Alternating theoretical and experimental optimization of a new amino-phosphite ligand library for asymmetric Pd-catalyzed allylic substitution

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Dedication ((optional))

Abstract: A new library of modular amino-phosphite ligands obtained in a few synthetic steps from enantiopure aminoalcohols has been tested in the asymmetric Pd-catalyzed allylic substitution. The modular ligand design has been shown to be crucial in finding highly selective catalysts for each substrate type using a wide range of C, N and O-nucleophiles. A DFT study of the species responsible for the enantiocontrol was used for optimizing the ligand structure. By selecting the ligand components we were able to identify unprecedented catalytic systems that can create new chiral C-C, C-N and C-O bonds in a variety of substrate types (hindered and unhindered) in high yields and enantioselectivities (ee's up to 99%). Further studies on the Pd-π-allyl intermediates provided a deep understanding of the effect of ligand structure in the origin of enantioselectivity. Potential applications of the new Pd-amino-phosphite catalysts were demonstrated by the practical synthesis of a range of chiral carbocycles by simple tandem reactions, with no loss of enantioselectivity.

1. Introduction

The syntheses of chiral C-X bonds, where X is a C atom or an heteroatom, are the most significant processes in the preparation of complex chiral molecules from simple ones. Of all the C-X bond forming strategies, enantioselective Pd-catalyzed allylic substitution is among the most studied. Some advantages include a high functional group tolerance, mild reaction conditions and high versatility of the alkene functionality of the substrate for further stereoselective functionalization.[1] Most of the top ligands reported to date for Pd-allylic substitution use the capacity of the ligand to direct the nucleophilic attack to one of the allylic terminal atoms, by means of either a secondary ligand-nucleophile interaction[2] or an electronic discrimination[3].[1] The latter approach uses heterodonor ligands to electronically differentiate between the two allylic terminal carbon atoms because of the different *trans* influences of the donor groups. Mixed phosphine/phosphinite-oxazoline ligands have played a dominant role among heterodonor.[1] Our group has also contributed in the Pd-catalyzed allylic substitution with an improved generation of ligands. We have shown that some common limitations of this process, such as low reaction rates and high substrate specificity are overcome by introducing biaryl-phosphite moieties into the ligand design.[4] As a result increased reaction rates are achieved thanks to the larger π-acceptor ability of the phosphite groups and substrate versatility is increased because the flexibility of the phosphite moieties allows the catalyst chiral pocket to adapt to both hindered and unhindered substrates. We have therefore reported several phosphite-oxazolines as extremely effective ligands for this process.[5] Despite the important advances, the application of P-oxazoline ligands is mainly limited to the use of few nucleophiles, mainly dimethyl malonate and benzylamine. The use of functionalized malonates and alkyl alcohols has scarcely been reported.[1] In addition, only a few catalysts have been efficiently applied in the allylic substitution of a several type of substrates, with different electronic and steric proprieties, using a broad range of nucleophiles.[6] More effort has therefore to be made to expand the range of nucleophiles and substrates with the aim to synthesize more complex chiral organic molecules.

To expand the range of ligands and improve performance, we have recently moved our research towards developing heterodonor ligands that contain groups more robust than oxazolines. In this context, we reported the application of Pd-phosphite-pyridine/thioether catalytic systems in the allylic substitution of several substrate types using a large variety of nucleophiles.[7] A part from this, the successful use in this process of other heterodonor P-X ligands where X are more robust groups than oxazoline has not been reported yet, and a systematic study of the scope of this family of ligands is still missing. Although other researchers have developed heterodonor phosphine/phosphinite-ligands, containing groups more robust than oxazoline (such as amine,[8] imine,[9] pyridine,[10] thioether,[11] etc.), only a few of them have been successfully applied and these are limited in substrate and nucleophile scope (enantioselectivities are mainly high in the allylic substitution of hindered standard substrate *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** using dimethylmalonate as nucleophile). To be of practical interest, substantial improvements in terms of enantioselectivity, chemical yield and substrate and nucleophile versatility are still needed.

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To address this point, in this study we prepared and tested a new family of chiral ligands that are readily accessible, easier to handle and that expand the application range. We therefore report a highly modular amino-phosphite ligand library (Figure 1) for the Pd-allylic substitution of hindered and unhindered substrates with a large number of nucleophiles. These ligands are easily prepared in few steps from readily available enantiopure aminoalcohols. They also incorporate the advantages of the robustness of the amine moiety and the additional control provided by either the adaptability of the chiral cavity due to the biaryl-phosphite groups and the flexibility of the chiral pocket through a highly modular ligand scaffold. In a simple two/three step procedure (Scheme 1), several ligand parameters could be easily tuned to maximize the catalyst performance so that we could investigate the effect of systematically changing the substituents (ligands **L1**, **L5** and **L6**) and configuration (ligands **L1** and **L4**) at the ligand backbone, the amine substituents (ligands **L1**-**L3**) and the substituents and configurations in the biaryl phosphite moiety (**a**-**g**). By judicious choice of the ligand components, we achieved high enantioselectivities and activities in a number of substrates using a wide range of C-, N- and O-nucleophiles. The potential application of these new Pd/amino-phosphite catalytic systems has also been demonstrated by the practical synthesis of chiral carbocycles by simple sequential reactions, with no loss in enantiomeric excess.

Despite the recent success of Pd/phosphite-nitrogen catalyst systems, the mechanistic aspects of these ligands are not sufficiently understood to predict, a priori, the type of ligand needed to obtain a high selectivity. To address this important point, in this paper we also carried out DFT calculations and the synthesis and characterization of the Pd-π-allyl intermediates in order to explain the origin of enantioselectivity using these highly versatile catalytic systems. It should be noted that these DFT calculations have also been crucial in the optimization of the ligand design.

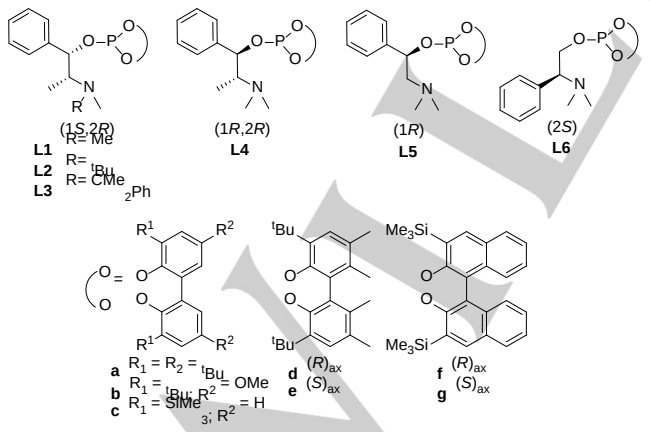
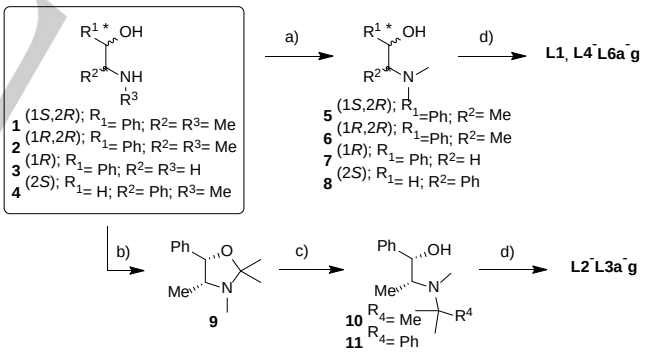


Figure 1. Amino-phosphite ligand library **L1**-**L6a**-**g**

2. Results and Discussion

2.1. Synthesis of ligand library

Ligands **L1**-**L6a**-**g** were synthesized from the corresponding easily accessible enantiopure aminoalcohols (**1**-**4**, Scheme 1). Amino-alcohols **1**-**4** already incorporate the desired diversity in the substituents and in the configurations of the aminoalcohol backbone. The diversity at the amino group was achieved by either direct methylation of **1**-**4** using formic acid and formaldehyde to afford compounds **5**-**8**[12] (Scheme 1, step a) or by formation of oxazolidine **9**[13] (Scheme 1, step b) from **1**, followed by ring-opening with the corresponding Grignard reagents (compounds **10**-**11**, step c)[14]. Finally, reaction of amino-alcohols **5**-**8**, **10** and **11** with one equivalent of the desired insitu formed phosphorocholoridite gave access to amino-phosphite ligands **L1**-**L6a**-**g** (step d) with the desired substituents and configurations of the biaryl phosphite group (**a**-**g**). Ligands **L1**-**L6a**-**g** were isolated in moderate-to-good yields as white solids after purification on neutral alumina under an atmosphere of argon. Advantageously, they were stable in air and very stable to hydrolysis, so further manipulation/storage was carried out in air. The HRMS-ESI spectra were in agreement with the assigned structure. Ligands **L1**-**L6a**-**g** were also characterized by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments, made using ^{1}H–^{1}H and ^{13}C–^{1}H correlation measurements, were as expected for these C_1-symmetric ligands. One singlet for each compound was observed in the ^{31}P NMR spectrum. Rapid ring inversions (tropoisomerization) in the biphenyl-phosphorus moieties (**a**-**c**) occurred on the NMR time scale because the expected diastereoisomers were not detected by low-temperature ^{31}P NMR (in CD_2Cl_2 +35 to -85 °C).[15]

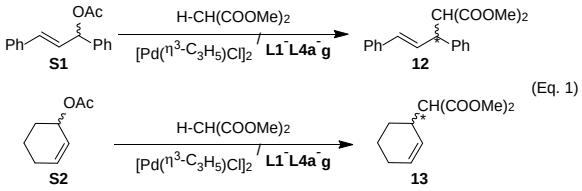


Scheme 1. Synthesis of amino-phosphites **L1-L6a-g.** a) Formic acid/paraformaldehyde/H_2O (yields 90-95%);[12] b) 2,2-dimethoxypropane/toluene (yield 72%);[13] c) MeMgBr/Et_2O or PhMgBr/THF (yields 87-93%)[14] and d) $ClP(OR)_2$; $(OR)_2$ = **a**-**g**/Py/toluene (yields 30-95%)

2.2. Allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene S1 and *rac*-3-acetoxycyclohexene S2 with ephedrine-based ligands L1-L4a-g. Computational study for ligand optimization

First, we tested the efficiency of the ephedrine-based amino-phosphite ligands **L1**-**L4a**-**g**. As mentioned previously, the asymmetric Pd-catalyzed allylic alkylation is highly dependent on

the olefin geometry.[1] The effectiveness of the catalyst in transferring the chiral information to the alkylated product mainly depends on its ability to adapt to the variation of the steric demands of the substrate. In order to assess the performance of ligands **L1**-**L4a**-**g** in the allylic alkylation of substrates with different steric requirements, we initially evaluated them in the asymmetric Pd-catalyzed allylic alkylation of the model substrates *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) and *rac*-3-acetoxycyclohexene (**S2**) (Equation 1). Because of the presence of less bulky anti substituents, the enantioselectivity for cyclic substrate **S2** is more difficult to control.[1] There are, therefore, fewer successful catalysts for **S2**. In all the cases, the catalysts were generated *in situ* from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the corresponding ligand.



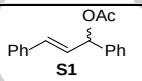
(Eq. 1)

The results, summarized in Table 1, indicate that enantioselectivity is mainly affected by the substituents/configuration at the biaryl phosphite moiety (**a**-**g**) and by the amine substituents, while the configuration of the ephedrine-backbone affects less. The sense of the enantioselectivity is therefore mostly controlled by the biaryl phosphite moiety, regardless of the configuration of the ephedrine-backbone. The effect of the substituents/configuration of the biaryl phosphite moiety was studied with ligands **L1a-g** (Table 1, entries 1-7). Results indicate that the presence of trimethylsilyl groups at the *ortho* positions of the biaryl phosphite moiety affects negatively both the activity and the enantioselectivity (entry 3 vs 1-2 and entries 6-7 vs 4-5). Also, by comparing the results from using ligand **L1a** with the related enantiopure biaryl ligands **L1d** and **L1e** (entry 1 vs 4 and 5), we can conclude that the tropoisomeric biphenyl moiety in ligands **L1a**-**c** is not controlled when coordinated in the Pd-π-allyl intermediate species. The best enantioselectivities are therefore obtained with ligands containing enantiopure biaryl phosphite moieties, with *tert*-butyl groups at the *ortho* positions (**d** and **e**; entries 4 and 5).

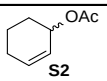
We then evaluated the effect of the amine substituents with ligands **L1**-**L3**. In general, the use of ligands **L1**, with a dimethyl amine group, yielded higher enantioselectivities than ligands **L2** and **L3** (i.e. entries 4 vs 9 and 12). A plausible explanation may be the formation of mixtures of diastereomeric amino complexes with ligands **L2** and **L3** (note that the N atom in ligands **L2** and **L3** becomes a stereogenic center when coordinated to the metal). In addition, **L1** have the advantage that can be synthesized in fewer steps than **L2**-**L3** (Scheme 1).

Finally, the configuration of the ephedrine backbone was studied by comparing ligands **L1** and **L4**. A cooperative effect between the configurations of both the ephedrine-backbone and the biaryl phosphite moiety was observed. Such a cooperative effect depends of the steric demands of the substrate. While for **S1** the cooperative effect results in a matched combination for ligands **L1d** and **L4d** (81% ee, entries 4 and 15), containing a *R*-biphenyl moiety, the matched combination for substrate **S2**, was achieved using *pseudo*-ephedrine ligand **L4e** (70% ee, entry 16), containing a *S*-biphenyl phosphite moiety.

Table 1. Pd-catalyzed allylic alkylation of substrates **S1**-**S2** with dimethyl malonate as nucleophile using ephedrine-based amino-phosphite ligands **L1-L4a**-**g**.[a]



S1



S2

Entry	Ligand	% Conv (% Yield)[b]	% ee[c]	% Conv (% Yield)[d]	% ee[e]
1	**L1a**	100 (94)	31 (*R*)	100 (93)	9 (*R*)
2	**L1b**	100 (92)	29 (*R*)	100 (94)	8 (*R*)
3	**L1c**	51 (48)	11 (*R*)	98 (91)	3 (*R*)
4	**L1d**	100 (94)	81 (*R*)	100 (90)	60 (*R*)
5	**L1e**	100 (93)	75 (*S*)	100 (93)	60 (*S*)
6	**L1f**	50 (45)	64 (*R*)	95 (89)	39 (*R*)
7	**L1g**	36 (31)	27 (*S*)	97 (91)	58 (*S*)
8	**L2a**	29 (24)	6 (*S*)	100 (92)	9 (*S*)
9	**L2d**	100 (96)	42 (*R*)	100 (88)	36 (*R*)
10	**L2e**	70 (66)	33 (*S*)	100 (93)	56 (*S*)
11	**L3a**	56 (51)	0	100 (91)	9 (*S*)
12	**L3d**	100 (93)	42 (*R*)	100 (92)	53 (*S*)
13	**L3e**	84 (80)	29 (*S*)	100 (89)	68 (*S*)
14	**L4a**	62 (57)	8 (*R*)	100 (93)	7 (*R*)
15	**L4d**	100 (96)	81 (*R*)	100 (91)	45 (*R*)
16	**L4e**	89 (85)	60 (*S*)	100 (93)	70 (*S*)

[a] Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (1 mol%), CH_2Cl_2 as solvent, BSA (3 eq), dimethyl malonate (3 eq), KOAc (3 mg). [b] Conversions and yields determined after 6 h. [c] Enantiomeric excesses determined by HPLC. [d] Conversions and yields determined after 18 h. [e] Enantiomeric excesses determined by GC.

To find what ligand parameters should be further modified to increase enantioselectivity, we performed a DFT computational study of the key intermediates and transition states involved in the enantiocontrol of the Pd-catalyzed allylic substitution of substrate **S1**, using ligands **L4d** and **L4e** as models. The mechanistic studies found in the literature have shown that enantioselectivity is controlled in the effectively irreversible nucleophilic attack, but transition state (TS) for this step can be either early or late depending on the nature of the nucleophile, ligands, and reaction conditions. In an early transition state, the interactions leading to stereochemical differentiation can be

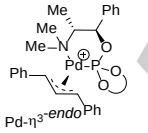
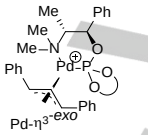
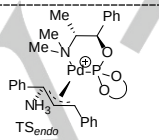
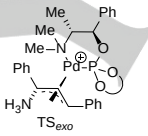
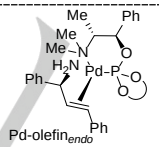
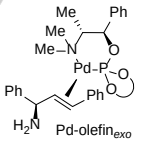
understood from the structure of the Pd-allyl intermediate,[16] whereas the late transition state is more reminiscent of the Pd-alkene product complex.[17] A sterically encumbered ligand can in fact be employed to push the allyl into a more product-like orientation, strongly affecting the regiochemical preference in the nucleophilic attack.[18] In our experience, a diffuse anion like malonate, or a neutral nucleophile like amine, would be expected to give relatively early transition states, whereas a highly concentrated charge like a fluoride anion gives a late TS.[19]

For the early TS case, stereochemistry is governed by both the population of the Pd-η^3-allyl intermediates and the relative electrophilicity of the allylic carbon atoms, with an allyl terminus *trans* to a phosphorus atom generally being more reactive than one *trans* to a nitrogen. When the TS is late, the formation of the most stable Pd-olefin complex controls enantioselectivity. Calculation were carried out using the B3LYP functional, the 6-31G*/LANL2DZ basis set, and the PCM solvent model with parameters for CH_2Cl_2, as implemented in Gaussian 09. The energies were further refined by performing single-point calculations at the 6-311+G** level, and by dispersion correction with the DFT-D3 model. Previous experience has shown that ammonia can be used as a good model nucleophile,[2b,20] avoiding the problems related to charge separation in conjunction with a continuum solvent model. Note that the use of ammonia as nucleophile instead of dimethyl malonate 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.

We initially calculated the relative stability of the Pd-η^3-diphenylallyl complexes. Only the two *syn-syn* η^3-allyl complexes (named Pd-η^3-*endo* and the Pd-η^3-*exo*, Table 2) were calculated. In accordance to what has already been described in the literature, the contribution of the other allylic species of higher energy (*anti-anti* and *syn-anti* Pd-η^3) was neglected.[1d] In line with the catalytic results (Table 1), the DFT results indicate that the configuration of the biaryl-phosphite moiety controls the preferential formation of one of the *syn-syn* Pd-allyl intermediates. Thus, while for ligand **L4d** the formation of the Pd-η^3-*exo* is preferred (ΔG = 7.6 kJ/mol), the most stable Pd-allyl intermediate for **L4e** is Pd-η^3-*endo* (ΔG = 8.2 kJ/mol). Assuming that the allyl intermediates are in rapid equilibrium[21] and that the nucleophile will always attack *trans* to phosphorus, we can see that the preferred intermediate leads to the preferred product in this case.

We then calculated the transition states TS_{endo} and TS_{exo}, using NH_3 as nucleophile (Table 2). The energy differences of the calculated TSs agree with the catalytic results. The energy difference between both TSs of ligand **L4d** ($\Delta G^{\#}$= 4 kJ/mol) is higher than for ligand **L4e** ($\Delta G^{\#}$= 2 kJ/mol). This is in good agreement with the higher enantioselectivities achieved using ligand **L4d** (Table 1, 81% ee for **L4d** vs 60% ee for **L4e**). In addition, the formation of opposite enantiomers of the substituted product is predicted when using ligands **L4d** and **L4e**. Finally, we calculated the Pd-olefin intermediates ($Pd\text{-}olefin_{endo}$ and $Pd\text{-}olefin_{exo}$). The results (Table 2) indicated that the larger energy difference of the Pd-olefin complexes is achieved with ligand **L4e** ($\Delta G^{\#}$= 5 kJ/mol for **L4e** vs 1.8 kJ/mol for **L4d**). Thus, in the current case, the product complex energies do not correlate with the transition state energies or with the experimental selectivities. The structural elucidation of the Pd-allyl intermediates and the determination of their relative reactivity towards the nucleophile are therefore crucial to understand their catalytic behavior (see below, Section 2.5).

Table 2. Calculated energies for the *endo* and *exo* Pd-η^3-allyl intermediates, TSs and Pd-π-olefin complexes using **S1** and NH_3 as nucleophile.[a]

	L4d	L4e
 Pd-η^3-*endo*	0	8.2
 Pd-η^3-*exo*	7.6	0
 TS_{endo}	0	2
 TS_{exo}	4	0
 $Pd\text{-}olefin_{endo}$	0	0
 $Pd\text{-}olefin_{exo}$	1.8	5

[a] Relative energies in kJ/mol.

Figure 2 shows the calculated TSs for the major and the minor pathway with both ligands. A special feature of all these TSs is that the methyl substituent of the ephedrine-backbone is pointing in the opposite direction to the coordination sphere. This finding suggests that the methyl group should have little impact on the enantioselectivity. To prove this, we recalculated the TSs by removing the methyl substituent of the ephedrine-backbone (new ligand **L5e**; Figure 1). Surprisingly, the calculated energy difference between the two TSs for the formation of both enantiomers of the alkylated product (Figure 3a) was 8.5 kJ/mol (ligand **L5e**) surpassing the values for ligands **L4d** and **L4e** (4 kJ/mol and 2 kJ/mol, respectively), indicating that ligand **L5e** should provide higher enantioselectivity than the ephedrine-based ligands **L4d** and **L4e**.

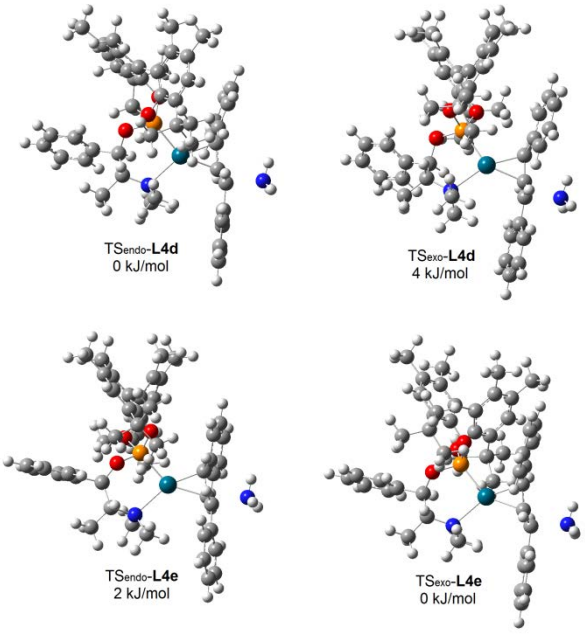


Figure 2. Calculated transition states using ephedrine-based ligands **L4d** and **L4e**

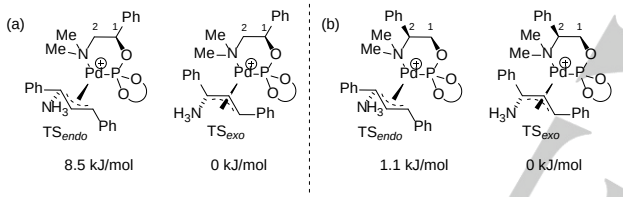
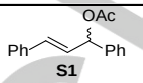


Figure 3. Calculated energies of transition states (TSs) using (a) ligands **L5e** and (b) **L6e**

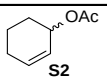
To study the effect of the other stereogenic center of the ephedrine-backbone (C-2), the phenyl substituent was switched from C-1 to C-2 (new ligand **L6e**, Figure 1). Slightly lower energy difference between the TSs were achieved than using Pd-**L4e** (Figure 3b), which suggest that this modification should provide lower enantioselectivities than **L4e**.

These theoretical results prompted us to prepare and screen amino-phosphite ligands **L5-L6d-e** (Scheme 1) in the asymmetric allylic substitution of substrates **S1** and **S2**. The experimental results are shown in Table 3. As predicted by the theoretical calculations, the use of ligand **L5e**, without the methyl substituent at stereogenic C-2 of the ephedrine backbone, in the allylic alkylation of **S1** provided the highest enantioselectivities (Table 3, entry 2, 94% (*S*) ee), while the use of ligand **L6e** led to similar enantioselectivities to **L4e** (entry 4). The same behavior is observed in the allylic alkylation of cylic substrate **S2**. Using ligand **L5e** we could therefore increase enantioselectivity from 70% ee to 82% ee (Table 3, entry 2). Interestingly, for substrate **S1**, ligand **L5d** provided similar high enantioselectivities like **L5e** did, but in the opposite enantiomer of the substitution product (92% (*R*) ee, entry 1). Both enantiomers of the substitution products can be therefore obtained by simply changing the configuration of the biaryl phosphite moiety in ligands **L5**. All these results show the importance of using modular scaffold to build new ligand systems.

Table 3. Pd-catalyzed allylic alkylation of substrates **S1** and **S2** with dimethyl malonate using amino-phosphite ligands **L5-L6d-e**.[a]



S1



S2

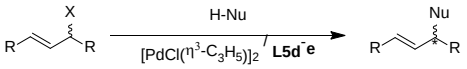
Entry	Ligand	% Conv (% Yield)[b]	% ee[c]	% Conv (% Yield)[d]	% ee[e]
1	**L5d**	100 (94)	92 (*R*)	100 (90)	70 (*R*)
2	**L5e**	100 (96)	94 (*S*)	100 (89)	82 (*S*)
3	**L6d**	100 (92)	41 (*R*)	100 (91)	46 (*R*)
4	**L6e**	100 (93)	62 (*S*)	100 (92)	62 (*S*)
5[f]	**L5e**	100 (95)	97 (*S*)	100 (91)	86 (*S*)
6[g]	**L5e**	98 (91)	92 (*S*)	94 (87)	83 (*S*)
7[h]	**L5e**	38 (32)	89 (*S*)	56 (49)	74 (*S*)

[a] Reactions were run at 23 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), ligand (1 mol%), CH_2Cl_2 as solvent, BSA (3 eq), dimethyl malonate (3 eq), KOAc (3 mg). [b] Conversions and yields determined after 6 h. [c] Enantiomeric excesses determined by HPLC. [d] Conversions and yields determined after 18 h. [e] Enantiomeric excesses determined by GC. [f] Reactions carried out at 5 °C for 18 h. [g] Reactions carried out at 0 °C for 18 h. [h] Reactions carried out at -15 °C for 18 h.

Enantioselectivity can be improved by controlling not only the structural but also the reaction parameters. We therefore studied these reactions at a low reaction temperature (entries 5-7). Enantioselectivity was further improved (ee's up to 97% for **S1** and 86% for **S2**) by lowering the reaction temperature to 5 ºC (Table 3, entry 5).

2.3. Allylic substitution of symmetrical 1,3-disubstituted allylic substrates S1-S10 with other C-, N- and O-nucleophiles. Scope and limitations

With the optimal amino-phosphite ligands **L5e** and **L5d** we investigated the substrate and nucleophile scope. The following linear and cyclic disubstituted substrates with different steric properties were studied (Equation 2): *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**), *rac*-1,3-di(4-tolyl)-3-acetoxyprop-1-ene (**S3**), *rac*-1,3-di(4-bromophenyl)-3-acetoxyprop-1-ene (**S4**), *rac*-1,3-di(3-methoxyphenyl)-3-acetoxyprop-1-ene (**S5**), *rac*-1,3-di(2-tolyl)-3-acetoxyprop-1-ene (**S6**), *rac*-1,3-dimethyl-3-acetoxyprop-1-ene (**S7**), *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate (**S8**), *rac*-3-acetoxycyclohexene (**S2**), *rac*-3-acetoxycyclopentene (**S9**) and *rac*-3-acetoxycycloheptene (**S10**). The range of nucleophiles was also expanded, compared to previous work, with special attention to the more challenging and interesting, from a synthetic point of view, functionalized malonates, β-diketones and alkyl alcohols, which have hardly been reported.

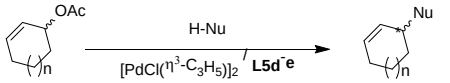


(Eq. 2)

S1 R= Ph; X= OAc
S3 R= *p*Me-C$_6$H$_4$; X= OAc
S4 R= *p*Br-C$_6$H$_4$; X= OAc
S5 R= *m*OMe-C$_6$H$_4$; X= OAc
S6 R= *o*Me-C$_6$H$_4$; X= OAc
S7 R= Me; X= OAc
S8 R= ^{i}Pr; X= OCO$_2$Et

14 R= Ph; H-Nu= H-CH(CO$_2$Et)$_2$
15 R= Ph; H-Nu= H-CH(CO$_2$Bn)$_2$
16 R= Ph; H-Nu= H-CMe(CO$_2$Me)$_2$
17 R= Ph; H-Nu= H-CAllyl(CO$_2$Me)$_2$
18 R= Ph; H-Nu= H-CButenyl(CO$_2$Et)$_2$
19 R= Ph; H-Nu= H-CPentenyl(CO$_2$Et)$_2$
20 R= Ph; H-Nu= H-Propargyl(CO$_2$Me)$_2$
21 R= Ph; H-Nu= H-CH(COMe)$_2$
22 R= Ph; H-Nu= H-NHCH$_2$Ph
23 R= Ph; H-Nu= H-OCH$_2$Ph
24 R= Ph; H-Nu= H-OCH$_2$(*p*Me-C$_6$H$_4$)

25 R= Ph; H-Nu= H-OCH$_2$(*p*CF$_3$-C$_6$H$_4$)
26 R= Ph; H-Nu= H-OCH$_2$(*m*Me-C$_6$H$_4$)
27 R= *p*Me-C$_6$H$_4$; H-Nu= H-CH(CO$_2$Me)$_2$
28 R= *p*Me-C$_6$H$_4$; H-Nu= H-CAllyl(CO$_2$Me)$_2$
29 R= *p*Me-C$_6$H$_4$; H-Nu= H-CButenyl(CO$_2$Et)$_2$
30 R= *p*Br-C$_6$H$_4$; H-Nu= H-CH(CO$_2$Me)$_2$
31 R= *m*OMe-C$_6$H$_4$; H-Nu= H-CH(CO$_2$Me)$_2$
32 R= *o*Me-C$_6$H$_4$; H-Nu= H-CH(CO$_2$Me)$_2$
33 R= Me; H-Nu= H-CH(CO$_2$Me)$_2$
34 R= Me; H-Nu= H-CMe(CO$_2$Me)$_2$
35 R= Me; H-Nu= H-CAllyl(CO$_2$Me)$_2$
36 R= ^{i}Pr; H-Nu= H-CH(CO$_2$Me)$_2$

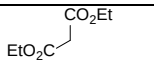
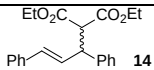
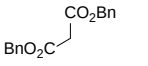
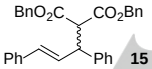
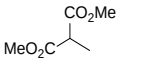
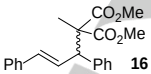
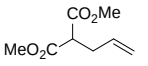
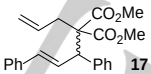
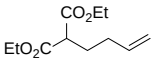
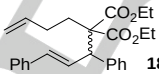
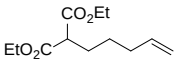
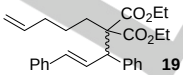
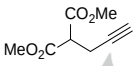
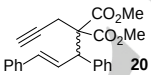
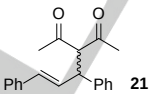
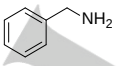
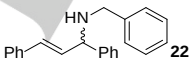
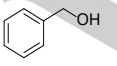
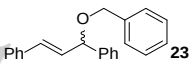
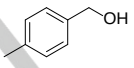
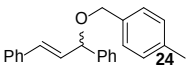
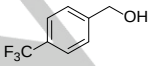
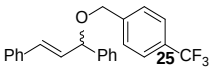
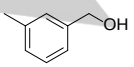
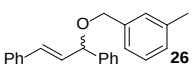


S2 n=1
S9 n=0
S10 n=2

37 n=1; H-Nu= H-CH(CO$_2$Et)$_2$
38 n=1; H-Nu= H-CMe(CO$_2$Me)$_2$
39 n=1; H-Nu= H-CAllyl(CO$_2$Me)$_2$
40 n=1; H-Nu= H-CPropargyl(CO$_2$Me)$_2$
41 n=1; H-Nu= H-CH(COMe)$_2$

42 n=0; H-Nu= H-CH(CO$_2$Me)$_2$
43 n=0; H-Nu= H-CPropargyl(CO$_2$Me)$_2$
44 n=2; H-Nu= H-CH(CO$_2$Me)$_2$
45 n=2; H-Nu= H-CPropargyl(CO$_2$Me)$_2$

Table 4. Allylic substitution of **S1** with other several C-, N- and O-nucleophiles using Pd/**L5d**-**e** catalytic systems.[a]

			L5d		L5e	
Entry	Nucleophile	Product	% Yield[b]	% ee[c]	% Yield[b]	% ee[c]
1		 **14**	91	92 (*R*)	92	93 (*S*)
2[d]			88	94 (*R*)	87	95 (*S*)
3		 **15**	93	92 (*R*)	91	94 (*S*)
4[d]			91	94 (*R*)	93	96 (*S*)
5		 **16**	92	95 (*S*)	90	96 (*R*)
6[d]			91	98 (*S*)	92	99 (*R*)
7		 **17**	94	96 (*S*)	93	97 (*R*)
8[d]			92	99 (*S*)	91	99 (*R*)
9[d]		 **18**	95	94 (*S*)	92	95 (*R*)
10		 **19**	93	95 (*S*)	94	97 (*R*)
11[d]			94	97 (*S*)	91	99 (*R*)
12		 **20**	91	94 (*R*)	90	96 (*R*)
13[d]			92	97 (*R*)	93	98 (*R*)
14		 **21**	93	96 (*R*)	94	96 (*S*)
15[d]			91	98 (*R*)	93	99 (*S*)
16		 **22**	89	97 (*S*)	92	99 (*R*)
17[e]		 **23**	92	53 (*S*)	95	56 (*R*)
18[e]		 **24**	91	28 (+)	94	30 (-)
19[e]		 **25**	92	91 (+)	94	94 (-)
20[e]		 **26**	93	68 (+)	91	70 (-)

[a] Reactions were run at 23 °C with [PdCl(η^3-C$_3$H$_5$)]$_2$ (0.5 mol%), CH$_2$Cl$_2$ as solvent, ligand (1 mol%), BSA (3 eq), KOAc (3 mg). [b] Full conversions were achieved after 12 h and 24 h for reactions carried out at 23 °C and 5 °C, respectively. [c] Enantiomeric excess determined by chiral HPLC or GC. [d] Reactions carried out at 5 °C for 24 h. [e] Reactions carried out using 2 mol% [PdCl(η^3-C$_3$H$_5$)]$_2$, 4 mol% ligand, Cs$_2$CO$_3$ (3 eq). Full conversions were achieved in all cases.

The results of Pd/**L5e** and Pd/**L5d** in the allylic substitution of **S1** using a wide range of C-, N- and O-nucleophiles are shown in Table 4. It can be observed that enantioselectivity was relatively unaffected by a change in the steric nature of the ester groups and in the substituents of the malonate nucleophiles (entries 1-13). Therefore, a variety of malonates, including those α-substituted, reacted cleanly with **S1** to afford products **14**-**20** in high yields, and with enantioselectivities that were as high as or higher than those obtained with dimethyl malonate (ee's up to 99% ee, entries 1-13). Among them, it should be stressed the high enantioselectivities using allyl-, butenyl, pentenyl- and propargyl-substituted malonates (entries 7-13, between 95-99% ee). This is advantageous because the resulting products are important precursors for more complex chiral molecules (see section 2.4 below). Excellent enantiocontrol was also achieved when the β-diketone acetophenone and the *N*-benzylamine were used as nucleophiles (ee's up to 99%; entries 14-16). It should be pointed out that the excellent results achieved using benzylamine validates the use of ammonia as nucleophile for the computational model. In all cases, both enantiomers of the substituted product can be obtained in high yields and enantioselectivities.

We then went on to study the allylic substitution of **S1** using alkyl alcohols as a challenging class of *O*-nucleophiles. The stereoselective construction of compounds with ether groups next to a chiral carbon is important for the preparation of biologically active compounds.[22] Although the enantioselective Pd-allylic etherification is currently studied by important research groups, few successful examples have been reported. Among them phenols have been the most studied,[23] while the aliphatic alcohols have been explored less.[11f,24] The reaction of Pd/**L5e** and Pd/**L5d** with several substituted benzylic alcohols also proceeded smoothly to afford both enantiomers of the desired products in high yields (Table 4, entries 17-20). Furthermore, the enantioselectivity was seen to be influenced by the electronic nature of the substituted benzylic alcohol. The highest enantioselectivity (ee's up to 94%, entry 19) was obtained when the benzylic alcohol contained an electron deficient *para* CF_3 substituent, and the selectivity diminished gradually as the substituent was more electron-rich. This behavior is opposite to that observed in the etherification reaction with Pd/(*S*,*R*p)-FerroNPS catalytic system,[18c] which is one of the few Pd-catalysts that has been specially designed for this purpose and successfully applied. The Hammet plot of this electronic effect shows a linear free-energy relationship (Figure 4; ρ = 1.78) between enantioselectivity and the electronic character of the substituent.[25] This plot could therefore be used for predicting the enantioselectivity of asymmetric allylic substitution when *para*-substituted benzylic alcohols are used.

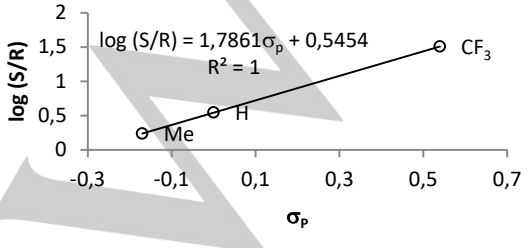


Figure 4. Hammet plot for the Pd-catalyzed allylic etherification of **S1** with ligand **L5e**

The scope of Pd/**L5d**-**L5e** catalytic systems was further studied by using other linear substrates (Equation 2) with different electronic (*rac*-1,3-di(4-tolyl)-3-acetoxyprop-1-ene **S3**, *rac*-1,3-di(4-bromophenyl)-3-acetoxyprop-1-ene **S4** and *rac*-1,3-di(3-methoxyphenyl)-3-acetoxyprop-1-ene **S5**) and steric requirements (*rac*-1,3-di(2-tolyl)-3-acetoxyprop-1-ene **S6**, *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S7** and *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S8**) than substrate **S1** (Figure 5, compounds **27**-**36**). The results using **S3** followed the same trend than for **S1**. High enantioselectivities, in both enantiomers of the substituted product, were obtained in the alkylation of **S3** using several malonates, including those α-substituted with allyl- and butenyl-groups (ee's up to 99%, compounds **27**-**29**). In addition, catalytic performance is unaffected by the presence of electronwithdrawing groups at the *para* position as well as by the introduction of *meta*- and *orto*-substituents at the phenyl groups. Thus, high enantioselectivities were also achieved for the allylic alkylation of substrates **S4**-**S6** (Figure 5; ee's up to 94%, compounds **30**-**32**). The allylic substitution of substrate **S7**, which is less sterically demanding and is substituted much less enantioselectively than **S1**,[26] also proceeded smoothly (compounds **33**-**35**). Although enantioselectivity depended on the steric properties of the nucleophile, we were pleased to see that for the more challenging α-substituted malonates enantioselectivities were higher (compounds **34**-**35**, ee up to 81%) than for the standard dimethyl malonate. Finally, we were pleased to find out that Pd/**L5d**-**e** also provided high enantioselectivity, in both enantiomers of the alkylated product, of the more demanding substrate **S8** (95% ee) which usually reacts with lower yields and enantioselectivities than model substrate **S1**.

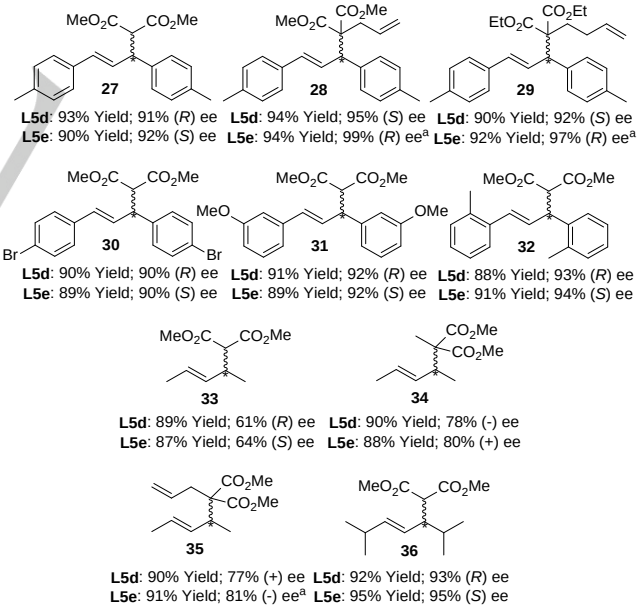
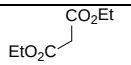
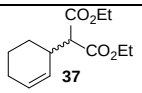
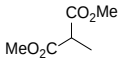
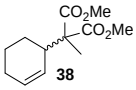
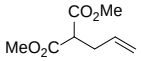
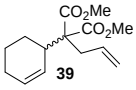
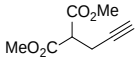
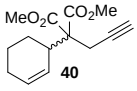
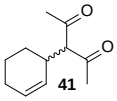
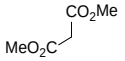
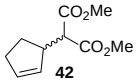
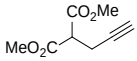
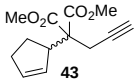
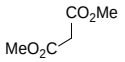
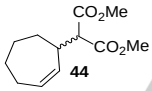
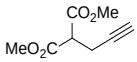
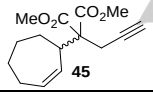


Figure 5. Pd-allylic substitution of **S3**-**S8** using several C-nucleophiles. Full conversions were achieved in all cases. 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, CH_2Cl_2 as solvent, ligand (1 mol%), 23 °C, 18 h. [a] Reaction carried out at 5 °C for 24 h

Finally, the good performance of Pd/**L5e** was also seen in the allylic substitution of cyclic substrates using a range of C-nucleophiles, including the less studied α-substituted malonates and β-diketones. For substrate **S2**, enantioselectivities were as high as those obtained with dimethyl malonate (Table 5, entries 1-5, products **37**-**41**). Even more interesting is the high

enantioselectivity achieved using other cyclic substrates with different ring size (*rac*-acetoycyclopentene **S9** and *rac*-acetoxycycloheptene **S10**). The enantiocontrol was high in both cases, even in the allylic substitution of *rac*-3-acetoxycyclopentene (products **42** and **43**), which is usually alkylated much less enantioselectively than 6- and 7-membered cyclic substrates.

Table 5. Allylic substitution of cyclic substrates **S2**, **S6** and **S7** with other several C-nucleophiles using the Pd/**L5e** catalytic system.[a]

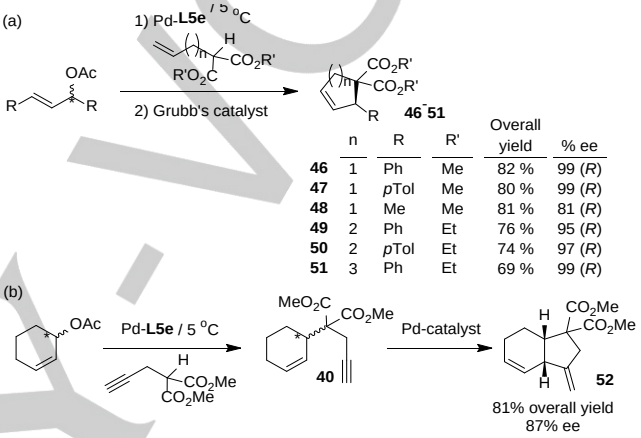
Entry	Substrate	Nucleophile	Product	% Yield[b]	% ee[c]
1	**S2**		 **37**	89	83 (*S*)
2	**S2**		 **38**	91	86 (+)
3	**S2**		 **39**	94	90 (-)
4	**S2**		 **40**	93	87 (*S*)
5	**S2**		 **41**	92	76 (-)
6	**S6**		 **42**	88	75 (-)
7	**S6**		 **43**	92	84 (*S*)
8	**S7**		 **44**	93	91 (*S*)
9	**S7**		 **45**	94	93 (*S*)

[a] Reactions were run at 5 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol%), CH_2Cl_2 as solvent, ligand (1 mol%), BSA (3 eq), KOAc (3 mg). [b] Full conversions were achieved after 24 h. [c] Enantiomeric excess determined by chiral HPLC or GC.

In summary, by a theoretically-guided optimization of the crucial stereodefining moieties in this new family of modular amino-phosphite ligand library, we have been able to identified one of the very few catalytic systems that can create new C-C, C-N and C-O bonds, in a number of substrate types, with different electronic and steric proprieties, using a wide range of nucleophiles, in high activities and enantioselectivities.

2.4. Synthetic applications of the allylic substitution compounds. Preparation of chiral carbocycles

Asymmetric allylic alkylation (AAA) is a relevant method for creating chiral C-C and C-heteroatom bonds. Furthermore, functionalized substrates (see for example the above compounds **17**-**19**, **28**-**29** and **35**, formed by Pd-AAA with nucleophiles containing allyl-, butenyl- and pentenyl groups) open up new pathways to easily build up more complex molecules. To illustrate these aspects, we have prepared a range of chiral carbocycles (**46**-**51**) by simple tandem reactions involving allylic substitution of the substrate and ring-closing metathesis reactions (Scheme 2a) or the sequential allylic substitution and cycloisomerization of 1,6-enyne (Scheme 2b) reactions. Thus, the allylic substitution compounds (**17**-**19**, **28**-**29** and **35**; Equation 2), bearing a terminal alkene, can undergo clean ring-closing metathesis with no loss in enantiomeric excess. A range of 5-, 6- and 7-membered carbocycles with different R substituents (R= Me, Ph, *p*Tol) were therefore prepared in good yields and high enantioselectivities (compounds **46**-**51**; Scheme 2a). Also, the carbobicycle hyndrindane **52** is obtained by cycloisomerization of the 1,6-enyne **40**, produced from the AAA of **S2** with dimethyl propargylmalonate, using the methodology described by Uozumi and coworkers (Scheme 2b).

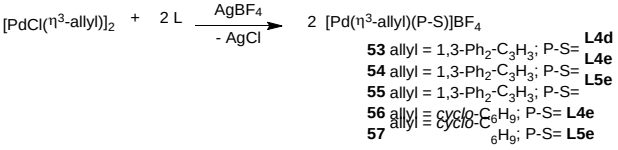


	n	R	R'	Overall yield	% ee
46	1	Ph	Me	82 %	99 (*R*)
47	1	*p*Tol	Me	80 %	99 (*R*)
48	1	Me	Me	81 %	81 (*R*)
49	2	Ph	Et	76 %	95 (*R*)
50	2	*p*Tol	Et	74 %	97 (*R*)
51	3	Ph	Et	69 %	99 (*R*)

Scheme 2. Preparation of chiral carbocycles via sequential allylic substitution of functionalized olefins/cyclation reactions

2.5. NMR study of key Pd-η^3-allyl intermediates

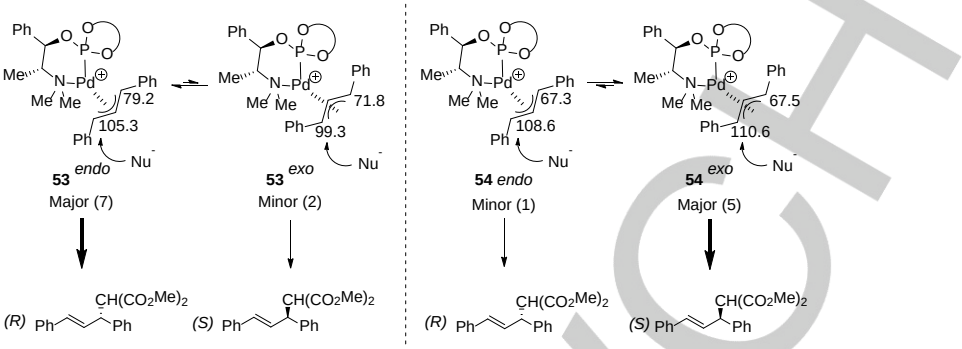
Our DFT studies have shown that enantioselectivity is determined during the nucleophilic attack (see above section 2.2). Consequently structural elucidation of the Pd-allyl intermediates and the determination of their relative reactivity towards the nucleophile are essential to understand their catalytic behavior. For this purpose we studied the Pd-η^3-allyl compounds **53**-**57** $[Pd(\eta^3\text{-allyl})(P\text{-}S)]BF_4$ (P-S = **L4**-**L6d**-**e**) to obtain further insight into how ligand parameters affect catalytic performance (Scheme 3). These ionic palladium complexes, which contain 1,3-diphenyl or cyclohexenyl allyl groups, were prepared using the previously reported method from the corresponding Pd-allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate (Scheme 3).[27] The complexes were characterized by elemental analysis and by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The spectral assignments were based on information from ^1H-^1H, ^{31}P-^1H and ^{13}C-^1H correlation measurements in combination with ^1H-^1H NOESY experiments. Unfortunately, we were unable to obtain crystal of sufficient quality to perform X-ray diffraction measurements.



Scheme 3. Preparation of $[Pd(\eta^3\text{-allyl})(P\text{-}S)]BF_4$ complexes **53**-**57**

2.5.1. Palladium 1,3-diphenyl-allyl complexes

The VT-NMR study (30 ºC to -80 ºC) of Pd-allyl intermediates **53** and **54**, which respectively contains ephedrine-based ligands **L4d** and **L4e**, showed a mixture of two isomers in equilibrium at a ratio of 7:2 and 1:5, respectively.[28] Both isomers were unambiguously assigned by NMR to the two *syn*/*syn* Pd-η^3-*endo* and *exo* isomers (Scheme 4).



Scheme 4. Diastereoisomer Pd-allyl intermediates for **S1** with ligands **L4d** and **L4e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown

In all cases, the NOE indicated interactions between the two terminal protons of the allyl group, which clearly indicates a *syn*/*syn* disposition (Figure 6). In addition, for the major isomer of **53** and the minor isomer of **54**, one of the methyl substituents of the amino group (the one that shows NOE interaction with the hydrogen attached to C-2) showed NOE between the terminal allyl proton *trans* to the phosphite moiety, while this interaction appeared with the central allyl proton in the minor isomer **53** and major isomer of **54** (Figure 6). Moreover, the other methyl substituent of the amino group (the one that shows NOE with the hydrogen attached to C-1) also shows NOE interaction with the central allyl proton in major isomer **53** and the minor isomer of **54**, while this interaction appears with the terminal allyl proton *trans* to the phosphite moiety for minor and major isomers of **54** and **54**, respectively. Finally, the minor isomer of **53** and major isomer of **54** also showed NOE interactions between the terminal allyl proton *trans* to the amino group with one of the *tert*-butyl substituents at the biaryl phosphite moiety (the one that shows NOE contacts with the hydrogen attached to C-1). These interactions can be explained by assuming a *syn*/*syn* endo disposition for major and minor isomers of **53** and **54**, and a *syn*/*syn* exo disposition for minor and major isomers of **53** and **54** (Scheme 4). Although the population of the Pd-allyl intermediates obtained by DFT calculations is different than those find by NMR, the general trend is reproduced well. Thus, while for Pd/**L4d** the major isomer is Pd-η^3-*endo*, for Pd-**L4e** the major isomer is Pd-η^3-*exo*.

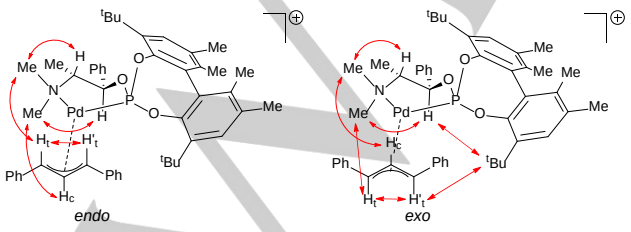
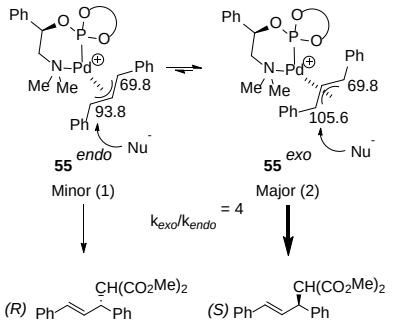


Figure 6. Relevant NOE contacts from the NOESY experiment of [Pd(η^3-1,3-diphenylallyl)(**L4d**)]BF_4 (**53**) isomers are shown as example. The same NOE contacts were observed for [Pd(η^3-1,3-diphenylallyl)(**L4e**)]BF_4 (**54**) isomers

In all isomers, the carbon NMR chemical shifts indicate that the most electrophilic allyl carbon terminus is *trans* to the phosphite moiety (Scheme 4). Assuming that the nucleophilic attack takes place at the more electrophilic allyl carbon terminus,[1] and in line with the DFT calculations, the stereochemical outcome of the reaction is not fully controlled by the population of the Pd-allyl intermediates (note that the diastereomeric excesses differ from the enantiomeric excesses). So, the relative electrophilicity of the terminal allylic carbons of each isomer plays an important role and have to been taken into account. In this respect, Pd/**L4d** catalyst shows higher electronic differentiation between the more electrophilic allylic terminal carbon atoms of both isomers ($\Delta(\delta^{13}C)$= 6 ppm) than in Pd/**L4e** ($\Delta(\delta^{13}C)$= 2 ppm). This higher electronic differentiation makes the major isomer of Pd/**L4d** to react faster than the major isomer of Pd/**L4e** and fully accounts for the higher enantioselectivity achieved with Pd/**L4d** than with Pd/**L4e**.

The VT-NMR study of Pd-allyl intermediate **55** containing ligand **L5e**, which differs from previous Pd/**L4d**-**e** catalysts in that the methyl substituent of the ephedrine ligand backbone has been removed, also had a mixture of two *syn*/*syn* Pd-η^3-*endo* and *exo* isomers, at a ratio 1:2 (Scheme 5).



Scheme 5. Diastereoisomer Pd-allyl intermediates for **S1** with ligand **L5e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown

Also, the most electrophilic allyl carbon terminus was *trans* to the phosphite moiety. However, an important difference between complexes **53** and **54** is the higher electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers in complex **555** ($\Delta(\delta^{13}C)$= 11 ppm) than in previous complexes **53** and **54** ($\Delta(\delta^{13}C)$= 6 and 2 ppm, respectively). This higher electronic differentiation may explain the higher enantioselectivity obtained with Pd/**L5e** than with Pd/**L4d**-**e**. Accordingly, the reactivity of the Pd-intermediates with sodium malonate at low temperature by in situ NMR indicates that the major Pd-η^3-*exo* isomer reacts 4 times faster than minor Pd-η^3-*endo* isomer (Figure 7), which fully agrees with the ee obtained experimentally.

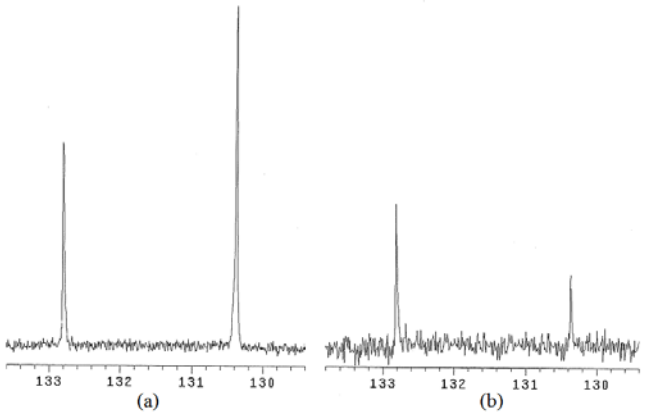


Figure 7. ^{31}P-{^1H}NMR spectra of [Pd(η^3-1,3-diphenylallyl)(**L5e**)]BF4 (**55**) in CD_2Cl_2 at -80 ºC (a) before the addition of sodium malonate and (b) after the addition of sodium malonate

2.5.2. Palladium 1,3-cyclohexenyl-allyl complexes

Finally, in an attempt to provide further information about the positive effect on enantioselectivity observed in the allylic substitution of the unhindered cyclic substrate **S2** when the methyl substituent of the ephedrine backbone was removed, we also studied the Pd-1,3-cyclohexenyl-allyl intermediate **56**, which contains ephedrine-based amino-phosphite ligand **L4e**, and compared it with its related amino-phosphite counterpart (Pd/**L5e**). The VT-NMR (35 °C to –80 °C) of Pd intermediates **56** and **57** showed a mixture of the two possible isomers at a ratio of 10:1 and 20:1, respectively (Scheme 6). The major isomers were unambiguously assigned by NOE to Pd-η^3-*endo* isomers (Figure 8). In both cases, the NOE indicates interactions between the central allyl proton and one of the methyl substituents of the amino group (the one that shows NOE with the hydrogen attached to C-1 of the ligand backbone) and with one of the *tert*-butyl substituents at the biaryl phosphite moiety (the one that also shows NOE contact with the hydrogen attached to C-1) (Figure 8). The carbon NMR chemical shifts indicated that the most electrophilic allylic terminus carbon is *trans* to the phosphite moiety. Assuming that the nucleophilic attack takes place at the most electrophilic allyl carbon terminus, and taking into account the observed stereochemical outcome of the reaction (70% (*S*) for complex **56** and 82% (*S*) for **57**), and the fact that the enantiomeric excesses of alkylation product **13** are different from the diastereoisomeric excesses of the Pd-intermediates (de = 81% (*S*) for **56** and de= 90% (*S*) for **57**), the minor isomers must react slightly faster than major isomers. This is in agreement with the slightly higher electrophilicity of the allylic terminus carbon *trans* to the phosphite moiety located at the minor isomers (i.e. $\Delta(\delta^{13}C)$ around 1 ppm for Pd/**L4e**). The lower enantioselectivities obtained with Pd/ephedrine-based amino-phosphite ligand **L4e** than with related Pd/**L5e** catalytic system can therefore be attributed to the increase in the relative amount of fast reacting isomer *exo* with respect to isomer *endo* compared with the population of *endo* and *exo* isomers in Pd/**L5e**.

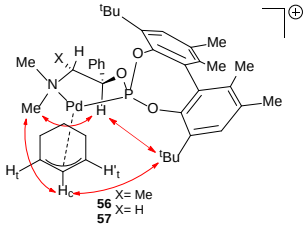
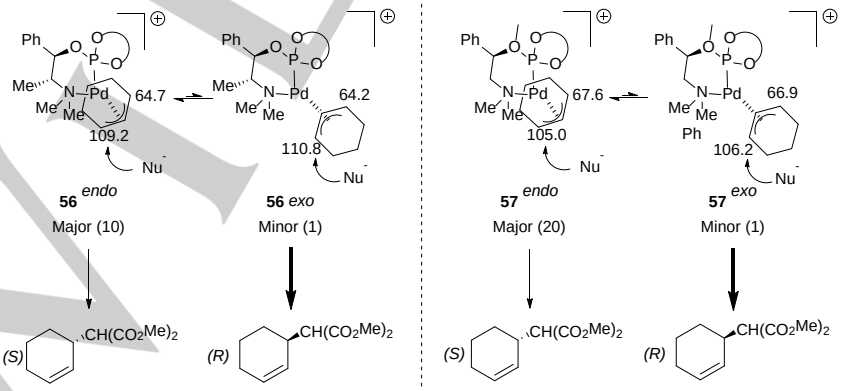


Figure 8. Relevant NOE contacts from the NOESY experiments for the major isomers of [Pd(η^3-1,3-cyclohexenylallyl)(L)]BF_4 (**56** and **57**; L= **L4e** and **L5e**, respectively)



Scheme 6. Diastereoisomer Pd-allyl intermediates for **S2** with ligands **L4e** and **L5e**. The relative amounts of each isomer are shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown

3. Conclusions

A new library of modular amino-phosphite ligands has been successfully tested in the asymmetric Pd-catalyzed allylic substitution of substrates with different steric and electronic requirements applying a large variety of nucleophiles. These ligands, which are prepared in a few steps from readily available enantiopure aminoalcohols, include the benefits of a high stability of the amine moiety and the additional control provided by both the adaptability of the chiral cavity due to the biaryl-phosphite groups and the flexibility of the chiral pocket through a highly modular ligand scaffold. Other advantages of these ligands are that they are solid, stable to air and other oxidizing agents and therefore easy to handle and can be manipulated and stored in air. In simple two or three steps, several ligand parameters have been tuned to maximize the catalyst performance. Enantioselectivity is mainly controlled by the substituents/configuration at the biaryl phosphite moiety and by the amine substituents, while the configuration of the ephedrine-backbone affects less. Theoretically-guided optimization based on DFT studies allowed rationalizing the modifications required in the ligand for improving selectivity. Their results led to identifying one of the very few catalytic systems that can create C-C, C-N and C-O bonds in substrates with a variety of electronic and steric proprieties, using a wide range of nucleophiles, in high yields and enantioselectivities (ee's up to 99%). Further studies on the Pd-π-allyl intermediates provided a deep understanding of the effect of ligand parameters on the origin of enantioselectivity. Potential applications of the new Pd-amino-phosphite catalysts were demonstrated by the synthesis of a range of chiral 5-, 6- and 7-carbocycles by simple tandem reactions with no loss in the enantioselectivity. These results open up the asymmetric Pd-catalyzed allylic substitution of several substrate types with a wide range of nucleophiles to the potential effective use of readily available and highly modular amino-phosphite ligands.

4. Experimental section

4.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphorochloridites were easily prepared in one step from the corresponding biaryls.[29] Enantiopure amino-alcohol compounds **5**-**8**[12] and oxazolidine **9**[13] were prepared as previously described. Racemic substrates **S1**-**S10** were prepared as previously reported.[30] $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mu\text{-}Cl)]$[31] and $[Pd(\eta^3\text{-cyclohexenyl})(\mu\text{-}Cl)]_2$[32] were prepared as previously described. Carbocyclic compound **49** was prepared following the methodology described by Uozumi et al.[33] ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. ^1H, ^{13}C and ^{31}P assignments were made on the basis of ^1H-^1H gCOSY, ^1H-^{13}C gHSQC and ^1H-^{31}P gHMBC experiments.

4.2. Preparation of (1*S*,2*R*)-2-(*tert*-butyl(methyl)amino)-1-phenylpropan-1-ol 10

Compound **9** (1g, 4.88 mmol) was dissolved in dry ether (20 mL). The solution was stirred in an ice-bath for 5 minutes. Then, MeMgBr (3 M in diethyl ether) (4.96 mL, 14.64 mmol) was added dropwise. The solution was warmed up to reflux and the reaction was kept at that temperature for 8 hours. The reaction was quenched with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the removal of solvents provided **10** as a yellow-pale solid. Yield: 1.0 g (93%). ^1H NMR ($CDCl_3$): δ = 0.94 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.06 (s, 9H, ^{t}Bu), 2.0 (s, 3H, CH_3-N), 3.35 (m, 1H, CH-N), 4.50 (m, 1H, CH-O), 7.21-7.32 (m, 4H, CH=). ^{13}C NMR ($CDCl_3$): δ = 12.9 (CH_3), 27.1 (CH_3, ^{t}Bu), 30.9 (CH_3, NMe), 55.1 (C, ^{t}Bu), 55.2 (CH-N), 75.3 (CH-O), 126.7 (CH=), 126.8 (CH=), 127.5 (CH=), 143.1 (C).

4.3. Preparation of (1*S*,2*R*)-2-(methyl(2-phenylpropan-2-yl)amino)-1-phenylpropan-1-ol 11

Compound **9** (1g, 4.88 mmol) was dissolved in dry THF (20 mL). The solution was stirred in an ice-bath for 5 minutes. Then, PhMgBr (1.M in THF) (14.7 mL, 14.64 mmol) was added dropwise. Then, the reaction was warmed up to reflux and the reaction was kept at that temperature for 8 hours. The reaction was quenched with saturated NH_4Cl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over MgSO4. The organic solvents were removed and the crude was purified by silica flash chromatography (AcOEt:light petroleum:NEt_3 6:2:0.1) to afford **11** as a white solid. Yield: 1.2 g (87%). ^1H NMR ($CDCl_3$): δ = 0.95 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.1 Hz), 1.34 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.13 (s, 3H, CH_3-N), 3.20 (m, 1H, CH-N), 4.50 (d, 1H, CH-O, $^3J_{H\text{-}H}$ = 4.8 Hz), 7.10-7.38 (m, 10H, CH=). ^{13}C NMR ($CDCl_3$): δ = 11.7 (CH_3), 24.8 (CH_3), 25.6 (CH_3), 30.9 (CH_3, NMe), 56.4 (C, CMe_2Ph), 61.0 (CH-N), 77.6 (CH-O), 126.2 (CH=), 126.3 (CH=), 126.4 (CH=), 126.8 (CH=), 127.7 (CH=), 127.9 (CH=), 143.3 (C), 149.0 (C).

4.4. General procedure for the preparation of amino-phosphite ligands L1-L6a-g

Phosphorochloridite (1.1 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.18 mL, 2.3 mmol) was added. Amino-alcohol (1 mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (5 mL), to which pyridine (0.18 mL, 2.3 mmol) was added. The phosphorochloridite solution was transferred slowly to the solution of amino-alcohol. The reaction mixture was stirred at room temperature for 90 hours (ligands **L1**, **L4**-**L6a**-**g**) or 15 hours (ligands **L2**-**L3a**-**g**), and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (toluene/NEt_3 100:1) to produce the corresponding ligand as white solid.

L1a: Yield: 303 mg (49%). ^{31}P NMR (C_6D_6): δ = 150.5 (s). ^1H NMR (C_6D_6): δ = 0.98 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 6.8 Hz), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.3 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.14 (s, 6H, CH_3, NMe_2), 2.59 (m, 1H, CH-N), 5.55 (dd, 1H, CH-O, $^3J_{H\text{-}P}$= 8 Hz, $^3J_{H\text{-}H}$ = 4 Hz,), 7.03-7.25 (m, 7H, CH=), 7.33 (d, 1H, CH=, $^4J_{H\text{-}H}$ = 2.4 Hz), 7.37 (d, 1H, CH=, $^4J_{H\text{-}H}$ = 2.4 Hz), 7.58 (d, 1H, CH=, $^4J_{H\text{-}H}$ = 2.0 Hz), 7.61 (d, 1H, CH=, $^4J_{H\text{-}H}$ = 2.8Hz). ^{13}C NMR (C_6D_6): δ = 8.4 (CH_3), 28.8 (CH_3,^{t}Bu), 28.9 (CH_3, ^{t}Bu), 29.9 (CH_3,^{t}Bu), 30.2 (CH_3,^{t}Bu), 33.2 (C, ^{t}Bu), 34.1 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 40.9 (CH_3, NMe), 41.0 (CH_3, NMe), 64.7 (d, CH-N, $^3J_{C\text{-}P}$= 9.2 Hz), 76.6 (d, CH-O, $^2J_{C\text{-}P}$ = 9.2 Hz), 122.6-145.4 (aromatic carbons). TOF-MS (ESI+): m/z = 618.4101, calcd. for $C_{39}H_{56}NO_3P$ $[M+H]^+$: 618.4071

L1b: Yield: 170 mg (30%). ^{31}P NMR (C_6D_6): δ = 150.2 (s). ^1H NMR (C_6D_6): δ = 1.00 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 6.4 Hz), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 2.14 (s, 6H, CH_3, NMe_2), 2.57 (m, 1H, CH-N), 3.33 (s, 3H, CH_3, OMe), 3.34 (s, 3H, CH_3, OMe), 5.5 (dd, 1H, CH-O, $^3J_{H\text{-}P}$= 8.0 Hz, $^3J_{H\text{-}H}$ = 4.0 Hz), 6.67 (d, 1H, CH=, $^4J_{H\text{-}H}$ = 2.8 Hz), 6.72 (d, 1H, CH=, $^4J_{H\text{-}H}$ = 3.2 Hz), 7.01-7.26 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 9.5 (CH_3), 30.6 (CH_3,^{t}Bu), 30.7 (CH_3, ^{t}Bu), 35.1(C, ^{t}Bu), 35.2 (C, ^{t}Bu), 41.9 (CH_3, NMe), 42.1 (CH_3, NMe), 54.7 (CH_3, OMe), 65.8 (CH-N), 77.6 (d, CH-O,

$^{2}J_{C\text{-}P}$ = 9.9 Hz), 112.6-155.9 (aromatic carbons). TOF-MS (ESI+): m/z = 566.3028, calcd. for $C_{33}H_{44}NO_5P$ $[M+H]^+$: 566.3030

L1c: Yield: 194 mg (32%). ^{31}P NMR (C_6D_6): δ = 152.4 (s). ^{1}H NMR (C_6D_6): δ = 0.33 (s, 9H, CH_3-Si), 0.44 (s, 9H, CH_3-Si), 0.95 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$ = 6.8 Hz), 2.10 (s, 6H, CH_3, NMe_2), 2.68 (m, 1H, CH-N), 5.45 (dd, 1H, CH-O, $^{3}J_{H\text{-}P}$= 8.8 Hz, $^{3}J_{H\text{-}H}$ = 5.6 Hz), 7.03-7.46 (m, 11H, CH=). ^{13}C NMR (C_6D_6): δ = 0.0 (CH_3-Si), 0.1 (CH_3-Si), 9.7 (CH_3), 42.1 (CH_3, NMe_2), 65.8 (d, CH-N, $^{3}J_{C\text{-}P}$= 2.3 Hz), 78.1 (d, CH-O, $^{2}J_{C\text{-}P}$ = 4.8 Hz), 124.7-155.2 (aromatic carbons). TOF-MS (ESI+): m/z = 538.2354, calcd. for $C_{29}H_{40}NO_3PSi_2$ $[M+H]^+$: 538.2357

L1d: Yield: 188 mg (32%). ^{31}P NMR (C_6D_6): δ = 141.1 (s). ^{1}H NMR (C_6D_6): δ = 1.12 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$ = 7.2 Hz), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.16 (s, 6H, CH_3, NMe_2), 2.82 (m, 1H, CH-N), 5.4 (dd, 1H, CH-O, $^{3}J_{H\text{-}P}$= 8.0 Hz, $^{3}J_{H\text{-}H}$ = 5.6 Hz), 7.0-7.3 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 8.1 (CH_3), 15.1 (CH_3), 15.3 (CH_3), 19.0 (CH_3), 19.1 (CH_3), 29.9 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.4 Hz), 30.4 (CH_3, ^{t}Bu), 33.2 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 40.5 (CH_3, NMe), 40.6 (CH_3, NMe), 63.9 (d, CH-N, $^{3}J_{C\text{-}P}$= 6.1 Hz), 77.3 (d, CH-O, $^{2}J_{C\text{-}P}$ = 6.2 Hz), 124.3-144.6 (aromatic carbons). TOF-MS (ESI+): m/z = 562.3452, calcd. for $C_{35}H_{48}NO_3P$ $[M+H]^+$: 562.3445

L1e: Yield: 182 mg (31%). ^{31}P NMR (C_6D_6): δ = 144.9 (s). ^{1}H NMR (C_6D_6): δ = 0.78 (d, CH_3, 3H, $^{3}J_{H\text{-}H}$ = 6.4 Hz), 1.41 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.11 (s, 6H, CH_3, NMe_2), 2.37 (m, 1H, CH-N), 5.41 (dd, 1H, CH-O, $^{3}J_{H\text{-}P}$= 8.0 Hz, $^{3}J_{H\text{-}H}$ = 4.0 Hz), 6.95-7.22 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 9.7 (CH_3), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1(CH_3), 30.9 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 4.6 Hz), 31.2 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.7 (C, ^{t}Bu), 42.0 (CH_3, NMe), 42.3 (CH_3, NMe), 62.2 (CH-N), 77.2 (d, CH-O, $^{2}J_{C\text{-}P}$ = 10.7 Hz), 125.3-146.2 (aromatic carbons). TOF-MS (ESI+): m/z = 562.3448, calcd. for $C_{35}H_{48}NO_3P$ $[M+H]^+$: 562.3445

L1f: Yield: 439 mg (69%). ^{31}P NMR (C_6D_6): δ = 155.8 (s). ^{1}H NMR (C_6D_6): δ = 0.40 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 0.72 (d, CH_3, 3H, $^{3}J_{H\text{-}H}$ = 6.8 Hz), 1.96 (s, 6H, CH_3, NMe_2), 2.50 (m, 1H, CH-N), 5.43 (dd, 1H, CH-O, $^{3}J_{H\text{-}P}$= 8.4 Hz, $^{3}J_{H\text{-}H}$ = 4.8 Hz), 6.82-7.4 (m, 5H, CH=), 7.4 (d, 1H, CH=, $^{3}J_{H\text{-}H}$ = 8.4Hz), 7.70 (d, 1H, CH=, $^{3}J_{H\text{-}H}$ = 8.0 Hz), 7.8 (d, 1H, CH=, $^{3}J_{H\text{-}H}$ = 8.4 Hz), 8.1 (s, 1H, CH=), 7.9 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ = -0.4 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$= 4.6 Hz), -0.1 (CH_3, $SiMe_3$), 9.3 (CH_3), 41.8 (CH_3, NMe_2), 66.0 (CH-N), 77.5 (d, CH-O, $^{2}J_{C\text{-}P}$ = 5.3 Hz), 122.8-152.6 (aromatic carbons). TOF-MS (ESI+): m/z = 638.2673, calcd. for $C_{37}H_{44}NO_3PSi_2$ $[M+H]^+$: 638.2670

L1g: Yield: 400 mg (63%). ^{31}P NMR (C_6D_6): δ = 148.5 (s). ^{1}H NMR (C_6D_6): δ = 0.51 (s, 9H, CH_3, $SiMe_3$), 0.52 (s, 9H, CH_3, $SiMe_3$), 1.09 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$ = 6.4 Hz), 2.05 (s, 6H, CH_3, NMe_2), 2.87 (m, 1H, CH-N), 5.35 (dd, 1H, CH-O, $^{3}J_{H\text{-}P}$= 8.4 Hz, $^{3}J_{H\text{-}H}$ = 6.5 Hz), 6.7-7.3 (m, 6H, CH=), 7.68 (m, 2H, CH=), 7.95 (s, 1H; CH=), 8.05 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ = -0.2 (d, CH_3, $SiMe_3$, $J_{C\text{-}P}$ = 4.6 Hz), -0.1 (CH_3, $SiMe_3$), 9.2 (CH_3), 41.3 (CH_3, NMe_2), 64.3 (d, CH-N, $^{3}J_{C\text{-}P}$= 4.6 Hz), 78.9 (d, CH-O, $^{2}J_{C\text{-}P}$ = 2.3 Hz), 122.4-152.3 (aromatic carbons). TOF-MS (ESI+): m/z = 638.2669, calcd. for $C_{37}H_{44}NO_3PSi_2$ $[M+H]^+$: 638.2670

L2a: Yield: 330 mg (50%). ^{31}P NMR (C_6D_6): δ = 148.4 (s). ^{1}H NMR (C_6D_6): δ = 0.83 (s, 9H, CH_3, ^{t}Bu, $N^{t}Bu$), 1.21 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.4 Hz), 1.31 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 9H,CH_3, ^{t}Bu), 1.56 (s, 9H, CH_3, ^{t}Bu), 1.61 (s, 9H, CH_3, ^{t}Bu), 2.11 (s, 3H, NMe), 3.4 (m, 1H, CH-N), 5.25 (m, 1H, CH-O), 7.0-7.2 (m, 6H, CH=), 7.37 (m, 2H, CH=), 7.60 (d, 1H, CH=, $^{4}J_{H\text{-}H}$= 2Hz). ^{13}C NMR (C_6D_6): δ = 12.8 (CH_3), 26.8 (CH_3, ^{t}Bu), 29.3 (NMe), 31.0 (CH_3, ^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 54.1 (C, ^{t}Bu, $N^{t}Bu$), 56.6 (d, CH-N, $^{3}J_{C\text{-}P}$ = 3.1 Hz), 81.3 (d, CH-O, $^{2}J_{C\text{-}P}$= 5.43 Hz), 123.8-146.7 (aromatic carbons). TOF-MS (ESI+): m/z = 660.5438, calcd. for $C_{42}H_{62}NO_3P$ $[M+H]^+$: 660.4540

L2d: Yield: 422.6 mg (70%). ^{31}P NMR (C_6D_6): δ = 141.1 (s). ^{1}H NMR (C_6D_6): δ = 0.84 (s, 9H, CH_3, ^{t}Bu, $N^{t}Bu$), 2.15 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.4 Hz), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 9H,CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3), 1.71 (s, 3H, CH_3,) , 2.04 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.16 (s, 3H, NMe), 3.4 (m, 1H, CH-N), 5.1 (m, 1H, CH-O), 7.0-7.3 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 12.7 (CH_3), 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 26.8 (CH_3, ^{t}Bu), 29.4 (NMe), 31.1 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$ = 5.3 Hz), 31.4 (CH_3, ^{t}Bu), 34.4(C, ^{t}Bu), 34.7 (C, ^{t}Bu), 54.2 (C, ^{t}Bu, $N^{t}Bu$), 56.4 (d, CH-N, $^{3}J_{C\text{-}P}$ = 5.6 Hz), 81.6 (d, CH-O, $^{2}J_{C\text{-}P}$= 3.0 Hz), 125.3-145.6 (aromatic carbons). TOF-MS (ESI+): m/z = 604.3917, calcd. for $C_{39}H_{56}NO_3P$ $[M+H]^+$: 604.3914

L2e: Yield: 392 mg (65%). ^{31}P NMR (C_6D_6): δ = 142.9 (s). ^{1}H NMR (C_6D_6): δ = 0.60 (s, 9H, CH_3, ^{t}Bu, $N^{t}Bu$), 1.0 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.8 Hz), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H,CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.75 (s, 3H, CH_3,) , 1.95 (s, 3H, NMe), 2.0 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 3.2 (m, 1H, CH-N), 5.0 (m, 1H, CH-O), 7.0-7.45 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 13.8 (CH_3), 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 26.8 (CH_3, ^{t}Bu), 28.7 (NMe), 31.2 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$ = 5.4 Hz), 31.6 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 53.7 (C, ^{t}Bu, $N^{t}Bu$), 56.7 (d, CH-N, $^{3}J_{C\text{-}P}$ = 2.3 Hz), 80.3 (d, CH-O, $^{2}J_{C\text{-}P}$= 5.3 Hz), 125.9-145.6 (aromatic carbons). TOF-MS (ESI+): m/z = 604.3912, calcd. for $C_{39}H_{56}NO_3P$ $[M+H]^+$: 604.3914

L3a: Yield: 262 mg (37%). ^{31}P NMR (C_6D_6): δ = 148.90 (s). ^{1}H NMR (C_6D_6): δ = 1.01 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.8 Hz), 1.09 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.28 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.86 (s, 9H, CH_3, ^{t}Bu), 2.2 (s, 3H, NMe), 3.2 (m, 1H, CH-N), 5.4 (dd, 1H, CH-O, $^{3}J_{H\text{-}P}$= 9.6 Hz, $^{3}J_{H\text{-}H}$ = 4.4 Hz), 7.0-7.4 (m, 12H, CH=), 7.58 (d, 1H, CH=, $^{4}J_{H\text{-}H}$ = 2.8 Hz), 7.62 (d, 1H, CH=, $^{4}J_{H\text{-}H}$ = 2.8 Hz). ^{13}C NMR (C_6D_6): δ = 9.9 (CH_3), 22.3 (CH_3), 25.2 (CH_3), 28.9 (NMe), 29.9 (CH_3, ^{t}Bu), 30.0 (CH_3, ^{t}Bu), 30.1 (CH_3, ^{t}Bu), 30.2 (CH_3, ^{t}Bu), 33.2 (C, ^{t}Bu), 34.2(C, ^{t}Bu), 34.3 (C, ^{t}Bu), 56.4 (d, CH-N, $^{3}J_{C\text{-}P}$ = 3.8 Hz), 59.8 (C, N-CMe_2Ph), 81.2 (d, CH-O, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 122.7-148.7 (aromatic carbons). TOF-MS (ESI+): m/z = 722.4694, calcd. for $C_{47}H_{64}NO_3P$ $[M+H]^+$: 722.4697

L3d: Yield: 244 mg (37%). ^{31}P NMR (C_6D_6): δ = 143.4 (s). ^{1}H NMR (C_6D_6): δ = 1.01 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.9 Hz), 1.03, (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.8 (s, 3H, CH_3), 1.91 (s, 3H, NMe), 2.06 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.3 (m, 1H, CH-N), 5.3 (m, 1H, CH-O), 7.0-7.3 (m, 12H, CH=). ^{13}C NMR (C_6D_6): δ = 10.9 (CH_3), 15.2 (CH_3), 15.4 (CH_3), 19.0 (CH_3) 23.4 (CH_3), 24.7 (CH_3), 28.2 (NMe), 30.2 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.3 Hz), 30.5 (CH_3, ^{t}Bu), 33.4 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 56.3 (d, CH-N, $^{3}J_{C\text{-}P}$= 2.3 Hz), 59.4 (C, N-CMe_2Ph), 80.7 (d, CH-O, $^{2}J_{C\text{-}P}$ = 6.1 Hz), 124.3-148.8 (aromatic carbons). TOF-MS (ESI+): m/z = 666.4068, calcd. for $C_{43}H_{56}NO_3P$ $[M+H]^+$: 666.4071

L3e: Yield: 331.0 mg (50%). ^{31}P NMR (C_6D_6): δ = 148.90 (s). ^{1}H NMR (C_6D_6): δ = 1.02 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$= 6.8 Hz), 1.03 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.59 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 9H, CH_3, ^{t}Bu), 1.71 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.01 (s, 3H, CH_3, NMe), 2.06 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.31 (m, 1H, CH-N), 5.3 (m, 1H, CH-O), 7.0-7.4 (m, 12H, CH=). ^{13}C NMR (C_6D_6): δ = 11.9 (CH_3), 16.2 (CH_3), 16.5 (CH_3), 20.1 (CH_3) 24.6 (CH_3), 25.7 (CH_3), 29.2 (NMe), 31.2 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 5.3 Hz), 31.5 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.8(C, ^{t}Bu), 57.3 (CH-N), 60.5 (C, N-CMe_2Ph), 81.7 (d, CH-O, $^{2}J_{C\text{-}P}$ = 6.1 Hz), 125.3-149.9 (aromatic carbons). TOF-MS (ESI+): m/z = 666.4072, calcd. for $C_{43}H_{56}NO_3P$ $[M+H]^+$: 666.4071

L4a: Yield: 276 mg (43%). ^{31}P NMR (C_6D_6): δ = 148.4 (s). ^{1}H NMR (C_6D_6): δ = 0.47 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$ = 6.8 Hz), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 2.09 (s, 6H, CH_3, NMe_2), 2.78 (m, 1H, CH-N), 5.06 (dd, 1H, CH-O, $^{3}J_{H\text{-}P}$ = 8 Hz, $^{3}J_{H\text{-}H}$ = 4 Hz), 6.9-7.1 (m, 7H, CH=), 7.27 (d, 1H, CH=, $^{4}J_{H\text{-}H}$ = 2.4 Hz), 7.33 (d, 1H, CH=, $^{4}J_{H\text{-}H}$ = 2.8 Hz), 7.46 (d, 1H, CH=, $^{4}J_{H\text{-}H}$ = 2.4 Hz), 7.57 (d, 1H, CH=, $^{4}J_{H\text{-}H}$ = 2.4 Hz). ^{13}C NMR (C_6D_6): δ = 7.9 (CH_3), 30.9 (CH_3,^{t}Bu), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 33.2 (C, ^{t}Bu), 34.3 (C, ^{t}Bu), 40.9 (CH_3, NMe), 41.0 (CH_3, NMe), 64.7 (d, CH-N, $^{3}J_{C\text{-}P}$= 1.5 Hz), 76.6 (d, CH-O, $^{2}J_{C\text{-}P}$ = 9.2Hz), 123.6-145.8 (aromatic carbons).

TOF-MS (ESI+): m/z = 618.4070, calcd. for $C_{39}H_{56}NO_3P$ $[M+H]^+$: 618.4071

L4d: Yield: 344 mg (61%). ^{31}P NMR (C_6D_6): δ = 139.0 (s). ^1H NMR (C_6D_6): δ = 0.62 (d, 3H, CH_3, $^3J_{H-H}$ = 7.2 Hz), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.6 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 2.15 (s, 6H, CH_3, NMe_2), 3.0 (m, 1H, CH-N), 5.1 (dd, 1H, CH-O, $^3J_{H-H}$ = 5.6 Hz, $^3J_{H-P}$= 8.0 Hz), 6.9-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 7.4 (CH_3), 15.1 (CH_3), 15.3 (CH_3), 19.0 (CH_3), 30.0 (d, CH_3, ^{t}Bu, J_{C-P}= 5.4 Hz), 30.4 (CH_3, ^{t}Bu), 33.3 (C, ^{t}Bu), 33.7 (C, ^{t}Bu), 40.1 (CH_3, NMe), 40.2 (CH_3, NMe), 63.9 (d, CH-N, $^3J_{C-P}$= 3.8 Hz), 77.6 (d, CH-O, $^2J_{C-P}$ = 10.7 Hz), 126.3-144.6 (aromatic carbons). TOF-MS (ESI+): m/z = 562.3440, calcd. for $C_{35}H_{48}NO_3P$ $[M+H]^+$: 562.3445

L4e: Yield: 324 mg (58%). ^{31}P NMR (C_6D_6): δ = 144.7 (s). ^1H NMR (C_6D_6): δ = 0.4 (d, 3H, CH_3, $^3J_{H-H}$ = 7.2 Hz), 1.29 (s, 9H, CH_3, ^{t}Bu), 1.67 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.11 (s, 6H, CH_3, NMe_2), 2.65 (m, 1H, CH-N), 4.95 (m, 1H, CH-O), 7.05-7.25 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 7.5 (CH_3), 16.2 (CH_3), 16.3 (CH_3), 19.9 (CH_3), 20.1 (CH_3), 30.9 (d , CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 31.4 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 42.0 (CH_3, NMe), 42.3 (CH_3, NMe), 64.8 (CH-N), 78.7 (d, CH-O, $^2J_{C-P}$ = 13.9 Hz), 127.3-146.7 (aromatic carbons). TOF-MS (ESI+): m/z = 562.3442, calcd. for $C_{35}H_{48}NO_3P$ $[M+H]^+$: 562.3445

L4f: Yield: 467 mg (73%). ^{31}P NMR (C_6D_6): δ = 143.7 (s). ^1H NMR (C_6D_6): δ = 0.47 (s, 9H, CH_3, $SiMe_3$) , 0.52 (s, 9H, CH_3, $SiMe_3$), 0.64 (d, 3H, CH_3, $^3J_{H-H}$ = 6.8 Hz), 2.02 (s, 6H, CH_3, NMe_2), 3.0 (m, 1H, CH-N), 5.1 (dd, 1H, CH-O, $^3J_{H-H}$ = 6.8 Hz; $^3J_{H-P}$= 10.4 Hz), 6.82-7.27 (m, 5H, CH=), 7.7 (m, 2H, CH=), 8.0 (s, 1H, CH=), 8.1 (s, 1H, CH=). ^{13}C NMR (C_6D_6): δ = -0.0 (CH_3, $SiMe_3$), 9.11 (CH_3), 41.4 (CH_3, NMe_2), 63.9 (d, CH-N, $^3J_{C-P}$= 3.1 Hz), 78.7 (CH-O), 122.0-152.8 (aromatic carbons). TOF-MS (ESI+): m/z = 638.2665, calcd. for $C_{37}H_{44}NO_3PSi_2$ $[M+H]^+$: 638.2670

L4g: Yield: 666 mg (95%). ^{31}P NMR (C_6D_6): δ = 151. (s). ^1H NMR (C_6D_6): δ = 0.4 (s, 9H, CH_3, $SiMe_3$) , 0.47 (s, 9H, CH_3, $SiMe_3$), 0.55 (d, 3H, CH_3, $^3J_{H-H}$ = 6.8 Hz), 1.85 (s, 6H, CH_3, NMe_2), 2.57 (m, 1H, CH-N), 5.2 (m, 1H, CH-O), 6.79-7.16 (m, 9H, CH=), 7.19 (d, 1H, CH=, $^4J_{H-H}$ = 8 Hz), 7.32 (d, 1H, CH=, $^4J_{H-H}$ = 8 Hz), 7.66 (d, 1H, CH=, $^4J_{H-H}$ = 8.8 Hz), 7.73 (d, 1H, CH=, $^4J_{H-H}$ = 8.4 Hz), 8.0 (s, 2H, CH=). ^{13}C NMR (C_6D_6): δ = -0.3 (d, 9H, CH_3, $SiMe_3$, J_{C-P} = 4.6 Hz), -0.1 ($SiMe_3$), 9.1 (CH_3), 41.2 (CH_3, NMe_2), 64.2 (CH-N), 78.4 (d, CH-O, $^2J_{C-P}$ = 2.3 Hz), 122.6-152.9 (aromatic carbons). TOF-MS (ESI+): m/z = 638.2669, calcd. for $C_{37}H_{44}NO_3PSi_2$ $[M+H]^+$: 638.2670

L5d: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ = 143.7 (s). ^1H NMR (C_6D_6): δ = 1.51 (s, 9H, CH_3, ^{t}Bu), 1.76 (s, 9H, CH_3, ^{t}Bu), 1.82 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 2.17 (s, 6H, CH_3, NMe_2), 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.30 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.4 Hz, $^3J_{H-H}$ = 5.6 Hz), 2.73 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.4 Hz, $^3J_{H-H}$ = 6 Hz), 5.33 (m, 1H, CH-O), 7.13-7.4 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 16.1 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 4.6 Hz), 31.3 (CH_3, ^{t}Bu), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 45.5 (CH_3, NMe), 45.6 (CH_3, NMe), 67.6 (CH_2-N), 75.2 (d, CH-O, $^2J_{C-P}$ = 13.6 Hz), 125.3-146.3 (aromatic carbons). TOF-MS (ESI+): m/z = 548.3287, calcd. for $C_{34}H_{46}NO_3P$ $[M+H]^+$: 548.3288

L5e: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ = 138.1 (s). ^1H NMR (C_6D_6): δ = 1.44 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.65 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.98 (s, 6H, CH_3, NMe_2), 2.07 (s, 3H, CH_3), 2.1(s, 3H, CH_3), 2.43 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.4 Hz, $^3J_{H-H}$ = 5.6 Hz), 2.85 (dd, 1H, CH_2, $^2J_{H-H}$ = 12.4 Hz, $^3J_{H-H}$ = 6 Hz), 5.1 (m, 1H, CH-O), 6.95-7.19 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (d, CH_3, ^{t}Bu, J_{C-P}= 5.3 Hz), 31.3 (CH_3, ^{t}Bu), 34.3 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 45.6 (CH_3, NMe_2), 66.7 (d, CH_2-N, $^2J_{C-P}$ = 3.8 Hz), 75.2 (d, CH-O, $^2J_{C-P}$ = 8.4 Hz), 125.3-145.8 (aromatic carbons). TOF-MS (ESI+): m/z = 548.3287, calcd. for $C_{34}H_{46}NO_3P$ $[M+H]^+$: 548.3288

L6d: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ = 129.7 (s). ^1H NMR (C_6D_6): δ = 1.48 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 6H, CH_3, NMe_2), 3.4 (m, 1H, CH-N), 3.6 (m, 1H, CH_2-O), 4.3 (m, 1H, CH_2-O), 6.95-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (d, CH_3,^{t}Bu, J_{C-P}= 5.3 Hz), 34.4 (C, ^{t}Bu), 34.5 (C, ^{t}Bu), 42.9 (CH_3, NMe_2), 66.4 (CH_2-O), 70.6 (d, CH-N, $^2J_{C-P}$ = 3.0 Hz), 125.3-146.1(aromatic carbons). TOF-MS (ESI+): m/z = 548.3489, calcd. for $C_{34}H_{46}NO_3P$ $[M+H]^+$: 548.3288

L6e: Yield: 362 mg (64%). ^{31}P NMR (C_6D_6): δ = 131.1 (s). ^1H NMR (C_6D_6): δ = 1.46 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.64 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.06 (s, 6H, CH_3, NMe_2), 3.6 (m, 1H, CH-N), 3.8 (m, 1H, CH_2-O), 4.0 (m, 1H, CH_2-O), 6.95-7.2 (m, 7H, CH=). ^{13}C NMR (C_6D_6): δ = 16.1 (CH_3), 16.3 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 30.9 (CH_3, ^{t}Bu), 31.2 (d, CH_3,^{t}Bu, J_{C-P}= 5.3 Hz), 34.5 (C, ^{t}Bu), 34.6 (C, ^{t}Bu), 42.9 (CH_3, NMe_2), 66.1 (CH_2-O), 70.6 (d, CH-N, $^2J_{C-P}$ = 2.3 Hz), 125.3-146.1 (aromatic carbons). TOF-MS (ESI+): m/z = 548.3287, calcd. for $C_{34}H_{46}NO_3P$ $[M+H]^+$: 548.3288

4.5. General procedure for the preparation of [Pd(η^3-allyl)(P-S)]BF_4 complexes 53-57

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(η^3-1,3-allyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.05 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over celite under argon and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated as pale yellow solids by adding hexane.

[Pd(η^3-1,3-diphenylallyl)(L4d)]BF_4 (53). Isomer *endo* (77%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 136.8 (s, 1P). ^1H NMR(CD_2Cl_2, 298 K), δ: 0.50 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.22 (s, 9H, CH_3, ^{t}Bu), 1.47 (s, 3H, CH_3-Ar), 1.66 (s, 3H, CH_3-Ar), 1.71 (s, 9H, CH_3, ^{t}Bu), 2.13 (s, 3H, CH_3-Ar), 2.29 (s, 3H, CH_3-Ar), 2.75 (s, 3H, CH_3-N), 2.76 (s, 3H, CH_3-N), 3.19 (m, 1H, CH-N), 5.35 (dd, 1H, CH allyl *trans* to N, $^3J_{H-H}$= 12.0 Hz, $^3J_{H-P}$= 4.4 Hz), 5.64 (dd, 1H, CH allyl *trans* to P, $^3J_{H-H}$= 12.0 Hz, $^3J_{H-P}$= 16.4 Hz), 5.79 (dd, 1H, CH-O, $^3J_{H-H}$= 4.8 Hz, J_{C-P}= 7.2 Hz), 6.68 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 10.4 (CH_3), 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.5 (CH_3, Ar), 20.7 (CH_3, Ar), 32.0 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 42.9 (CH_3-N), 48.6 (CH_3-N), 73.5 (CH-N), 79.2 (d, CH allyl *trans* to N, J_{C-P}= 8.3 Hz), 84.6 (d, CH-O, J_{C-P}= 11.5 Hz), 105.3 (d, CH allyl *trans* to P, J_{C-P}= 33.8 Hz), 114.8 (d, CH allyl central, J_{C-P}= 12.2 Hz), 123-145 (aromatic carbons). Isomer *exo* (23%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 132.9 (s, 1P). ^1H NMR(CD_2Cl_2, 298 K), δ: 0.50 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 0.91 (s, 9H, CH_3, ^{t}Bu), 1.59 (s, 3H, CH_3-Ar), 1.74 (s, 3H, CH_3-Ar), 1.79 (s, 9H, CH_3, ^{t}Bu), 2.17 (s, 6H, CH_3-N and CH_3-Ar), 2.21 (s, 3H, CH_3-N), 2.43 (s, 3H, CH_3-Ar), 3.10 (m, 1H, CH-N), 4.50 (m, 1H, CH allyl *trans* to N), 5.22 (m, 1H, CH-O), 5.45 (m, 1H, CH allyl *trans* to P), 6.59 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 10.1 (CH_3), 17.1 (CH_3, Ar), 17.3 (CH_3, Ar), 20.4 (CH_3, Ar), 20.8 (CH_3, Ar), 31.9 (CH_3, ^{t}Bu), 32.8 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 38.8 (CH_3-N), 50.5 (CH_3-N), 71.8 (d, CH allyl *trans* to N, J_{C-P}= 9.2 Hz), 72.1 (CH-N), 84.0 (d, CH-O, J_{C-P}= 9.1 Hz), 99.3 (d, CH allyl *trans* to P, J_{C-P}= 33.0 Hz), 113.4 (d, CH allyl central, J_{C-P}= 14.0 Hz), 123-145 (aromatic carbons). Anal. calcd (%) for $C_{50}H_{61}BF_4NO_3PPd$: C 63.33, H 6.48, N 1.48; found: C 63.12, H 6.43, N 1.45.

[Pd(η^3-1,3-diphenylallyl)(L4e)]BF_4 (54). Isomer *endo* (17%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 129.8 (s, 1P). ^1H NMR(CD_2Cl_2, 298 K), δ: 0.43 (d, 3H, CH_3, $^3J_{H-H}$= 6.8 Hz), 1.33 (s, 9H, CH_3, ^{t}Bu), 1.66 (s, 3H, CH_3-Ar), 1.74 (s, 9H, CH_3, ^{t}Bu), 1.84 (s, 3H, CH_3-N), 2.14 (s, 3H, CH_3-Ar), 2.23 (s, 3H, CH_3-Ar), 2.26 (s, 3H, CH_3-N), 2.40 (s, 3H, CH_3-Ar), 3.40 (m, 1H, CH-N), 3.72 (dd, 1H, CH allyl *trans* to N, $^3J_{H-H}$= 10.2 Hz, $^3J_{H-P}$= 6.8 Hz), 4.40 (m, 1H, CH allyl *trans* to P), 5.54 (m, 1H, CH-O), 6.60 (m, 1H, CH allyl central), 6.8-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 10.8 (CH_3), 16.7 (CH_3, Ar), 17.0 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar), 32.2 (d,

CH_3, ^{t}Bu, $J_{C\text{-}P}$= 6.3 Hz), 32.5 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 43.0 (CH_3-N), 49.1 (CH_3-N), 67.3 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 12.8 Hz), 68.7 (CH-N), 84.9 (CH-O), 108.6 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 32.4 Hz), 114.5 (d, CH allyl central, $J_{C\text{-}P}$= 12.4 Hz), 127-145 (aromatic carbons). Isomer *exo* (83%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 128.7 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 0.54 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 7.2 Hz), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.78 (s, 9H, CH_3, ^{t}Bu), 2.11 (s, 3H, CH_3-Ar), 2.19 (s, 3H, CH_3-Ar), 2.40 (s, 3H, CH_3-N), 2.42 (s, 3H, CH_3-Ar), 2.61 (s, 3H, CH_3-N), 3.16 (m, 1H, CH-N), 4.40 (m, 1H, CH allyl *trans* to N), 5.03 (m, 1H, CH-O), 5.73 (m, 1H, CH allyl *trans* to P), 6.60 (m, 1H, CH allyl central), 6.9-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 9.7 (CH_3), 16.9 (CH_3, Ar), 17.3 (CH_3, Ar), 20.5 (CH_3, Ar), 20.7 (CH_3, Ar), 32.0 (CH_3, ^{t}Bu), 32.6 (CH_3, ^{t}Bu), 35.0-35.8 (C, ^{t}Bu), 42.9 (CH_3-N), 48.8 (CH_3-N), 67.5 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 12.6 Hz), 69.4 (CH-N), 81.4 (CH-O), 110.6 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 30.6 Hz), 113.5 (d, CH allyl central, $J_{C\text{-}P}$= 13.8 Hz), 123-145 (aromatic carbons). Anal. calcd (%) for $C_{50}H_{61}BF_4NO_3PPd$: C 63.33, H 6.48, N 1.48; found: C 63.02, H 6.43, N 1.44.

[Pd(η^3-1,3-diphenylallyl)(L5e)]BF$_4$ (55). Isomer *endo* (33%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 132.7 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 1.45 (s, 9H, CH_3, ^{t}Bu), 1.68 (s, 3H, CH_3-Ar), 1.71 (s, 3H, CH_3-Ar), 1.73 (s, 9H, CH_3, ^{t}Bu), 2.11 (s, 3H, CH_3-Ar), 2.30 (s, 3H, CH_3-Ar), 2.32 (s, 3H, CH_3-N), 2.42 (m, 1H, CH_2), 2.70 (s, 3H, CH_3-N), 3.56 (dd, 1H, CH_2, $^3J_{H\text{-}H}$= 10.0 Hz, $^3J_{H\text{-}P}$= 14.4 Hz), 4.49 (m, 1H, CH allyl *trans* to N), 4.84 (m, 1H, CH allyl *trans* to P), 5.23 (m, 1H, CH-O), 6.19 (m, 1H, CH allyl central), 6.7-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 16.5 (CH_3, Ar), 16.7 (CH_3, Ar), 20.0 (CH_3, Ar), 20.1 (CH_3, Ar), 31.9 (CH_3, ^{t}Bu), 32.4 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 4.6 Hz), 34.4-35.3 (C, ^{t}Bu), 48.7 (CH_3-N), 54.3 (CH_3-N), 69.8 (m, CH allyl *trans* to N), 70.9 (CH_2), 74.8 (CH-O), 93.8 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 39.7 Hz), 114.1 (d, CH allyl central, $J_{C\text{-}P}$= 12.2 Hz), 125-146 (aromatic carbons). Isomer *exo* (67%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 130.3 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 1.31 (s, 9H, CH_3, ^{t}Bu), 1.60 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.74 (s, 3H, CH_3-Ar), 2.16 (s, 6H, CH_3-Ar and CH_3-N), 2.45 (s, 3H, CH_3-Ar), 2.52 (m, 1H, CH_2), 2.75 (s, 3H, CH_3-N), 3.19 (dd, 1H, CH_2, $^3J_{H\text{-}H}$= 9.6 Hz, $^3J_{H\text{-}P}$= 14.4 Hz), 4.52 (m, 1H, CH allyl *trans* to N), 5.30 (m, 1H, CH-O), 5.61 (m, 1H, CH allyl *trans* to P), 6.54 (m, 1H, CH allyl central), 6.7-7.8 (m, 17H, CH=). ^{13}C NMR (C_6D_6, 298 K), δ: 16.2 (CH_3, Ar), 16.7 (CH_3, Ar), 20.0 (CH_3, Ar), 20.2 (CH_3, Ar), 31.6 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 34.4-35.3 (C, ^{t}Bu), 49.9 (CH_3-N), 51.6 (CH_3-N), 69.8 (m, CH allyl *trans* to N), 71.2 (CH_2), 75.6 (CH-O), 105.6 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 32.0 Hz), 112.3 (d, CH allyl central, $J_{C\text{-}P}$= 10.7 Hz), 125-146 (aromatic carbons). Anal. calcd (%) for $C_{49}H_{59}BF_4NO_3PPd$: C 63.00, H 6.37, N 1.50; found: C 59.61, H 6.31, N 1.46.

[Pd(η^3-1,3-cyclohexenylallyl)(L4e)]BF$_4$ (56). Isomer *endo* (91%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 134.4 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 0.74 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 1.2-1.6 (m, 4H, CH_2), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.69 (s, 3H, CH_3-Ar), 1.80 (m, 1H, CH_2), 1.87 (s, 3H, CH_3-Ar), 2.21 (m, 1H, CH_2), 2.23 (s, 3H, CH_3-Ar), 2.34 (s, 3H, CH_3-Ar), 2.82 (s, 3H, CH_3-N), 3.24 (s, 3H, CH_3-N), 3.31 (m, 1H, CH allyl *trans* to N), 3.38 (m, 1H, CH-N), 4.97 (dd, 1H, CH-O, $^3J_{H\text{-}H}$= 7.2 Hz, $^3J_{H\text{-}P}$= 12 Hz), 5.49 (m, 1H, CH allyl central), 5.96 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (C_6D_6, 298 K), δ: 9.9 (CH_3), 16.7 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar), 21.4 (b, CH_2), 27.4 (b, CH_2), 21.4 (d, CH_2, $J_{C\text{-}P}$= 8.4 Hz), 31.7 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.2-35.4 (C, ^{t}Bu), 44.8 (CH_3-N), 53.4 (CH_3-N), 64.7 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 10 Hz), 69.7 (CH-N), 82.7 (d, CH-O, $J_{C\text{-}P}$= 6.1 Hz), 109.2 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 40 Hz), 113.5 (d, CH allyl central, $J_{C\text{-}P}$= 10.7 Hz), 127-145 (aromatic carbons). Isomer *exo* (9%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 133.0 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 0.72 (d, 3H, CH_3, $^3J_{H\text{-}H}$= 6.8 Hz), 1.2-1.6 (m, 4H, CH_2), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 3H, CH_3-Ar), 1.80 (m, 1H, CH_2), 1.89 (s, 3H, CH_3-Ar), 2.21 (m, 1H, CH_2), 2.27 (s, 3H, CH_3-Ar), 2.29 (s, 3H, CH_3-Ar), 2.68 (s, 3H, CH_3-N), 3.20 (s, 3H, CH_3-N), 3.36 (m, 1H, CH allyl *trans* to N), 3.42 (m, 1H, CH-N), 5.21 (m, 1H, CH-O), 5.68 (m, 1H, CH allyl central), 6.08 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (C_6D_6, 298 K), δ: 9.2 (CH_3), 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.4 (CH_3, Ar), 20.6 (CH_3, Ar), 21.4 (b, CH_2), 27.4 (b, CH_2), 21.4 (d, CH_2, $J_{C\text{-}P}$= 8.4 Hz), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 35.2-35.4 (C, ^{t}Bu), 45 (CH_3-N), 52.8 (CH_3-N), 64.2 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 9.2 Hz), 69.7 (CH-N), 81.9 (d, CH-O, $J_{C\text{-}P}$= 7.3 Hz), 110.8 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 38.6 Hz), 113.2 (d, CH allyl central, $J_{C\text{-}P}$= 9.6 Hz), 127-145 (aromatic carbons). Anal. calcd (%) for $C_{41}H_{57}BF_4NO_3PPd$: C 58.90, H 6.87, N 1.68; found: C 58.21, H 6.84, N 1.65.

[Pd(η^3-1,3-cyclohexenylallyl)(L5e)]BF$_4$ (57).[34] Isomer *endo* (96%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 135.2 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 1.25 (m, 1H, CH_2), 1.43 (m, 2H, CH_2), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 1H, CH_2), 1.73 (s, 3H, CH_3-Ar), 1.88 (s, 3H, CH_3-Ar), 1.90 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 2.24 (s, 3H, CH_3-Ar), 2.35 (s, 3H, CH_3-Ar), 2.71 (d, 1H, CH_2-N, $^3J_{H\text{-}H}$= 14.4 Hz), 2.90 (s, 3H, CH_3-N), 3.12 (s, 3H, CH_3-N), 3.42 (dd, 1H, CH_2-N, $^3J_{H\text{-}H}$= 14.4 Hz, $^3J_{H\text{-}P}$= 9.6 Hz), 3.49 (m, 1H, CH allyl *trans* to N), 5.23 (m, 1H, CH-O), 5.44 (m, 1H, CH allyl central), 6.03 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=).^{13}C NMR (C_6D_6, 298 K), δ: 16.7 (CH_3, Ar), 16.8 (CH_3, Ar), 20.5 (CH_3, Ar), 20.6 (CH_3, Ar),), 20.9 (d, CH_2, $J_{C\text{-}P}$= 2.3 Hz), 27.6 (b, CH_2), 28.5 (d, CH_2, $J_{C\text{-}P}$= 7.6 Hz),31.8 (CH_3, ^{t}Bu), 32.0 (d, CH_3, ^{t}Bu, $J_{C\text{-}P}$= 1.5 Hz)), 35.2 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 51.8 (CH_3-N), 56.7 (CH_3-N), 67.6 (d, CH allyl *trans* to N, $J_{C\text{-}P}$= 9.1 Hz), 71.8 (CH-N), 77.9 (d, CH-O, $J_{C\text{-}P}$= 6.8 Hz), 105.0 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 40.3 Hz), 113.5 (d, CH allyl central, $J_{C\text{-}P}$= 10.6 Hz), 126-146 (aromatic carbons). Isomer *exo* (4%): ^{31}P NMR (CD_2Cl_2, 298 K), δ: 134.2 (s, 1P). ^{1}H NMR(CD_2Cl_2, 298 K), δ: 1.25 (m, 1H, CH_2), 1.43 (m, 2H, CH_2), 1.47 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.70 (m, 1H, CH_2), 1.74 (s, 3H, CH_3-Ar), 1.90 (bs, 4H, CH_3-Ar and CH_2), 2.16 (m, 1H, CH_2), 2.24 (s, 3H, CH_3-Ar), 2.35 (s, 3H, CH_3-Ar), 2.81 (d, 1H, CH_2-N, $^3J_{H\text{-}H}$= 14.0 Hz), 2.91 (s, 3H, CH_3-N), 3.09 (s, 3H, CH_3-N), 3.27 (dd, 1H, CH_2-N, $^3J_{H\text{-}H}$= 14.0 Hz, $^3J_{H\text{-}P}$= 8.4 Hz), 3.39 (m, 1H, CH allyl *trans* to N), 5.39 (m, 1H, CH-O), 5.54 (m, 1H, CH allyl central), 5.84 (m, 1H, CH allyl *trans* to P), 7.2-7.5 (m, 7H, CH=). Anal. calcd (%) for $C_{40}H_{55}BF_4NO_3PPd$: C 58.44, H 6.74, N 1.70; found: C 58.06, H 6.70, N 1.67.

4.6. Study of the reactivity of the [Pd(η^3-allyl)(L))]BF$_4$ with sodium malonate by in situ NMR[35]

A solution of *in situ* prepared [Pd(η^3-allyl)(L)]BF_4 (L= phosphite-pyridine, 0.05 mmol) in CD_2Cl_2 (1 mL) was cooled in the NMR at -80 °C. At this temperature, a solution of cooled sodium malonate (0.1 mmol) was added. The reaction was then followed by ^{31}P NMR. The relative reaction rates were calculated using a capillary containing a solution of triphenylphosphine in CD_2Cl_2 as external standard.

4.7. Typical procedure for the allylic alkylation of linear (S1 and S3-S8) and cyclic (S2, S9 and S10) substrates

A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (0.5 mmol) in dichloromethane (1.5 mL), nucleophile (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (3 mg, 0.03 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. For compounds **12**, **14**-**21**, **27**-**32**, **35**, **37**-**39** and **45**, the solvent was removed, conversions were measured by ^{1}H-NMR and enantiomeric excesses were determined by HPLC. For compounds **13**, **33**-**34**, **40**-**41** and **43**-**44**, conversion and enantiomeric excesses were determined by GC. For compounds **36** and **42**, conversion were measured by ^{1}H-NMR and ees were determined by ^{1}H-NMR using [Eu(hfc)$_3$]. For characterization and ee determination details see Supporting Information.

4.8. Typical procedure for the allylic amination of substrate S1

A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (0.5 mmol) in dichloromethane (1.5

mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversion was measured by ^{1}H-NMR and enantiomeric excess was determined by HPLC. For characterization and ee determination details see Supporting Information.

4.9. Typical procedure for the allylic etherification of substrate S1

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the corresponding amino-phosphite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of the corresponding substrate (31.5 mg, 0.125 mmol) in dichloromethane (1.5 mL) was added. After 10 minutes, Cs_2CO_3 (122 mg, 0.375 mmol) and alkyl alcohol (0.375 mmol) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Conversion was measured by ^{1}H-NMR. HPLC was used to determine enantiomeric excesses. For characterization and ee determination details see Supporting Information.

4.10. Typical procedure for the preparation of carbocyclic compounds 46-51

A solution of Grubbs II catalyst (5 mg, 0.006 mmol) and the corresponding alkylated product (0.12 mmol) in CH_2Cl_2 (3 mL) was stirred for 16 h. The solution was directly purified by flash chromatography (95:5; Hex: EtOAc) to obtained the desired carbocycle compounds. For characterization and ee determination details see Supporting Information.

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Keywords: Palladium • amino-phosphite • allylic substitution • asymmetric catalysis • mechanistic studies

[1] For reviews, see: a) *Palladium Reagents and Catalysis, Innovations in Organic Synthesis*; Tsuji, J., Ed.; Wiley: New York, 1995. b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. d) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 24. e) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. f) Masdeu-Bultó, A. M.; Diéguez, M.; Martín, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159. g) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. h) Martín, E.; Diéguez, M. *C. R. Chemie* **2007**, *10*, 188. i) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258. j) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. k) Trost, B. M. *Org. ProcessRes. Dev.* **2012**, *16*, 185.

[2] a) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. b) Recently this concept has also been use to explain the chiral induction by the Trost ligand, see: Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P. O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.

[3] See, for instance: a) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149. b) von Matt, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566. c) Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595.

[4] See, for instance: a) Pàmies, O.; Diéguez, M. *Acc. Chem. Res.* **2010**, *43*, 212. b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077. c) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49. d) Pàmies, O.; Diéguez, M., Claver, C. *Adv. Synth. Catal.* **2007**, *349*, 836. e) Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2008**, *14*, 944. f) Raluy, E.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 1648.

[5] a) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646. b) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943. c) Diéguez, M.; Pàmies, O. *Chem. Eur. J.* **2008**, *14*, 3653. d) Mata, Y.; Pàmies, O.; Diéguez, M. *Adv. Synth. Catal.* **2009**, *351*, 3217.

[6] Only two ligand series (Trost-diphosphine and PHOX-type ligands) have been successfully applied in a very broad range of nucleophiles. However, while the use of Trost diphosphines has been mainly limited to unhindered substrates, the PHOX-type ligands have been mainly limited to hindered substrates.[1]

[7] a) Mazuela, J.; Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2013**, *19*, 2416. b) Coll, M.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2014**, *16*, 1892.

[8] See, for instance: a) Kubota, H.; Koga, K. *Heterocycles*, **1996**, *42*, 543 (up to >95% ee for **S1**). b) Jin, M.-J.; Jung, J.-A.; Kim, S.-H. *Tetrahedron Lett*. **1999**, *40*, 5197 (up to 98% ee at 0 °C for **S1**). c) Okuyama, Y.;Nakano, H.; Hongo, H. *Tetrahderon: Asymmetry* **2000**, *11*, 1193 (up to 96% ee for **S1**). d) Widhalm, M.; Nettekoven, U.; Kalchhauser, H.; Mereiter, K.; Calhorda, M. J.; Félix, V. *Organometallics* **2002**, *21*, 315 (up to 97% ee for **S1** and 49% ee for **S2**). e) Vasse, J.-L.; Stranne, R.; Zalubovskis, R.; Gayet, C.; Moberg, C. *J. Org. Chem.* **2003**, *68*, 3258 (up to 98% ee for **S1** and 27% ee for **S2**). f) Chen, G.; Li, X.; Zhang, H.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 809 (up to 95% ee at -20 °C for **S1**). g) Jin, M.-J.; Kim, S.-H.; Lee, S.-J.; Kim, Y.-M. *Tetrahedron Lett.* **2002**, *43*, 7409 (up to 99% ee at 10 °C for **S1**). h) Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837 (up to 95% ee at -20 °C for **S1**). i) Lee, E.-K.; Kim, S.-H.; Jung, B.-H.; Ahn, W.-S.; Kim, G.-J. *Tetrahedron Lett.* **2003**, *44*, 1971 (up to 98% ee at 0 °C for **S1**). j) Tanaka, Y.; Mino, T.; Akita, K.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2004**, *69*, 6679 (up to 98% ee at -20 °C for **S1**). k) Sun, X.-M.; Koizumi, M.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2005**, *347*, 1893 (up to 96% ee at -20 °C for **S1**).

[9] See for example: a) Jang, H.-Y.; Seo, H.; Han, J. W.; Chung, Y. K. *Tetrahedron Lett* **2000**, *41*, 5083 (up to 98% ee for **S1**). b) Lee, J. H.; Son, S. U.; Chung, Y. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2109 (up to 98% ee for **S1**). c) Hu, X.; Dai, H.; Hu, X.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2002**, *13*, 1687 (up to 96% ee at 0 °C for **S1**). d) Hu, X.; Dai, H.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 1065 (up to 99% ee at 0 °C for **S1** and 73% ee for **S2**). e) Thiesen, K. E.; Maitra, K.; Olmstead, M. M.; Attar, S. *Organometallics* **2010**, *29*, 6334 (up to 94% ee for **S1**). f) Tsarev, V. N.; Lyubimov, S. E.; Bondarev, O. G.; Korlyukov, A.; Antipin, M. Y.; Pretovskii, P. V.; Davankov, V. A.; Shiryaev, A. A.; Benetsky, E. B.; Vologzhanin, P. A.; Gavrilov, K. N. *Eur. J. Org. Chem.* **2005**, 2097 (up to 97% ee for **S1**).

[10] See for instance: a) Bunlaksananusorn, T.; Luna, A. P.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240 (up to 96% ee for **S1**). b) Ito, K.; Kashiwagi, R.; Iwsaki, K.; Katsuki, T. *Synlett* **1999**, 1563 (up to 96% ee for **S1**). c) Goldfuss, B.; Löschmann, T.; Rominger, F. *Chem. Eur. J.* **2004**, *10*, 5422 (up to 83% ee for **S1**). d) Liu, Q.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 2101 (up to 95% ee for **S1**). e) Meng, X.; Gao, Y.; Li, X.; Xu, D. *Cat. Commun.* **2009**, *10*, 950 (up to 97% ee for **S1** and 80% ee for **S2**). f) Leca, F.; Fernández, F.; Muller, G.; Lescop, C.; Réau, R.; Gómez, M. *Eur. J. Inorg. Chem.* **2009**, 5583 (up to 12% ee and 31% ee for **S1** and **S2**, respectively). g) Lega, M.; Margalef, J.; Ruffo, F.; Pàmies, O.; Diéguez, M. *Tetrahedron: Asymmetry* **2013**, *24*, 995 (up to 50% ee for **S1** and 86% ee at 0 °C for **S2**).

[11] See: a) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905 (up to 98%, 90%, and 65% ee at -20 °C for **S1**, **S2** and **S4**, respectively). b) Nakano, H.;

Okuyama, Y.; Hongo, H. *Tetrahedron Lett.* **2000**, *41*, 4615 (up to 94% ee at -30 °C for **S1**). c) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679 (up to 97% ee at -20 °C for **S1**). d) Enders, D.; Peters, R.; Runsink, J.; Bats, J. W. *Org. Lett.* **1999**, *1*, 1863 (up to 97% ee at -20 °C for **S1**). e) Guimet, E.; Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 959 (up to 93% ee at 0 °C for **S1**). f) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, *75*, 2628 (up to 96% ee at rt for **S1**).

[12] Bernardi, L.; Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Eur. J. Org. Chem.* **2002**, 2776.

[13] Khruscheva, N. S.; Loim, N. M.; Sokolov, V. I.; Makhaev, V. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2425.

[14] Page, P. C. P.; Heaney, H.; Reignier, S.; Rassias, G. A. *Synlett* **2003**, 22.

[15] Pàmies, O.; Diéguez, M.; Net, G. ; Ruiz, A. ; Claver, C. *Organometallics* **2000,** *19,* 1488.

[16] a) Oslob, J. D.; Åkermark, B.; Helquist, P.; Norrby, P.-O. *Organometallics* **1997**, *16,* 3015-3021. b) Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18,* 2884-2895

[17] a) Hagelin, H.; Svensson, M.; Åkermark, B.; Norrby, P.-O. *Organometallics* **1999**, *18,* 4574-4583. b) Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P.-O.; Hallberg, A.; Larhed, M.; Csöregh, I. *Pure Appl. Chem.* **1999**, *71,* 1477-1483.

[18] Peña-Cabrera, E.; Norrby, P.-O.; Sjögren, M. P. T.; Vitagliano, A.; deFelice, V.; Oslob, J. D.; Ishii, S.; Åkermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118,* 4299-4313.

[19] a) Katcher, M. H.; Norrby, P.-O.; Doyle, A.G. *Organometallics* **2014**, *33*, 2121-2133. b) Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Chem. Eur. J.* **1999**, *5,* 902-909.

[20] Fristrup, P.; Ahlquist, M.; Tanner, D.; Norrby, P.-O. *J. Phys. Chem.* **2008**, *112,* 12862-12867.

[21] a) Fristrup, P.; Jensen, T.; Hoppe, J.; Norrby, P.-O. *Chem. Eur. J.* **2006**, *12,* 5352-5360. b) Johansson, C.; Lloyd-Jones, G. C.; Norrby, P.-O. *Tetrahedron: Asymmetry.* **2010**, *21,* 1585-1592.

[22] a) *Dictionary of Natural Products*; Buckingham, J., Ed.; Cambridge University Press.: Cambridge, 1994. b) Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 1890.

[23] For successful examples of Pd-catalysts, see: a) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276. b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815; c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545; d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262; e) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, *17*, 161; f) Tietze, L. F.; Lohmann, J. K.; Stadler, C. *Synlett* **2004**, 1113. For successful applications of Ir-catalysts with phenols, see: g) Shu, C.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 4794. h) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628; i) Lopez, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426. j) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6204. k) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dubon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239. l) Kimura, M.; Uozumi, Y. *J. Org. Chem.* **2007**, *72*, 707.

[24] a) Iourtchenko, A.; Sinou, D. *J. Mol. Catal. A* **1997**, *122*, 91. b) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, *68*, 8092; c) Lam, F. L.; Au Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 1280. d) Ye, F.; Zheng, Z.-J.; Li, L.; Yang, K.-F. ; Xia, C. G.; Xu, L.-W. *Chem. Eur. J.* **2013**, *19*, 15452. e) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. f), Kato, M.; Nakamura, T.; Ogata, K.; Fukuzawa, S. *Eur. J. Org. Chem.* **2009**, 5232. g) Feng, B.; Cheng, H.-G.; Chen, J.-R.; Deng, Q.-H.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2014**, *50*, 9550. For a report based on Ir-catalysts, see: h) Ueno, S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 1928.

[25] For a review on Hammett studies, see: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[26] There are therefore fewer successful catalyst systems for the Pd-catalyzed allylic substitution of this substrate than for the allylic substitution of substrate **S1**. If enantiomeric excesses are to be high, the ligand must create a small chiral pocket around the metal center, mainly because of the presence of less sterically demanding methyl *syn* substituents.

[27] 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. *J. Org. Chem.* **2000**, *65*, 4810. 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. *Organometallics* **2005**, *24*, 3946.

[28] The equilibrium between the two diastereoisomers takes place via the so-called apparent π-allyl rotation. This has been shown to occur via dissociation of one of the coordinated atoms of the bidentate ligand, which allows the ligand to rotate. See: Gogoll, A.; Örnebro, J.; Grennberg, H.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1994**, *116*, 3631.

[29] Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625.

[30] a) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. b) Jia, C.; Müller, P.; Mimoun, H. *J. Mol. Cat. A: Chem.* **1995**, *101*, 127. c) Lehman, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863. d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301. e) Du, L.; Cao, P.; Liao, J. *Acta Chim. Sinica* **2013**, *71*, 1239. f) Jayakumar, S.; Kumarswamyreddy, N.; Prakash, M.; Kesavan V. *Org. Lett.* **2015**, *17*, 1066.

[31] von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265.

[32] Trost, B. M.; Strege, P. E.; Weber, L. *J. Am. Chem. Soc.* **1978**, *11*, 3407.

[33] Nakai, Y.; Uozumi, Y. *Org. Lett.* **2005**, *7*, 291.

[34] The chemicals shifts of allylic terminal carbons of the minor isomer of complex **54** were obtained from the HSQC experiment (the signals at the ^{13}C NMR spectra were not detected).

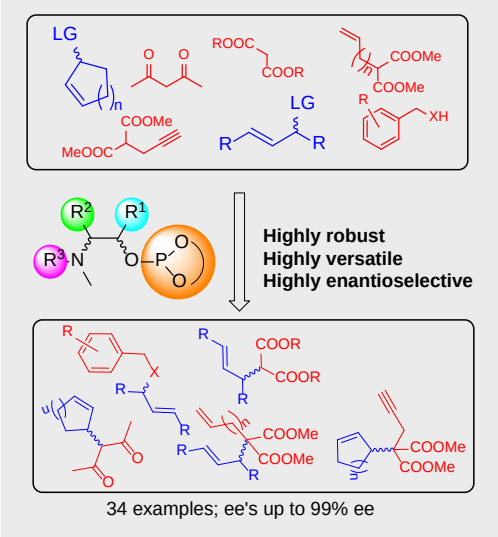
[35] van Haaren, R. J.; Keeven, P. H.; van der Veen, L. A.; Goubitz, K.; van Strijdonck, G. P. F.; Oevering, H.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W: N. M. *Inorg. Chim. Acta* **2002**, *327*, 108.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

By combining theoretical and experimental studies, we have identified unprecedented Pd-amino-phosphite catalytic systems that can create chiral C-C, C-N and C-O bonds in substrates with a variety of electronic and steric proprieties, using a wide range of nucleophiles in high yields and enantioselectivities.



Marc Magre, Maria Biosca, Per-Ola Norrby, Oscar Pàmies* and Montserrat Diéguez**

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Alternating theoretical and experimental optimization of a new amino-phosphite ligand library for asymmetric Pd-catalyzed allylic substitution