected by 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 many type 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 backbone, the right combination of ligand parameters provides ligands that are appropriated for both linear and cyclic substrates using dimethylmalonate as nucleophile.[3] The study of Pd-intermediates showed that the flexibility of the phosphite functionalities enables the chiral pocket of the catalyst to fit substrates with different steric hindrance. In addition, the π-acceptor capacity of the phosphite moiety has a positive influence on activities, providing higher TOF than the most common ligands.[2i,3,4] Encouraged by the high enantioselectivities achieved with heterodonor-based ligands in AAS we then started the development of heterodonor ligands with a biaryl phosphite moiety.[5] In this respect, we decided to change the phosphine group in privileged phosphine-oxazoline PHOX ligands **1**[2e,6] by a biaryl phosphite group (Figure 1, ligands **2**).[5a] Whereas Pd-**1** catalysts gave outstanding enantioselectivities with *rac*-(*E*)-1,3-diaryl-2propenyl substrates, moderate-to-good enantioselectivities with 1,3-dialkyl-2-propenyl substrates and racemic results for cyclic substrates,[2e] the Pd-phosphite-oxazoline counterparts **2** were very successful in all of them.[5a,7] Pd/**2** emerged as an unprecedented catalyst able to make C−C and C-X bonds with high enantiocontrol for several hindered and unhindered substrates using many C-, O-, and N-nucleophiles. In addition, the improvement in activity achieved with diphosphite ligands was maintained. Mechanistic studies established that the large substrate scope of Pd/**2** system is because the ligand is able to adapt the size of chiral pocket to the steric demands of the substrates.[7] This adaptability of the ligand also explains the excellent results achieved in other catalytic reactions.[8]

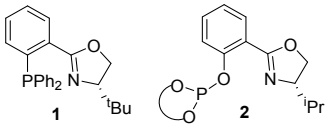


Figure 1. PHOX-based ligand **1** and the related phosphite-oxazoline ligands **2**.

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 influence of a new stereogenic center in the alkyl backbone chain and the influence 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 (including unsymmetrical 1,3-disubstituted and monosubstituted substrates) and cyclic substrates with many C-, O- and N-nucleophiles (73 substitution products in total). We also used DFT and NMR studies of the key Pd-allyl complexes to explain the enantioselectivities obtained experimentally. 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.

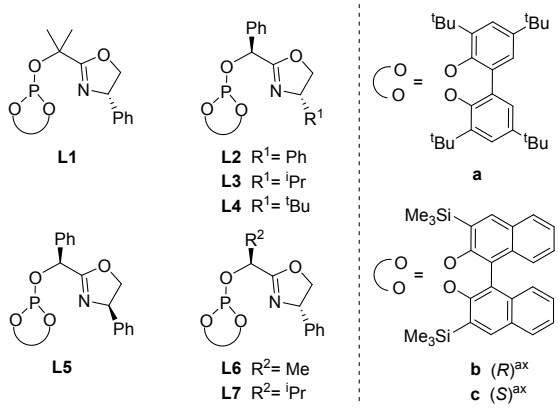
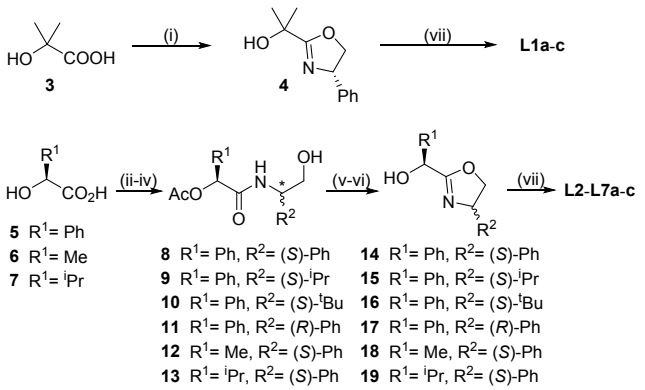


Figure 2. Phosphite-oxazoline compounds **L1**–**L7a**–**c**.

RESULTS AND DISCUSSION

Synthesis of ligands. Phosphite-oxazoline compounds **L1**–**L7a**–**c** were synthesized through a two or five step process, starting from commercial feedstocks (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 appropriated 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 compounds **L2**–**L7a**–**c**.

Advantageously, compounds **L1**–**L7a**–**c** were isolated as white air-stable solids that were used and kept in air. HRMS-ESI and ^1H, ^{13}C and ^{31}P NMR spectroscopy confirmed the formation of the ligands (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 ºC to rt for 3 h;[11,12] (vi) NaOH (aq), EtOH, 0 ºC, 3 h;[11,12] (vii) $ClP(OR)_2$; $(OR)_2$ = a–c, Py, toluene, 16 h.

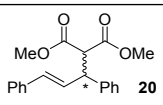
Allylic alkylation of disubstituted substrates S1–S2 using dimethyl malonate. The effectiveness of the phosphite-oxazoline compounds **L1**–**L7a**–**c** was first studied in the Pd-AAA of two benchmark substrates with different steric constrains, *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** and *rac*-3-acetoxycyclohexene **S2**. For comparison, we use the same optimal reaction conditions established in our previous study with related Pd/PHOX-based phosphite-oxazoline catalysts **2**.[5a] The reactions were therefore done at 23 °C with 0.5 mol% of catalyst and using dimethyl malonate. It should be noted, that for cyclic **S2** is more challenging to control the selectivity than for **S1** due to the presence of less bulky anti substituents. However, by judiciously choosing the ligand parameters we have been able to find 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 influenced by the substituents at both the alkyl backbone chain and at the oxazoline as well as by the biaryl phosphite groups. However, their influence on enantioselectivity is different for both substrates. While for substrate **S1** the best enantioselectivity was achieved with **L6c** (ee's up to 99%), for substrate **S2** ligand **L1c** provided the highest selectivity (ee's up to 99%).

The results with ligands **L1a**–**c**, with an achiral alkyl backbone chain (entries 1-3), showed that the ligand skeleton can only control the tropoisomerization of the biphenyl phosphite moiety (**a**) for substrate **S1**. While high enantioselectivities are attained with **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. Different from PHOX ligands **1**, bulky substituents at the oxazoline negatively affected 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 AAA of substrates S1 and S2 with ligands L1–L7a–c [a]



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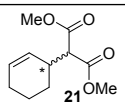

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Entry	L	% Conv[b]	%ee[c]	% Conv[d]	%ee[e]
1	**L1a**	100	96 (*S*)	100	60 (*S*)
2	**L1b**	100	86 (*S*)	100	78 (*R*)
3	**L1c**	100	96 (*S*)	100	99 (*S*)
4	**L2a**	100	93 (*S*)	100	40 (*S*)
5	**L2b**	100	40 (*S*)	100	74 (*R*)
6	**L2c**	100	90 (*S*)	100	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), BSA (3 equiv), dimethyl malonate (3 equiv), KOAc (3 mol%), CH_2Cl_2 (2 mL) 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 calculated by GC after 30 min. [e] Enantiomeric excesses calculated by GC. Absolute configuration drawn in parentheses. [f] Reactions performed with 0.1 mol% of catalyst precursor for 5 min.

The results comparing the use of diasteriomeric ligands **L2b–c** and **L5b–c** indicated the presence of a cooperative effect between the configurations of both, the biaryl phosphite group and the oxazoline substituent. The right combination of configurations occurred in ligands **L2c** and **L5b** (entries 6 and 10). In addition, while the configuration of the oxazoline substituent controls the sense of enantioselectivity for linear substrate **S1** (ligands **L2** provide the opposite enantiomer of alkylated products than ligands **L5**; entries 4–6 vs 9–11), it is the configuration of the biaryl phosphite who controls the sense of enantioselectivity for the cyclic substrate **S2** (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 influence of the substituent at the alkyl chain was examined using compounds **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** that have recently become one of the most effective catalysts for Pd-AAS, with the added advantage that the activity with Pd/**L1c** and Pd/**L6c** is much higher[13].

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

Initially, the nucleophile scope for the Pd-AAS of **S1** was examined with ligand **L6c** that gave the best ees in the AAA of **S1** using dimethyl malonate. The results showed that many C-, N- and O-nucleophiles could be efficiently used for this transformation (Figure 3).

In this respect, a broad range of malonates, containing allyl-, butenyl, pentenyl- and propargyl- groups, alkylated **S1** to give compounds **22**–**28** in excellent yields and enantioselectivities (ee's ≥99%). These results are relevant since 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**) produced two diastereoisomers,[15] albeit both diastereoisomers were obtained almost enantiopure (ee's up to 99%).

The nucleophile scope was expanded 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 -20 °C to attain high enantioselectivities[17a]. The difficulty of using pyrroles as C-nucleophiles is also manifested by the fact that two of the most successful ligands for Pd allylic alkylation (PHOX **1** and Trost diphosphine) did not perform well using pyrroles.[17a] By improving the Pd/**2** catalysts, we were pleased to see that we could reach for substituted pyrroles high ee's (up to 99%) and yields working at 23 °C.

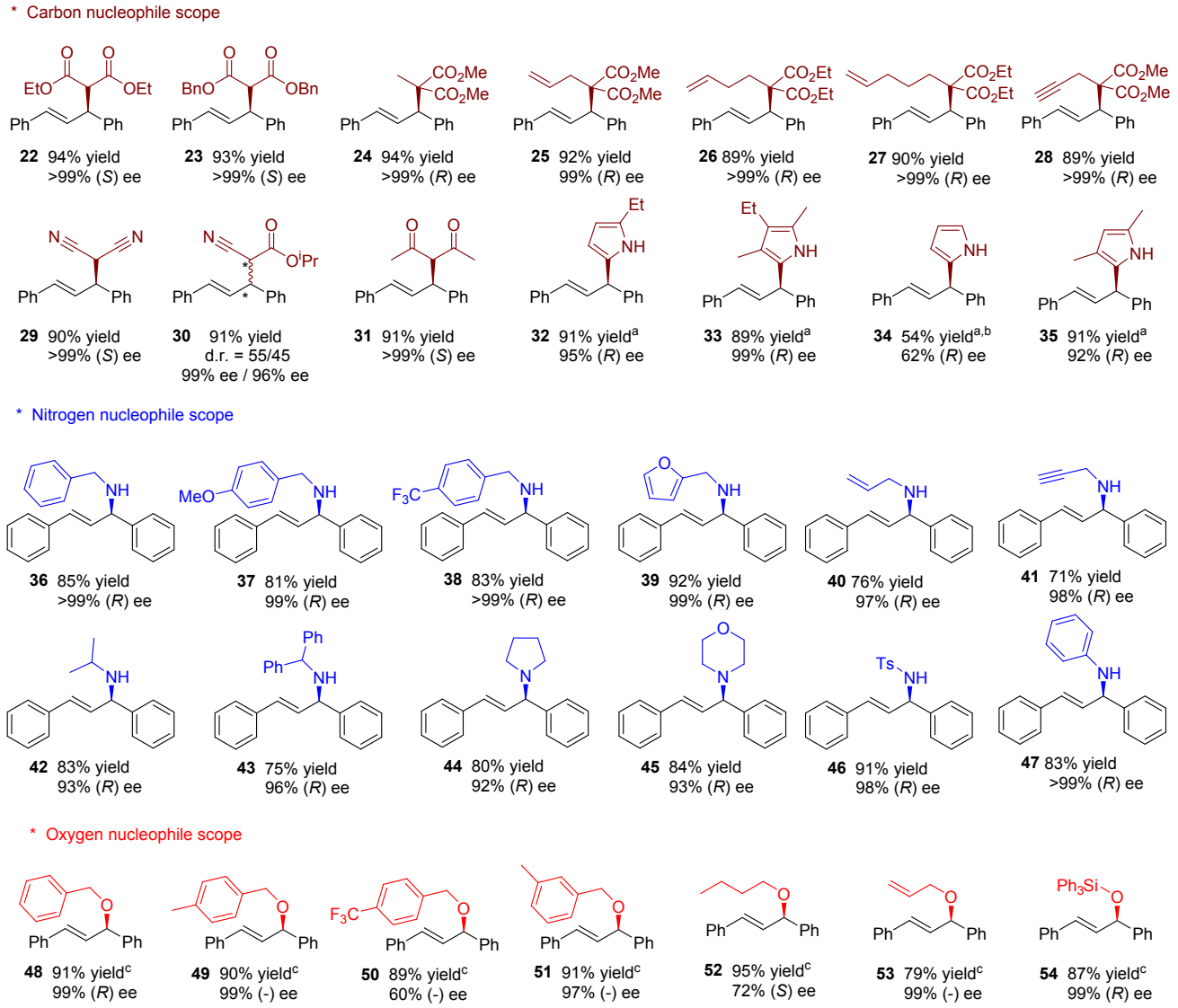


Figure 3. Allylic substitution of **S1** with other several C-, N- and O-nucleophiles with Pd/**L6c** catalytic system. Reaction conditions: 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, **L6c** (0.011 mmol), **S1** (1 mmol), BSA (3 equiv), nucleophile (3 equiv), KOAc (3 mol%), CH_2Cl_2 (2 mL) at 23 °C. Full conversions were attained in 2 h. [a] Reactions carried out using K_2CO_3 (3 equiv). [b] Reaction performed at -20 °C for 48 h. [c] Reactions performed with 2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, 4 mol% ligand, and Cs_2CO_3 (3 equiv). Full conversions were attained after 18 h.

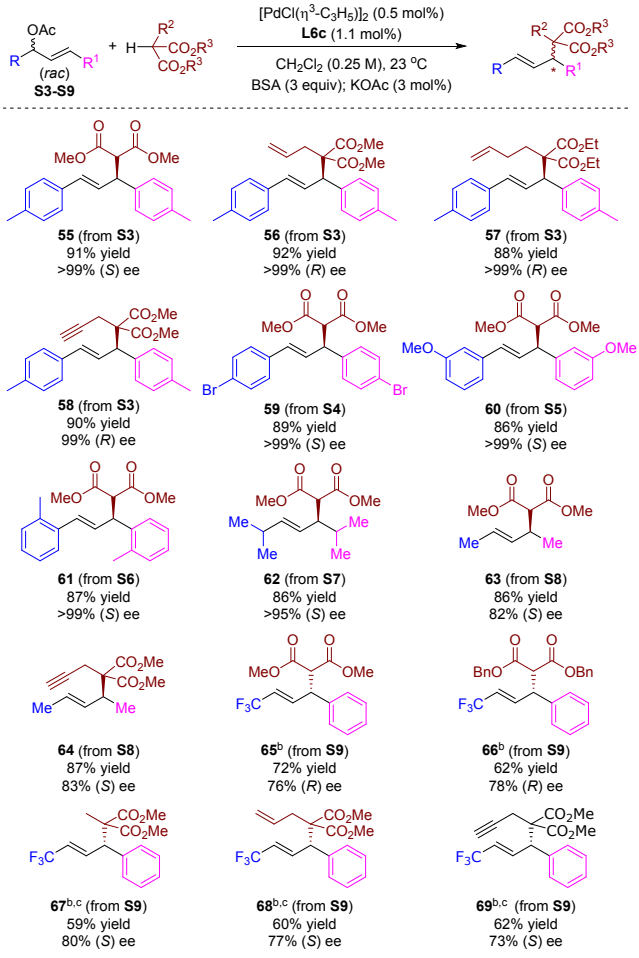
The reaction also performed well when using amines as nucleophiles. High yields and enantioselectivities in products **36**–**47**, comparable to those achieved with C-nucleophiles, were obtained with many primary and secondary amines (aryl-, alkyl-, allyl- and propargyl-substituted amines). Among them, several benzylic amines, including furfurylamine, afforded the substitution products **36**–**39** in excellent enantioselectivities (>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 when using sulfonamide and aromatic amines (compounds **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 attained 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 examined, there are few effective examples reported.[19] In addition, the type of aliphatic alcohol highly influences the enantioselectivity, whose value largely depends on the electronic characteristics of the alcohol. In this context, for previous Pd/phosphite-oxazoline PHOX systems **2** the highest enantioselectivity was only obtained when the benzylic alcohol had a *para*-CF_3 substituent (ee's up to 97%), and the selectivity decreased with electron-rich *para* substitutents.[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 provided lower enantioselectivity.

Similarly, the use of butanol gave the corresponding product **52** in 72% ee. Enantioselectivities up to 99% ee were also attained 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) that have different electronic and steric properties than substrate **S1**. The results indicated that Pd/**L6c** can also be used for the alkylation of substrates **S3**–**S5** (compounds **55**–**60**), with different aryl substitution patterns, even with highly interesting substituted malonates containing allyl, pentenyl and propargyl groups, with yields and enantioselectivities comparable to those of **S1** (compounds **55**–**60**, ee's ≥99%).

Table 2. Pd-AAS of S3-S9 with different C-nucleophiles with Pd/L6c.[a]



[a] Full conversions were attained 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.

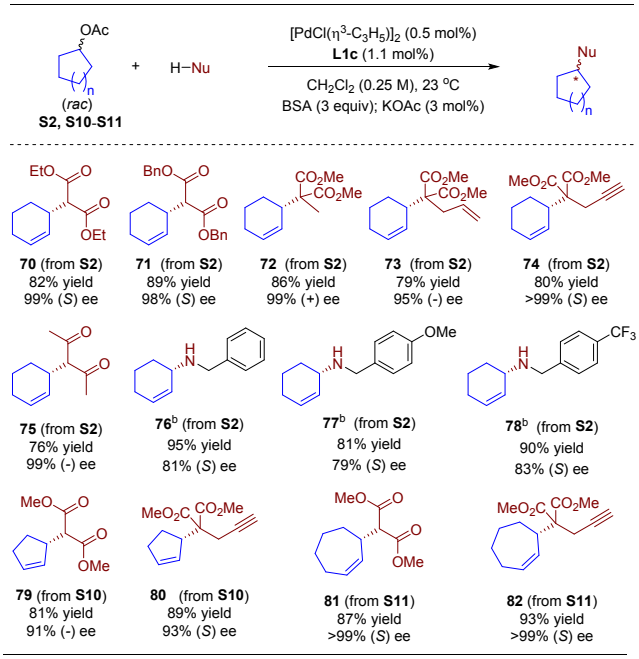
The scope of Pd/**L6c** was also studied with substrates **S6**–**S8** that have different steric constrains, and are typically alkylated with lower enantioselectivity than the benchmark substrate **S1**.[2] Thus, comparable high enantioselectivities were still attained in the alkylation of those more 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 high enantioselectivity has only been obtained with a few Pd-catalysts.[2]

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 relevance of chiral organofluorine molecules 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 a high catalyst loading (10 mol% Pd), a temperature of 60 °C and used 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 because the alkylated compound **69** can be used in the preparation of molecules of more complexity 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 5-, 6- and 7-membered cyclic substrates (**S2**, **S10** and **S11**) and with nucleophiles other than the dimethyl malonate (Table 3). These studies were carried out with ligand **L1c** that had shown the best enantioselectivities in the Pd-AAS of **S2** (see Table 1 above). For the Pd-AAA of **S2**, high yields and excellent enantioselectivities (ee's to >99%) were attained with many 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 substrate **S11** using dimethyl and propargyl malonates (ee's up to >99%; compounds **81**–**82**). The good results were also expanded to the more challenging five-membered cyclic substrate **S10** (compounds **79**–**80**). Note that the resulting propargylated compounds **74**, **80** and **82** are crucial intermediates for the construction 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 showed that the enantioselectivity is hardly influenced by the electronic properties of the group at the *para* position of the phenyl group.

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

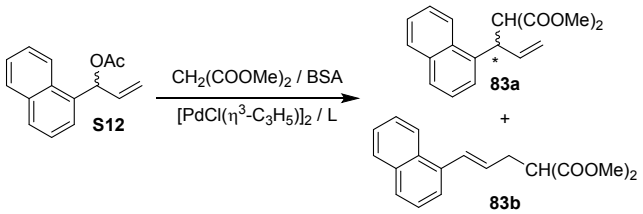


[a] Full conversions were attained after 2 h. [b] Reactions performed with cyclohex-2-en-1-yl ethyl carbonate as substrate and [PdCl(η³-C_3H_5)]$_2$ (1 mol%) for 18 h.

Allylic alkylation of monosubstituted substrates S12–S18. We tested whether the good catalytic performance obtained in the allylic alkylation of 1,3-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 monosubstituted substrates, the discovery of Pd-catalyst able to provide high regio- and enantioselectivities is still quite an unsolved issue.[25]

Table 4 collects the results in the allylic alkylation of benchmark monosubstituted subtrate **S12** under the optimized reaction conditions found with related Pd/**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 influence of the type of substituent at the alkyl backbone chain was different. Thus, Pd/**L7c** catalyst, which contains an isopropyl group at the alkyl backbone chain, provided the highest enantioselectivities (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 the configurations at both the biaryl phosphite group and at the oxazoline substituent (compare e.g., ligand **L2c**, entry 6 and ligand **L5b**, entry 8). The control on the ligand structure allowed us to reach both configurations of the alkylated compound in enantioselectivities as high as 98% ee.

Table 4. Regio- and enantioselective Pd-AAA of monosubstituted substrate S12.[a]

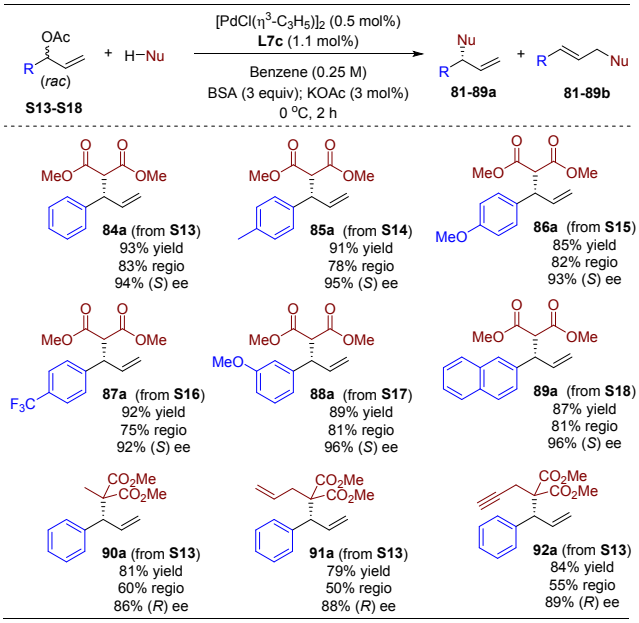


Entry	Ligand	% Conv[b] (% yield)	% branched[c]	% ee[d]
1	**L1a**	100 (88)	80	64 (*S*)
2	**L1b**	100 (89)	80	37 (*S*)
3	**L1c**	100 (88)	75	88 (*S*)
4	**L2a**	100 (91)	75	64 (*S*)
5	**L2b**	100 (89)	80	34 (*S*)
6	**L2c**	100 (90)	75	91 (*S*)
7	**L5a**	100 (89)	80	45 (*R*)
8	**L5b**	100 (88)	85	87 (*R*)
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(η³-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 determined by ^{1}H NMR. [d] Enantiomeric excesses measured by chiral HPLC.

With the optimal ligand **L7c**, we next studied the Pd-AAS of other challenging monosubstituted substrates that have different electronic and steric parameters, 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 reversed to the achiral linear product **83b** for substrates with electron-withdrawing substitutents 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 for substrates **84a**–**89a** with different electronic properties on the aromatic ring. 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-AAA of monosubstituted substrates S13–S18 with ligand L7c.[a]



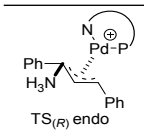
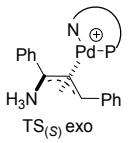
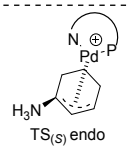
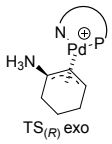
[a] Regioselectivities calculated by ^{1}H NMR and enantiomeric excesses determined by HPLC.

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 by an early transition state (TS).[7] Thus, the electrophilicity of the allylic carbon atoms governs the stereochemistry of the reaction. In accordance with the higher *trans* influence of the P, the allylic carbon *trans* to P is more reactive than the allylic carbon *trans* to the oxazoline group.[26] With the aim of identifying what properties of ligands **L1**–**L7a–c** are responsible for the catalytic performance, we carried a DFT 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] With these ligands we studied the effect on enantioselectivity of varying the configuration of the phosphite functionality (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, we used NH_3 as the nucleophile rather than dimethyl malonate.[28,29] Moreover, and in agreement with that already described in the literature, only the two *syn-syn* Pd-allyl compounds were considered (TS_{endo} and TS_{exo}), neglecting the involvement of the *anti-anti* and *syn-anti* allylic species of higher energy.[2d]

Table 6 collects the calculated energies for the most stable TSs, producing both enantiomers of the product ($TS_{(S)}$ and $TS_{(R)}$), with the three ligands (see Supporting Information for the full set of calculated coordinates and energies of all TSs). For both substrates, the calculated TSs energies agree with the experimental 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 properly predict the production of the reverse product enantiomers with **L1b** and **L1c**.

Table 6. Calculated energies for the most stable TSs with S1 and S2 and NH_3.[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 the phosphite group on enantioselectivity. Interestingly, for both catalytic systems (Pd/**L1b–c**) with substrate **S1** the *endo* TSs are destabilized through a steric repulsion generated between one of the phenyl substituents of **S1** and the oxazoline substituent. This repulsion is not observed for substrate **S2**. Accordingly, this unfavorable interaction causes a larger dihedral angle ω (C^1-N-C^2-C^3) in *exo* TSs than in *endo* TSs of **S1**. In the *endo* TSs of **S1** this unfavorable interaction shoves the oxazoline moiety away which causes a lower dihedral angle. These destabilized interactions justify that for both ligands the same configuration of the resulting product was achieved.

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 **S1** and the biaryl phosphite group (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)).

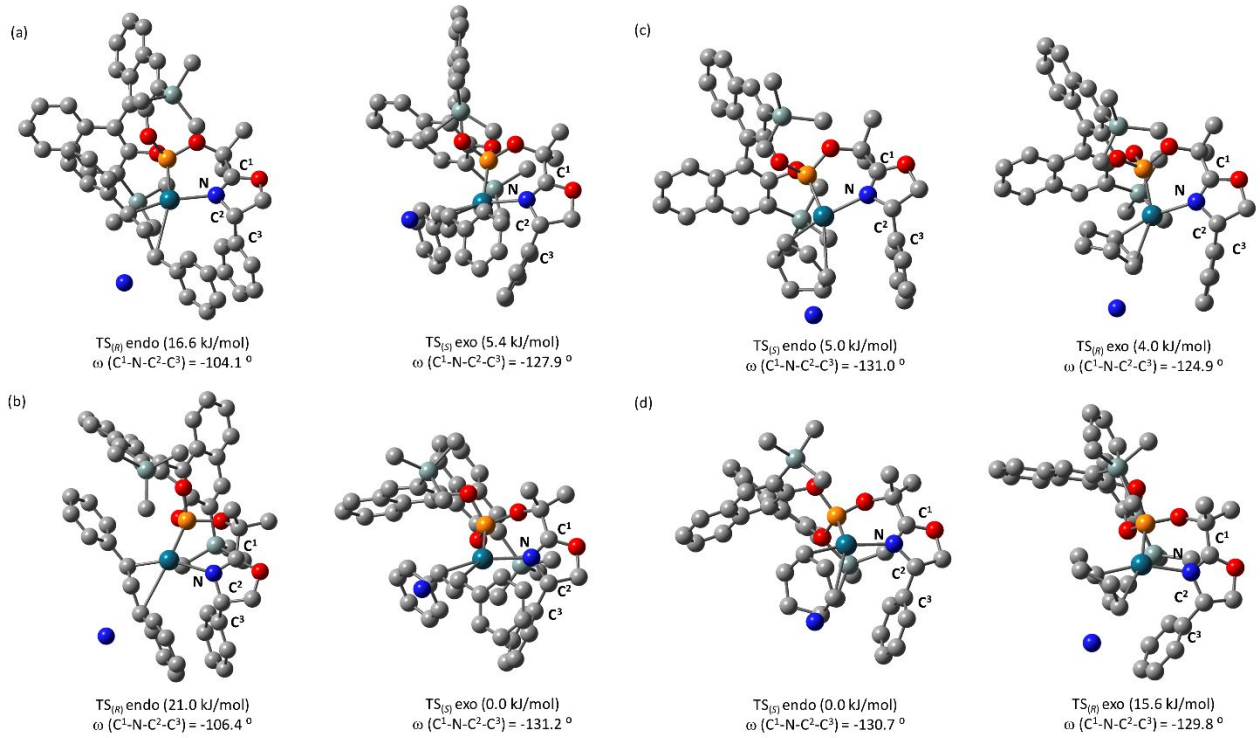


Figure 4. Most stable calculated TSs ($TS_{(R)}$ *endo* and $TS_{(S)}$ *exo*) from **S1** using ligands (a) **L1b** and (b) **L1c**; and from **S2** using ligands (c) **L1b** and (d) **L1c**. All hydrogens atoms are not shown for clarity. Relative free energies in solution and in kJ/mol respect to the corresponding lowest energy transition state.

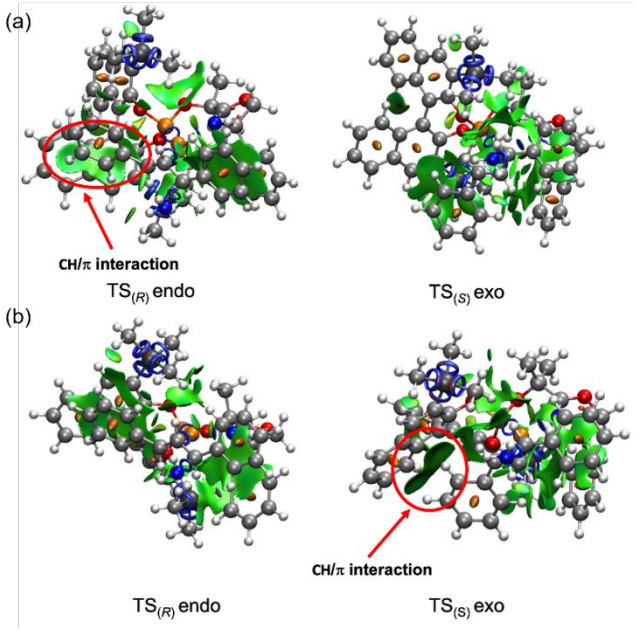


Figure 5. NCI plots of the most stable calculated TSs ($TS_{(R)}$ *endo* and $TS_{(S)}$ *exo*) from **S1** using ligands (a) **L1b** and (b) **L1c**. Strong and attractive interactions are blue, weak interactions are green and strong and repulsive interactions are red.

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 phosphite moiety (Figure 6). However, while with ligand **L1b** with an *R*- phosphite group 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**.

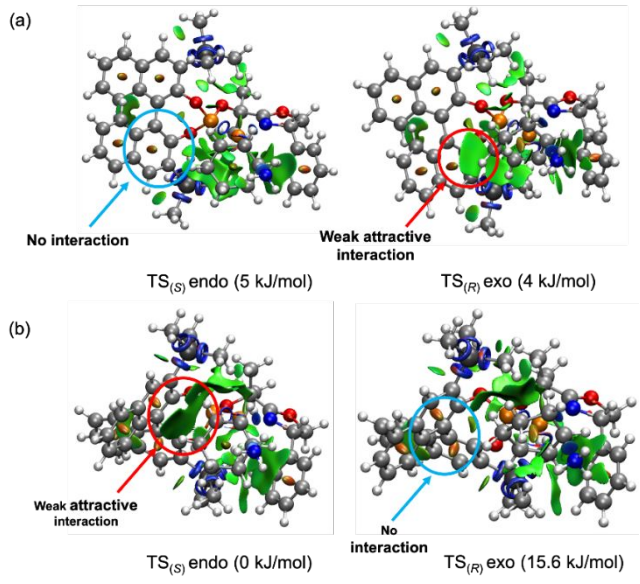


Figure 6. NCI plots of the most stable calculated TSs ($TS_{(R)}$ *endo* and $TS_{(S)}$ *exo*) from **S2** using ligands (a) **L1b** and (b) **L1c**. Strong and attractive interactions are blue, weak interactions are green and strong and repulsive interactions are red.

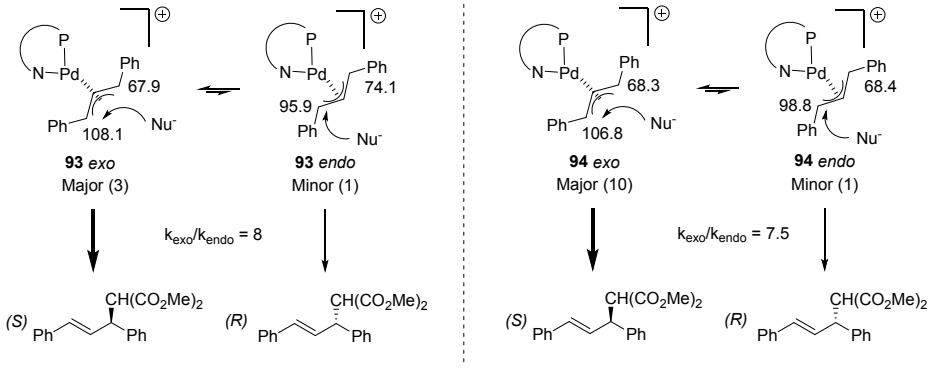
In summary, the DFT calculations showed that while for cyclic substrates the enantioselectivity is mostly controlled by the biaryl phosphite groups, for linear substrates the oxazoline substituent also has a crucial role.

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 complexes and their reactivity with the nucleophile will provide additional information about the influence of the ligand components on catalytic performance. For this purpose, we prepared the Pd-π-1,3-diphenyl/cyclohexenyl based allyl compounds **93**–**96** [Pd(η^3-allyl)(L)]BF_4 (L= **L2c** and **L6c**) (Scheme 2).[30] Ligands **L2c** and **L6c** were chosen to complete the study of the influence on enantioselectivity of different groups in the alkyl backbone chain.[31]

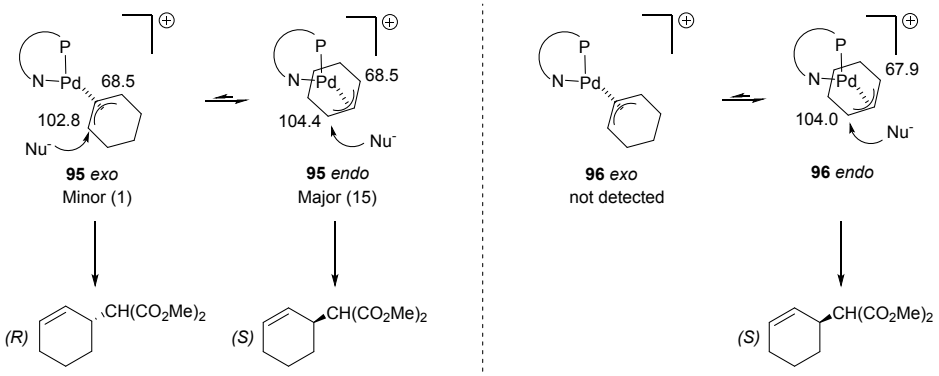
Scheme 2. Preparation of [Pd(η^3-allyl)(L)]BF_4 complexes **93**–**96**.

The variable temperature NMR study (30 °C to -80 °C) of Pd-1,3-diphenyl allyl complexes **93** and **94** displayed 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. The NOE shows interaction between the two terminal protons of the allyl group which agrees with a *syn*/*syn* disposition for these isomers. The NOE interactions also confirmed an *exo* and *endo* dispositions for the major and minor isomers, respectively (NOE details can be found in the Supporting Information). The carbon chemical shifts of compounds **93** and **94** showed that the most electrophilic allylic terminal carbons are *trans* to the P in the major *exo* isomers. Since the nucleophilic attack occurs at the more electron deficient allylic carbon terminus and the fact that the diastereomeric excesses of the intermediates vary from the enantiomeric excesses found experimentally, 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 reactivity, by *in situ* NMR, of complexes **93** and **94** with sodium dimethyl malonate, at low temperature, indicated that both isomers react with comparable rates: 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 complex **95** displayed 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.

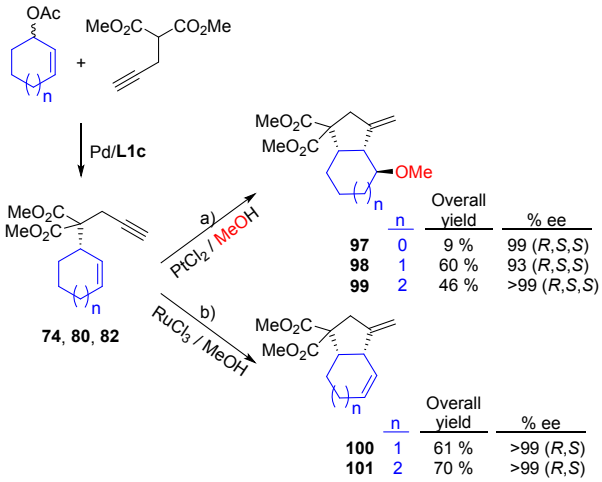


Scheme 4. Diastereoisomeric Pd-allyl intermediates for **S2** with ligands **L2c** (isomers **95**) and **L6c** (isomers **96**). The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

The major isomers of intermediates **95** and **96** were characterized by NOE as *endo* isomers (see Supporting Information for NOE details). Again the most electrophilic allylic carbon is *trans* to the P. Since for intermediate **95**, the electrophilicity of the allylic carbon *trans* to the P is very similar in *endo* and *exo* isomers ($\Delta\delta(^{13}C) \approx 1.6$ ppm), both isomers should react at a similar rate. Therefore, we can conclude that changing the substituent in the alkyl backbone chain modify the percentage of the species that let to both enantiomers. The enantioselectivity is therefore mostly governed by the relative ratio of the *endo* and *exo* isomers. The higher enantioselectivity provided by Pd/**L6c** can be due that only the *endo* isomer is detected.

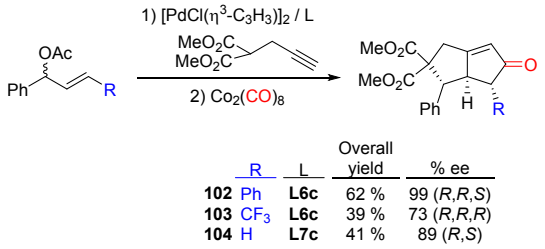
Synthetic applications of the allylic alkylated compounds. Construction of chiral carbobicycles. In this section we show a further application of the propargylated compounds **28**, **69**, **74**, **80**, **82** and **92**, prepared in previous section by Pd-AAS, to produce a range of chiral carbobicycles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

The first studied derivatization was a 1,6-enyne cyclization of the propargylated derivatives **74**, **80** and **82**, with different cycloalkane ring sizes (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 attained in good yields and maintaining the ee's achieved in the Pd-AAS. This derivatization was not affected by the substituents of the substrate (**102**–**104**).



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

CONCLUSIONS

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

monosubstituted) and cyclic substrates with different electronic and steric properties, with many C-, N- and O- nucleophiles. A total of 73 combinations of substrate-nucleophile have been studied. These catalysts derive from the successful Pd/**2** catalysts by replacing the *ortho*-phenylene tether by an alkyl backbone chain. With this simple modification, we have increased the number of ligand components than can be modified to increase activities and enantioselectivities for a major number of substrates and nucleophiles. We have been able to identify three ligands with high enantioselectivities 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 alkyl backbone chain substituent; whereas **L6c** has a methyl, **L7c** has isopropyl and **L1c** has two methyl groups. In comparison with Pd/**2** the new Pd-catalysts provided better activities for a broader substrate and nucleophile scope.

Mechanistic studies based on DFT calculations and NMR spectroscopy let us find the species responsible for the catalytic performance and the impact of the ligand components on the origin of enantioselectivity. Thus, these studies confirm that the ratio of the Pd-allyl intermediates that provide both enantiomers is influenced by the ligand parameters. The enantioselectivity is therefore mostly governed by the relative ratio 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 phosphite moiety 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 excellent transmission of the enantioselectivity.

EXPERIMENTAL SECTION

General considerations. All reactions were performed with standard Schlenk techniques using argon. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under inert atmosphere. ^{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], compounds **4**,[9] **8**–**13**[7,11] and **14**–**19**[7,11], phosphorochloridites[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, which is based on electron density and its gradient, is able of mapping real-space regions where NCI are relevant. The resulting NCI plots information is mainly qualitative. To perform these calculations, we used promolecular approximation using xyz files.

Typical methodology for the preparation of phosphite-oxazoline ligands. A solution of the desired alcohol-oxazoline (1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL) was added dropwise at -78 °C to a solution of phosphochloridite (1.1 mmol) and pyridine (0.16 mL, 2.0 mmol) in toluene (6 mL). 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 methodology for the preparation of [Pd(η³-allyl)(P-N)]BF_4 complexes 93–96. Compound $[Pd(\mu\text{-}Cl)(\eta^3\text{-}1,3\text{-allyl})]_2$ (0.025 mmol) and the corresponding ligand (0.05 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. After 30 minutes, $AgBF_4$ (9.8 mg, 0.05 mmol) was added and the mixture was stirred for 30 minutes. Silver salts were then removed by filtration over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the $[Pd(\eta^3\text{-allyl})(P\text{-}N)]BF_4$ complexes were precipitated by adding hexane as pale yellow solids.

[Pd(η³-1,3-diphenylallyl)(L2c)]BF_4 (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). ^1H 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)]BF_4 (94): Major isomer (91%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 140.3 (s). ^1H 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). ^1H 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)]BF_4 (95): Major isomer (95%): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 143.3 (s). ^1H 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). ^1H 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)]BF_4 (96): ^{31}P NMR (161.9 MHz, CD_2Cl_2): δ= 143.7 (s). ^1H 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 methodology for the allylic alkylation of linear (S1, S3–S9, S12–S18) and cyclic (S2, S10 and S11) substrates. A solution of the desired phosphite-oxazoline ligand (0.011 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was stirred. After 30 min a solution of substrate (1 mmol) in CH_2Cl_2 (1.5 mL), nucleophile (3 mmol), *N,O*-bis(trimethylsilyl)-acetamide (730 μL, 3 mmol) and KOAc (3 mg, 0.03 mmol) were subsequently added. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL). Saturated NH_4Cl (aq) (25 mL) was then added and 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 evaporated, conversions were measured by ^1H NMR and ees were calculated by HPLC. For compounds **21**, **63**, **70**–**71**, **74**–**75** and **80**–**81**, conversion and ees were determined by GC.[5g] For compounds **62** and **79**, conversion was measured by ^1H NMR and ees were determined by ^1H NMR using $[Eu(hfc)_3]$. See Supporting Information for characterization and enantiomeric excess determination details.

Typical methodology for the allylic amination of S1 and S2. A solution of the desired phosphite-oxazoline ligand (0.011 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was stirred. After 30 min, a solution of substrate (1 mmol) in CH_2Cl_2 (1.5 mL) and the corresponding amine (3 mmol) were subsequently added. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL). Saturated NH_4Cl (aq) (25 mL) was then added and the mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were determined by ^1H NMR. HPLC was employed to calculate enantiomeric excesses of compounds **36**–**47** and **76**–**78**. See Supporting Information for characterization and enantiomeric excess determination details.

Typical methodology for the allylic etherification and silylation of S1. A solution of the desired phosphite-oxazoline ligand (0.011 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was stirred. After 30 min, a solution of **S1** (31.5 mg, 0.125 mmol) in CH_2Cl_2 (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. . After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL). Saturated NH_4Cl (aq) (25 mL) was then added and the mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversions were determined by ^1H NMR. HPLC was employed to calculate

enantiomeric excesses of substrates **48**–**54**. See Supporting Information for characterization and enantiomeric excess determination details.

Typical methodology 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, the solvent was removed in vacuo 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 methodology 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 evaporated 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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REFERENCES

(1) (a) *Asymmetric Catalysis in Industrial Scale: Challenges, Approaches and Solutions,* Blaser, H. U, Schmidt, E., Eds.; Wiley-VCH: Weinheim, **2003**; (b) *Comprehensive Asymmetric Catalysis,* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, **1999**; (c) *Asymmetric Catalysis in Organic Synthesis*, Noyori, R., Ed.; Wiley: New York, **1994**; (d) *Applied Homogeneous Catalysis with Organometallics Compounds*, 2nd ed.; Cornils, B., Hermann, W. A., Eds.; WileyVCH: Weinheim, **2002**; (e) *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; Wiley: Hobocken, **2010**.

(2) For reviews, see: (a) Tsuji, J. In *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*; Wiley: New York, **1995**; (b) Trost, B. M.; van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395–422; (c) Johannsen, M.; Jorgensen, K. A. Allylic Amination. *Chem. Rev.* **1998**, *98*, 1689–1708; (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis,* Vol. 2; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, **1999**, Chapter 24, pp 833–884; (e) Helmchen, G.; Pfaltz, A. Phosphinooxazolines – A New Class of Versatile, Modular P,N-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33*, 336–345; (f) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921–2944; (g) Martin, E.; Diéguez, M. Thioether Containing Ligands for Asymmetric Allylic Substitution Reactions. *C. R. Chim.* **2007**, *10*, 188–205; (h) Lu, Z.; Ma, S. Metal-Catalyzed Enantioselective Allylation in Asymmetric Synthesis. *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; (i) Diéguez, M.; Pàmies, O. New Efficient Adaptative Ligands for Pd-Catalyzed Asymmetric Allylic Substitution Reactions. *Acc. Chem. Res.* **2010**, *43*, 312–322; (j) Trost, B. M.; Zhang, T.; Sieber, J. D. Catalytic Asymmetric Allylic Alkylation Employing Heteroatom Nucleophiles: a Powerful Method for C–X Bond Formation. *Chem. Sci.* **2010**, *1*, 427–440; (k) Trost, B. M. Mo-Catalyzed Asymmetric Allylic Alkylation. *Org. Process Res. Dev.* **2012**, *16*, 185–194; (l) Butt, N.; Zhang, W. Transition Metal-Catalyzed Allylic Substitution Reactions with Unactivated Allylic Substrates. *Chem. Soc. Rev.* **2015**, *44*, 7929−7967; (m) Grange, R. L.; Clizbe, E. A.; Evans, P. A. Recent Developments in Asymmetric Allylic Amination Reactions. *Synthesis* **2016**, *48*, 2911–2968; (n) Butt, N.; Yang, G.; Zhang, W. Allylic Alkylations with Enamine Nucleophiles. *Chem. Rec.* **2016**, *16*, 2683−2692.

(3) See for instance: (a) Diéguez, M.; Ruiz, A.; Müller, G.; Claver, C.; Jansat, S.; Gómez, M. Diphosphites as a Promising New Class of Ligands in Pd-catalysed Asymmetric Allylic Alkylation. *Chem. Commun.* **2001**, 1132–1133; (b) Diéguez, M.; Pàmies, O.; Claver, C. Modular Furanoside Diphosphite Ligands for Pd-Catalyzed Asymmetric Allylic Substitution Reactions: Scope and Limitations. *Adv. Synth. Catal.* **2005**, *347*, 1257–1266; (c) Diéguez, M.: Pàmies, O.; Claver, C. Palladium-Diphosphite Catalysts for the Asymmetric Allylic Substitution Reactions. *J. Org. Chem.* **2005**, *70*, 3363–3368. For reviews, see: (d) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. Phosphite-Containing Ligands for Asymmetric Catalysis. *Chem. Rev.* **2011**, *111*, 2077–2118; (e) Pàmies, O.; Diéguez, M. Adaptable P-X Biaryl Phosphite/Phosphoroamidite-Containing Ligands for Asymmetric Hydrogenation and C-X Bond-Forming Reactions: Ligand Libraries with Exceptionally Wide Substrate Scope. *Chem. Rec.* **2016**, *16*, 2460–2481.

(4) (a) Balanta, A.; Favier, I.; Teuma, E.; Castillón, S.; Godard, C.; Aghmiz, A.; Claver, C.; Gómez, M. An Outstanding Palladium System Containing a C_2-symmetrical Phosphite Ligand for Enantioselective Allylic Substitution Processes. *Chem. Commun.* **2008**, 6197–6199; (b) Gual, A.; Castillón, S.; Pàmies, O.; Diéguez, M.; Claver, C. C_1-Symmetric Carbohydrate Diphosphite Ligands for Asymmetric Pd-Allylic Alkylation Reactions. Study of the key Pd-allyl intermediates. *Dalton Trans.* **2011**, *40*, 2852–2860.

(5) For examples of heterodonor P,N ligands, see: (a) Pàmies, O.; Diéguez, M.; Claver, C. New Phosphite−Oxazoline Ligands for Efficient Pd-Catalyzed Substitution Reactions. *J. Am. Chem. Soc.* **2005**, *127*, 3646–3647; (b) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. New Carbohydrate-Based Phosphite-Oxazoline Ligands as Highly Versatile Ligands for Palladium-Catalyzed Allylic Substitution Reactions. *Adv. Synth. Catal.* **2005**, *347*, 1943–1947; (c) Diéguez, M.; Pàmies, O. Modular Phosphite–Oxazoline/Oxazine Ligand Library for Asymmetric Pd-Catalyzed Allylic Substitution Reactions: Scope and Limitations–Origin of Enantioselectivity. *Chem. Eur. J.* **2008**, *14*, 3653–3669; (d) Mata, Y.; Pàmies, O.; Diéguez, M. Pyranoside Phosphite-Oxazoline Ligand Library: Highly Efficient Modular P,N Ligands for Palladium-Catalyzed Allylic Substitution Reactions. A Study of the Key Palladium Allyl Intermediates. *Adv. Synth. Catal.* **2009**, *351*, 3217–3234; (e) Mazuela, J.; Pàmies, O.; Diéguez, M. A New Modular Phosphite-Pyridine Ligand Library for Asymmetric Pd-Catalyzed Allylic Substitution Reactions: A Study of the Key Pd-π-Allyl Intermediates. *Chem. Eur. J.* **2013**, *19*, 2416–2432; (f) Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M. Theoretical and Experimental Optimization of a New Amino Phosphite Ligand Library for Asymmetric Palladium-Catalyzed Allylic Substitution.

ChemCatChem **2015**, *7*, 4091–4107; (g) Borràs, C.; Elías-Rodríguez, P.; Carmona, A. T.; Robina, I.; Pàmies, O.; Diéguez, M. Amino-P Ligands from Iminosugars: New Readily Available and Modular Ligands for Enantioselective Pd-Catalyzed Allylic Substitutions. *Organometallics* **2018**, *37*, 1682–1694. For examples on heterodonor P-P' ligands, see: (h) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. First Chiral Phosphoroamidite-phosphite Ligands for Highly Enantioselective and Versatile Pd-Catalyzed Asymmetric Allylic Substitution Reactions. *Org. Lett.* **2007**, *9*, 49–52; (i) Pàmies, O.; Diéguez, M. Screening of a Phosphite–Phosphoramidite Ligand Library for Palladium-Catalysed Asymmetric Allylic Substitution Reactions: The Origin of Enantioselectivity. *Chem. Eur. J.* **2008**, *14*, 944–960; (j) Raluy, E.; Pàmies, O.; Diéguez, M. Modular Furanoside Phosphite-Phosphoroamidites, a Readily Available Ligand Library for Asymmetric Palladium-Catalyzed Allylic Substitution Reactions. Origin of Enantioselectivity. *Adv. Synth. Catal.* **2009**, *351*, 1648–1670. For examples on heterodonor P,S-ligands, see: (k) Coll, M.; Pàmies, O.; Diéguez, M. Highly Versatile Pd–Thioether–Phosphite Catalytic Systems for Asymmetric Allylic Alkylation, Amination, and Etherification Reactions. *Org. Lett.* **2014**, *16*, 1892–1895; (l) Margalef, J.; Coll, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M. Asymmetric Catalyzed Allylic Substitution Using a Pd/P–S Catalyst Library with Exceptional High Substrate and Nucleophile Versatility: DFT and Pd-π-allyl Key Intermediates Studies. *Organometallics* **2016**, *35*, 3323–3335.

(6) (a) von Matt, P.; Pfaltz, A. Chiral Phosphinoaryldihydrooxazoles as Ligands in Asymmetric Catalysis: Pd-Catalyzed Allylic Substitution. *Angew. Chem. Int. Ed.* **1993**, *32*, 566–568; (b) Sprinz, J.; Helmchen, G. Phosphinoaryl- and Phosphinoalkyloxazolines as New Chiral Ligands for Enantioselective Catalysis: Very High Enantioselectivity in Palladium Catalyzed Allylic Substitutions. *Tetrahedron Lett.* **1993**, *34*, 1769–1772; (c) Dawson, G. J.; Frost, C. G.; Williams,J. M. J.; Coote, S. J. Asymmetric Palladium Catalysed Allylic Substitution Using Phosphorus Containing Oxazoline Ligands. *Tetrahedron Lett.* **1993**, *34*, 3149–3150.

(7) Bellini, R.; Magre, M.; Biosca, M.; Norrby, P.-O.; Pàmies, O.; Diéguez, M.; Moberg, C. Conformational Preferences of a Tropos Biphenyl Phosphinooxazoline–a Ligand with Wide Substrate Scope. *ACS Catal.* **2016**, *6*, 1701–1712.

(8) See for example: (a) Mazuela, J.; Pàmies, O.; Diéguez, M. Biaryl Phosphite–Oxazoline Ligands from the Chiral Pool: Highly Efficient Modular Ligands for the Asymmetric Pd-Catalyzed Heck Reaction. *Chem. Eur. J.* **2010**, *16*, 3434−3440 (asymmetric Heck reaction); (b) Magre, M.; Biosca, M.; Pàmies, O.; Diéguez, M. Filling the Gaps in the Challenging Asymmetric Hydroboration of 1,1-Disubstituted Alkenes with Simple Phosphite-Based Phosphinooxazoline Iridium Catalysts. *ChemCatChem* **2015**, *7*, 114−120 (asymmetric hydroboration); (c) Biosca, M.; Magre, M.; Coll, M.; Pàmies, O.; Diéguez, M. Alternatives to Phosphinooxazoline (t-BuPHOX) Ligands in the Metal-Catalyzed Hydrogenation of Minimally Functionalized Olefins and Cyclic β-Enamides. *Adv. Synth. Catal.* **2017**, *359*, 2801–2814 (asymmetric hydrogenation).

(9) Allen, J. V.; Williams, J. M. J. Enantiomerically Pure Oxazolines Tethered to Alcohols. Preparation and Use in Asymmetric Catalysis. *Tetrahedron: Asymmetry* **1994**, *5*, 277–282.

(10) Biosca, M.; Magre, M.; Pàmies, O.; Diéguez, M. Asymmetric Hydrogenation of Disubstituted, Trisubstituted, and Tetrasubstituted Minimally Functionalized Olefins and Cyclic β-Enamides with Easily Accessible Ir–P,Oxazoline Catalysts. *ACS Catal.* **2018**, *8*, 10316–10320.

(11) (a) Bolm, V.; Zani, L.; Rudolph, J.; Schiffers, I. New Chiral Ligands Derived from Mandelic Acid: Synthesis and Application in the Asymmetric Phenyl Transfer Reaction to an Aromatic Aldehyde. *Synthesis* **2004**, *13*, 2173–2180; (b) Buisson, D.; Azerad, R. Preparation and Use of (S)-O-Acetyllactyl Chloride (Mosandl's Reagent) as a Chiral Derivatizing Agent. *Tetrahedron: Asymmetry* **1999**, *10*, 2997–3002; (c) Kardassi, G.; Brungs, P.; Nothelfer, C.; Eberhard, S. Electrogenerated Chiral Cationic Glycine Equivalents — Part 2: Chiral 3-Methoxy-2,5-morpholinediones from (S)-α-Hydroxy Acids and Dimethyl Aminomalonate. *Tetrahedron* **1998**, *54*, 3479–3488.

(12) Li, Z.-T.; Li, X.-S.; Li, L.-C.; Xu, D.-C. Convenient Synthesis of a New Class of Chiral Hydroxymethyldihydrooxazole Ligands and Their Application in Asymmetric Addition of Diethylzinc to Aromatic Aldehydes. *Russ. J. Organ. Chem.* **2006**, *42*, 545–549.

(13) Previous Pd/PHOX-based phosphite-oxazoline catalysts **2** provided TOF's up to >2400 mol substrate×(mol Pd×h)$^{-1}$, see ref. 5a.

(14) See for example: (a) Dugal-Tessier, J.; Dake, G. R.; Gates, D. P. Chiral Phosphaalkene−Oxazoline Ligands for the Palladium-Catalyzed Asymmetric Allylic Alkylation. *Org. Lett.* **2010**, *12*, 4667–4669; (b) Nakai, Y.; Uozumi, Y. Cycloisomerization of 1,6-Enynes: Asymmetric Multistep Preparation of a Hydrindane Framework in Water with Polymeric Catalysts. *Org. Lett.* **2005**, *7*, 291–293; (c) Son, S. U.; Park, K. H.; Seo, H.; Chung, Y. K.; Lee, S.-G. Catalytic Asymmetric Synthesis of Cyclopentenones from Propargyl Malonates and Allylic Acetate by Successive Action of Homogeneous Palladium(II) and Cobalt on Charcoal Catalysts in a One-pot Reaction. *Chem. Commun.* **2001**, 2440–2441; (d) Farwick, A.; Engelhart, J. U.; Tverskoy, O.; Welter, C.; Umlauf, Q. E.; Rominger, F.; WillKerr, W. J.; Helmchen, G. Bicyclic Cyclopentenones via the Combination of an Iridium- Catalyzed Allylic Substitution with a Diastereoselective Intramolecular Pauson–Khand Reaction. *Adv. Synth. Catal.* **2011**, *353*, 349–370.

(15) (a) Kmentová, I.; Gotov, B.; Solcániová, E.; Toma, Š. Study of Ligand and Base Effects on Enantioselective Allylation Catalyzed by Pd(0) Phosphine Complexes in [bmim][PF_6] Ionic Liquid. *Green Chem.* **2002**, *4*, 103–106; (b) Liu, J.; Chen, G.; Xing, J.; Liao, J. tert-Butanesulfinylthioether Ligands: Synthesis and Application in Palladium-catalyzed Asymmetric Allylic Alkylation. *Tetrahedron: Asymmetry* **2011**, *22*, 575–579; (c) Jin, Y.; Du, D. M. The Synthesis of Phosphine Oxide-linked Bis(oxazoline) Ligands and Their Application in Asymmetric Allylic Alkylation. *Tetrahedron* **2012**, *68*, 3633–6340; (d) Martin, C. J.; Rawson, D. J.; Williams, J. M. J. The Preparation of Enantiomerically Enriched γ-Amino Acids (GABAs) Using Palladium Catalysed Allylic Substitution. *Tetrahedron: Asymmetry* **1998**, *9*, 3723–3730. (e) Deng, W. H.; Ye, F.; Bai, X. F.; Zheng, Z. J.; Cui, Y. M.; Xu, L. W. Multistereogenic Phosphine Ligand-promoted Palladium-Catalyzed Allylic Alkylation of Cyanoesters. *ChemCatChem* **2015**, *7*, 75–79.

(16) For a recent review, see: d'Ischia, M.; Napolitano, A.; Pezzella, A. In *Comprehensive Heterocyclic Chemistry III: Pyrroles and their Benzo Derivatives: Applications;* Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., TaylorE. J. K., Eds.; Elsevier: Amsterdam, **2008**; Vol. 3, pp 353–388.

(17) (a) Liu, Y.; Cao, Z.; Du, H. Asymmetric Allylic Alkylation of Pyrroles and 4,7-Dihydroindoles with Alkene–Phosphine Ligands. *J. Org. Chem.* **2012**, *77*, 4479–4483; (b) Biosca, M.; Margalef, J.; Caldentey, X.; Besora, M.; Rodríguez-Escrich, C.; Saltó, J.; Cambeiro, X. C.; Maseras, F.; Pàmies, O.; Diéguez, M.; Pericàs, M. A. Computationally Guided Design of a Readily Assembled Phosphite–Thioether Ligand for a Broad Range of Pd-Catalyzed Asymmetric Allylic Substitutions. *ACS Catal.* **2018**, *8*, 3587–3601.

(18) (a) *Dictionary of Natural Products;* Buckingham, J, Ed.; Cambridge University Press.: Cambridge, **1994**; (b) Lumbroso, A.; Cooke, M. L.; Breit, B. Catalytic Asymmetric Synthesis of Allylic Alcohols and Derivatives and their Applications in Organic Synthesis. *Angew. Chem. Int., Ed.* **2013**, *52*, 1890–1893.

(19) The use of aliphatic alcohols has been much less studied than those using phenols. See: (a) Iourtchenko, A.; Sinou, D. Asymmetric Palladium(0)-Catalyzed Synthesis of Allylic Ethers. *J. Mol. Catal. A* **1997**, *122*, 91–93; (b) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. General Method for the Palladium-Catalyzed Allylation of Aliphatic Alcohols. *J. Org. Chem.* **2003**, *68*, 8092–8096; (c) Lam, F. L.; Au-Yeung, T. T. L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. Palladium–(S_pR)-FerroNPS-Catalyzed Asymmetric Allylic Etherification: Electronic Effect of Nonconjugated Substituents on Benzylic Alcohols on Enantioselectivity. *Angew. Chem. Int. Ed.* **2008**, *47*, 1280–1283; (d) Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F.; Xia, C.-G.; Xu, L.-W. Development of a Novel Multifunctional N,P Ligand for Highly Enantioselective Palladium-Catalyzed Asymmetric Allylic Etherification of Alcohols and Silanols. *Chem. Eur. J.* **2013**, *19*, 15452–15457; (e) Caldentey, X.; Pericàs, M. A. Modular P,S-Ligands

for Pd-Catalyzed Asymmetric Allylic Substitutions. *J. Org. Chem.* **2010**, *75*, 2628–2644; (f) Liu, Z.; Du, H. Development of Chiral Terminal-Alkene−Phosphine Hybrid Ligands for Palladium-Catalyzed Asymmetric Allylic Substitutions. *Org. Lett.* **2010**, *12*, 3054–3057; (g) Kato, M.; Nakamura, T.; Ogata, K.; Fukuzawa, S.-I. Synthesis of Novel Ferrocenyl-Based P,S Ligands (ThioClickFerrophos) and Their Use in Pd-Catalyzed Asymmetric Allylic Substitutions. *Eur. J. Org. Chem.* **2009**, 5232–5238; (h) Feng, B.; Cheng, H.-G.; Chen, J.-R.; Deng, Q.-R.; Lu, L.-Q.; Xiao, W.-J. Palladium/Sulfoxide–Phosphine-Catalyzed Highly Enantioselective Allylic Etherification and Amination. *Chem. Commun.* **2014**, *50*, 9550–9553.

(20) While low enantioselectivities were achieved for compounds **48**-**49** and **51** (ee's ranging from 25% to 37% ee), high ee's were achieved for compound **50** (97% ee) using Pd/**2** catalytic systems. See ref. 7.

(21) Silanols have been less studied than other type of nucleophile and there are only few catalytic systems that has provided high levels of enantioselectivity, see: (a) ref. 19d; (b) ref. 7.

(22) The isomerization of the Pd-allyl intermediates between the enantiomeric manifolds is usually very slow. For examples of successful kinetic resolutions, see: (a) Ramdeehul, S.; Dierkes, P.; Aguado, R.; Kamer, P. C. J.; van Leeuwen, P. W. N,. M.; Osborn, J. A. Mechanistic Implications of the Observation of Kinetic Resolution in a Palladium-Catalyzed Enantioselective Allylic Alkylation. *Angew. Chem., Int. Ed.* **1998**, *37*, 3118–3121; (b) Dominguez, B.; Hodnett, N. S.; Lloyd-Jones, G. C. Testing Racemic Chiral Catalysts for Kinetic Resolution Potential. *Angew. Chem., Int. Ed.* **2001**, *40*, 4289–4291; (c) Lüssemand, B. J.; Gais, H.-J. Palladium-Catalyzed Deracemization of Allylic Carbonates in Water with Formation of Allylic Alcohols: Hydrogen Carbonate Ion as Nucleophile in the Palladium-Catalyzed Allylic Substitution and Kinetic Resolution. *J. Am. Chem. Soc.* **2003**,*125*, 6066–6067; (d) Lei, B.-L.; Ding, C.-H.; Yang, X.-F.; Wan, X.-L.; Hou, X.-L. Kinetic Resolution of 2,3-Dihydro-2-substituted 4-Quinolones by Palladium-Catalyzed Asymmetric Allylic Alkylation. *J. Am. Chem. Soc.* **2009**, *131*, 18250–18251; (e) Cheung, H. Y.; Yu, W.-Y.; Au-Yeung, T. T. L.; Zhou, Z. A. S. C. Chan, Effective Chiral Ferrocenyl Phosphine-Thioether Ligands in Enantioselective Palladium-Catalyzed Allylic Alkylations. *Adv. Synth. Catal.* **2009**, *351*, 1412–1422; (f) Hirakawa, T.; Ikeda, K.; Ikeda, D.; Tanaka, T.; Ogasa, H.; Kawatsura, M.; Itoh, T. Regioselective Synthesis of Trifluoromethyl Group Containing Allylic Amines by Palladium-catalyzed Allylic Amination and Sequential Isomerization. *Tetrahedron* **2011**, *67*, 8238–8247; (g) Mao, B.; Ji, Y.; Fañanás-Mastral, M.; Caroli, G.; Meetsma, A.; Feringa, B. L. Highly Enantioselective Synthesis of 3-Substituted Furanones by Palladium-Catalyzed Kinetic Resolution of Unsymmetrical Allyl Acetates. *Angew. Chem., Int. Ed.* **2012**, *51*, 3168–3173.

(23) See for example: (a) Trost, B. M.; Toste, F. D. Regio- and Enantioselective Allylic Alkylation of an Unsymmetrical Substrate: A Working Model. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554; (b) Trost, B. M.; Toste, F. D. Palladium Catalyzed Kinetic and Dynamic Kinetic Asymmetric Transformations of γ-Acyloxybutenolides. Enantioselective Total Synthesis of (+)-Aflatoxin B_1 and B_{2a}. *J. Am. Chem. Soc.* **2003**, *125*, 3090–3100; (c) Dong, Y.; Teesdale-Spittle, P.; Hoberg, J. O. Regioselective Palladium-catalyzed Allylic Alkylations. *Tetrahedron Lett.* **2005**, *46*, 353–355; (d) Gais, H.-J.; Bondarev, O.; Hetzer, R. Palladium-catalyzed Asymmetric Synthesis of Allylic Alcohols from Unsymmetrical and Symmetrical Racemic Alylic Carbonates Featuring C–O-Bond Formation and Dynamic Kinetic Resolution. *Tetrahedron Lett.* **2005**, *46*, 6279–6283; (e) Kukkadapu, K. K.; Ouach, A.; Lozano, P.; Vaultier, M.; Pucheault, M. Achieving Chemo-, Regio-, and Stereoselectivity in Palladium-Catalyzed Reaction of γ-Borylated Allylic Acetates. *Org. Lett.* **2011**, *13*, 4132–4135; (f) Du, L.; Cao, P.; Xing, J.; Lou, Y.; Jiang, L.; Li, L.; Liao, J. Hydrogen-Bond-Promoted Palladium Catalysis: Allylic Alkylation of Indoles with Unsymmetrical 1,3-Disubstituted Allyl Acetates Using Chiral Bis(sulfoxide) Phosphine Ligands. *Angew. Chem. Int. Ed.* **2013**, *52*, 4207–4211; (g) Kawatsura, M.; Terasaki, S.; Minakawa, M.; Hirakawa, T.; Ikeda, K.; Itoh, T. Enantioselective Allylic Amination of Trifluoromethyl Group Substituted Racemic and Unsymmetrical 1,3-Disubstituted Allylic Esters by Palladium Catalysts. *Org. Lett.* **2014**, *16*, 2442–2445; (h) Ikeda, K.; Futamura, T.; Hanakawa, T.; Minakawa, M.; Kawatsura, M. Palladium-catalyzed Enantioselective Allylic Alkylation of Trifluoromethyl Group Substituted Racemic and Acyclic Unsymmetrical 1,3-Disubstituted Allylic Esters with Malonate Anions. *Org. Biomol. Chem.* **2016**, *14*, 3501–3505.

(24) (a) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. Chiral Mixed Phosphorus/Sulfur Ligands for Palladium-Catalyzed Allylic Alkylations and Aminations. *J. Org. Chem.* **1999**, *64*, 2994–2995; (b) Zhao, D.; Ding, K. A New Type of C2-Symmetric Bisphospine Ligands with a Cyclobutane Backbone: Practical Synthesis and Application. *Org. Lett.* **2003**, *5*, 1349–1351; c) Zhao, D.; Sun, J.; Ding, K. New Types of Soluble Polymer-Supported Bisphosphine Ligands with a Cyclobutane Backbone for Pd-Catalyzed Enantioselective Allylic Substitution Reactions. *Chem. Eur. J.* **2004**, *10*, 5952–5963.

(25) For successful applications of Pd-catalysts, see: (a) Prétôt, R.; Pfaltz, A. New Ligands for Regio- and Enantiocontrol in Pd-Catalyzed Allylic Alkylations. *Angew. Chem. Int. Ed.* **1998**, *37*, 323–325; (b) Hilgraf, R.; Pfaltz, A. Chiral Bis(N-tosylamino)phosphine- and TADDOL-Phosphite-Oxazolines as Ligands in Asymmetric Catalysis. *Synlett* **1999**, 1814–1816. (c) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. Highly Regio- and Enantioselective Pd-Catalyzed Allylic Alkylation and Amination of Monosubstituted Allylic Acetates with Novel Ferrocene P,N-Ligands. *J. Am. Chem. Soc.* **2001**, *123*, 7471–7472; (d) Hilgraf, R.; Pfaltz, A. Chiral Bis(N-sulfonylamino)phosphine- and TADDOL-Phosphite-Oxazoline Ligands: Synthesis and Application in Asymmetric Catalysis. *Adv. Synth. Catal*. **2005**, *347*, 61–77; (e) Chen, J.-P.; Ding, C.-H.; Liu, W.; Hou, X.-L.; Dai, L.-X. Palladium-Catalyzed Regio-, Diastereo-, and Enantioselective Allylic Alkylation of Acylsilanes with Monosubstituted Allyl Substrates. *J. Am. Chem. Soc.* **2010**, *132*, 15493–15495.

(26) (a) Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. Steric Influences on the Selectivity in Palladium-Catalyzed Allylation. *Organometallics* **1997**, *16*, 3015–3021; (b) Hagelin, H.; Åkermark, B.; Norrby, P.-O. New Molecular Mechanics (MM3*) Force Field Parameters for Calculations on (η^3-Allyl)palladium Complexes with Nitrogen and Phosphorus Ligands. *Organometallics* **1999**, *18*, 2884–2895.

(27) Considering the possibility of a late transition state the relative stability of the Pd-olefin intermediates (Pd-olefin$_{endo}$ and Pd-olefin$_{exo}$) after the addition of the nucleophile has also been calculated (the full set of calculation can be found in the Supporting Information, section). According to expectations the calculated energy of these Pd-olefin intermediates do not correlate well with the experimental results (see section 5 in the Supporting Information). For examples of late transition transition states, see: (a) Hagelin, H.; Svensson, M.; Äkermark, B.; Norrby, P.-O. Molecular Mechanics (MM3*) Force Field Parameters for Calculations on Palladium Olefin Complexes with Phosphorus Ligands. *Organometallics* **1999**, *18*, 4574–4583; (b) Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P.-O.; Hallberg, A.; Larhed, M.; Csçregh, I. Selectivity and Reactivity in Asymmetric Allylic Alkylation. *Pure Appl. Chem*. **1999**, *71*, 1477–1483.

(28) Note that using ammonia results in the inversion of the CIP descriptor in the 1,3-diphenylallyl case, due to the change in priority of the groups, although the sense of stereoselectivity is maintained.

(29) The use of ammonia as nucleophile circumvents the issues associated to charge separation along with a continuum solvent model when using malonates as nucleophiles. (a) Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. Structure-Based Rationale for Selectivity in the Asymmetric Allylic Alkylation of Cycloalkenyl Esters Employing the Trost 'Standard Ligand' (TSL): Isolation, Analysis and Alkylation of the Monomeric form of the Cationic η^3-Cyclohexenyl Complex [(η^3-c-C_6H_9)Pd(TSL)]$^+$. *J. Am. Chem. Soc.* **2009**, *131*, 9945–9957; (b) Fristrup, P.; Ahlquist, M.; Tanner, D.; Norrby, P.-O. On the Nature of the Intermediates and the Role of Chloride Ions in Pd-Catalyzed Allylic Alkylations: Added Insight from Density Functional Theory. *J. Phys. Chem.* **2008**, *112*, 12862–12867.

(30) (a) Deerenberg, S.; Schrekker, H. S.; van Strijdonck, G. P. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. New Chiral Phosphine−Phosphite Ligands in the Enantioselective Palladium-Catalyzed Allylic Alkylation. *J. Org. Chem.* **2000**, *65*, 4810–4817. (b) Fernández, F.; Gómez, M.; Jansat, S.; Muller, G.; Martín, E.; Flores Santos, L.; García, P. X.; Acosta, A.; Aghmiz, A.; Jiménez-Pedrós, M.; Masdeu-Bultó, A. M.; Diéguez, M.; Claver, C.; Maestro, M. A. Allylic Alkylations Catalyzed by Palladium Systems Containing Modular Chiral Dithioethers. A Structural Study of the Allylic Intermediates. *Organometallics* **2005**, *24*, 3946–3956.

(31) Complexes **93**–**96** were characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and HRMS. The structural assignments were supported by ^{1}H-^{1}H, ^{31}P-^{1}H, ^{13}C-^{1}H and ^{1}H-^{1}H NOESY experiments.

(32) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. Platinum-Catalyzed Alkoxy- and Hydroxycyclization of Enynes. *J. Am. Chem. Soc.* **2000**, *122*, 11549–11550.

(33) Sole, D.; Cancho, Y.; Llebaria, A.; Moreto, J. M.; Delgado, A. Intramolecular Nitrogen Assistance in the Nickel-Promoted Tandem Cyclization-Capture of Amino-Tethered Vinyl Bromides and Alkenes. *J. Am. Chem. Soc.* **1994**, *116*, 12133–12134

(34) (a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. Asymmetric Synthesis. Asymmetric Catalytic Allylation Using Palladium Chiral Phosphine Complexes. *J. Am. Chem. Soc.* **1985**, *107*, 2033–2046; (b) Jia, C.; Müller, P.; Mimoun, H. Palladium-catalyzed Allylic Acetoxylation of Olefins Using Hydrogen Peroxide as Oxidant. *J. Mol. Cat. A: Chem.* **1995**, *101*, 127–136; (c) Lehman, J.; Lloyd-Jones, G. C. Regiocontrol and Stereoselectivity in Tungsten-Bipyridine Catalysed Allylic Alkylation. *Tetrahedron* **1995**, *51*, 8863–8874; (d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine - Transition-metal Complexes. 8. Palladium-catalyzed Asymmetric Allylic Amination. *J. Am. Chem. Soc.* **1989**, *111*, 6301–6311; (e) Le, D.; Peng, C.; Jian, L. Bifunctional Ligand Promoted Pd-Catalyzed Asymmetric Allylic Etherification/Amination. *Acta Chim. Sinica* **2013**, *71*, 1239–1242; (f) Jayakumar, S.; Kumarswamyreddy, N.; Prakash, M.; Kesavan, V. Palladium Catalyzed Asymmetric Allylation of 3-OBoc-Oxindoles: An Efficient Synthesis of 3-Allyl-3-hydroxyoxindoles. *Org. Lett.* **2015**, *17*, 1066–1069; (g) Ref. 22f.

(35) Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Payne, C. C.; Semones, M. A.; Liebeskind, L. S. Synthesis, Characterization, and Configurational Lability of (.eta.3-Allyl)dicarbonyl[hydrotris(1-pyrazolyl)borato]molybdenum Complexes Bearing Substituents at the Termini: Thermodynamic Preference for the Anti Stereoisomer. *Organometallics* **1995**, *14*, 4132–4156.

(36) Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. Rhodium Catalysed Asymmetric Hydroformylation with Chiral Diphosphite Ligands. *Tetrahedron: Asymmetry* **1993**, *4*, 1625–1634.

(37) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E., Jr.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Revision A.02 ed; Gaussian: Wallingford, CT, **2009**.

(38) (a) Lee, C.; Yang,W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev.* B **1988**, 37, 785–789. (b) Becke, A. D. Density-Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys*. **1993**, 98, 5648–5652.

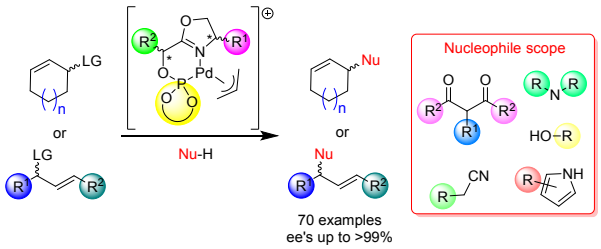
(39) Hay, P. J.; Wadt, W. R. Ab initio Effective Core Potentials for Molecular Calculations. Potentials for K to Au Including the Outermost Core Orbitals. *J. Chem. Phys.* **1985**, 82, 299–310.

(40) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self—Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian—Type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1972**, 56, 2257–2261. (b) Hariharan, P. C.; Pople, J. A. The Influence of Polarization Functions on Molecular Orbital Hydrogenation Energies. *Theor. Chim. Acta* **1973**, 28, 213–222. (c) Francl, M. M.; Pietro,W. J.; Hehre,W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XXIII. A Polarization-type Basis Set for Second-row Elements. *J. Chem. Phys*. **1982**, 77, 3654–3665.

(41) (a) Miertus, S.; Tomasi, J. Approximate Evaluations of the Electrostatic Free Energy and Internal Energy Changes in Solution Processes. *Chem. Phys.* **1982**, *65*, 239–245. (b) Mennucci, B.; Tomasi, J. Continuum Solvation Models: A New Approach to the Problem of Solute's Charge Distribution and Cavity Boundaries. *J. Chem. Phys.* **1997**, 106, 5151–5158. (c) Cossi, M.; Barone, V.; Menucci, B.; Tomasi, J. Ab initio Study of Ionic Solutions by a Polarizable Continuum Dielectric Model *Chem. Phys. Lett*. **1998**, 286, 253–260.

(42) (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XX. A Basis Set for Correlated Wave Functions. *J. Chem. Phys.* **1980**, 72, 650–654. (b) McLean, A. D.; Chandler, G. S. Contracted Gaussian Basis Sets for Molecular Calculations. I. Second Row Atoms, Z=11–18. *J. Chem. Phys*. **1980**, 72, 5639–5648.

(43) (a) Johnson, E.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498–6506; (b) Contreras-García, J.; Johnson, E.; Keinan, S.; Chaudret, R.; Piquemal, J.; Beratan, D.; Yang, W. *J. Chem. Theory Comput.* **2011**, *7*, 625–632; (c) Contreras-García, J.; Yang, W.; Johnson, E. *J. Phys. Chem. A* **2011**, *115*, 12983–12990.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