P-amino ligands from iminosugars: New readily available and modular ligands for the enantioselective Pd-catalyzed allylic substitutions

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Abstract

The construction of a novel class of amino-phosphite/phosphinite/phosphine ligands containing a protected pyrrolidine-3,4-diol moiety is presented. These ligands are obtained from readily available sugars. They thus contain the advantages of carbohydrates in terms of selection of the stereogenic carbons, polyfunctional groups able to modulate the electronic and sterical properties, and the general good stability of carbohydrate derivatives. They constitute a novel class of P,N-ligands that have been used in the enantioselective allylic substitutions of acyclic and cyclic substrates with varied electronic and steric requirements, using different C- and N-nucleophiles, with high enantioselectivities. Among the three groups of P,N-ligands (amino-P (P= phosphite, phosphinite and phosphine groups) the new amino-phosphite ligands gives the widest substrate and nucleophile scope, including the more challenging hindered linear and cyclic substrates. In particular, for carbohydrate derived amino-phosphite ligands and linear substrates, high enantioselectivity in the reactions requires an *R*-configuration of the binaphthyl moiety. However, for cyclic substrates both product's enantiomers can be reached by setting out the chirality of the binaphthyl phosphite moiety. A detailed investigation of the appropriate Pd intermediates is also presented.

Introduction

Catalysis has transformed the chemical production because catalysts are used in the preparation of the majority of chemicals, resulting in a multi-billion dollar business. The development and improvement of catalysts are therefore keys for attaining a sustainable construction of all kinds of chemicals. Chirality is a fundamental property for a large number of industrial and biological compounds.[1] Among the catalytic reactions leading to chiral products, asymmetric Pd-catalyzed allylic substitution builds a new stereogenic C-C or C-X bond creating chiral molecules that can be further transformed by taking advantage of the alkene functionality.[2] Other advantages of the Pd-catalyzed allylic substitution are its tolerance to several functional groups and the soft reaction conditions. Nowadays heterodonor compounds are among the ligands that have provided the best results in allylic alkylation reactions.[2] Their success derives mainly from the different *trans* influence of both types of functional groups that creates an electronic differentiation between the two allylic terminal carbons, and therefore favors the nucleophilic attack mostly *trans* to the donor group with stronger *trans* influence. Among the heterodonor compounds, phosphine/phosphinite-oxazoline ligands have been the most studied.[2] Other heterodonor phosphine/phosphinite-ligands containing a more stable group than oxazolines (such thioether,[3] pyridine,[4] imine[5] and amine[6]) have also been studied. Despite this, a few of them have provided excellent results in a large number of substrates and nucleophiles.[7] We have contributed with improvements in catalyst performance with heterodonor compounds that have biaryl phosphite functionalities.[2i,8] We found that biaryl phosphite moieties improve substrate versatility because the flexibility of these groups adapts the chiral pocket of the catalysts to the steric bulkiness of the substrate.[8e]

Regardless of all the notable progresses in catalyst design, still few ligands have been effectively used in the allylic substitution of substrates using different electronic and steric proprieties with a large number of nucleophiles. "Privileged" ligands[9] with a wide substrate scope and suitable for a large number of nucleophiles would allow us to reduce the time invested in their design/preparation, which is crucial for the sustainable construction of all types of C−X bonds necessary for the synthesis of complex molecules.

The search for such ligands that are solids and stable in air (easy to mannipulate), easy to prepare from simple starting materials, and that are good for several substrates and

nucleophiles, is a relevant topic in this reaction. Carbohydrates are particularly useful for preparing ligands because they are relative abundant in an enantiomerically pure form, present a wide stereochemical diversity, besides they are cheap and readily available. Their polyfunctional structure facilitates its modular reactivity in terms of electronic and sterical effects.[10] Series of ligands can be prepared and tested in the quest of the optimal ligand for each type of substrate. Since the pioneering work of Pregrosin,[11] among others,[12] on the use of carbohydrates as efficient ligands in allylic alkylations, many carbohydrates, mostly heterodonor, have been prepared. However, still few of them have shown a broad substrate scope.[13]

In our quest for efficient and stable catalysts, we herein present the synthesis and screening of a new sugar-based amino-phosphite/phosphinite/phosphine ligand library (**L1**–**L7a**–**d**; Figure 1) in the allylic substitution of a range of substrates with different steric requirements with several nucleophiles. These ligands have been prepared from amino-alcohols **1**–**6**, which are obtained from commercially available cheap carbohydrates. We believe that the modular nature of the iminosugar backbone together with the appropriate choice of the P functionality would be crucial to fix the configuration of the nitrogen upon the ligand coordination to palladium,[7] which in turn will aid in the development of efficient ligands for this transformation. To achieve such a control, several ligand parameters have been easily tuned. We have studied the result of systematic changing the substituent in the nitrogen moiety (**L1**–**L3**), the configuration of carbons bearing the isopropylidene group (ligands **L1** *vs* **L4**), the rigidity of the ligand skeleton (ligands **L7**) and the substituent/configuration of the biaryl phosphite functionality (**a**–**d**). The effect of changing the phosphite by a phosphinite (**L5**) or a phosphine (**L6**) groups was also investigated. We have also performed the synthesis and elucidation of the appropriate Pd-allyl intermediates to elucidate the enantioselectivities obtained.

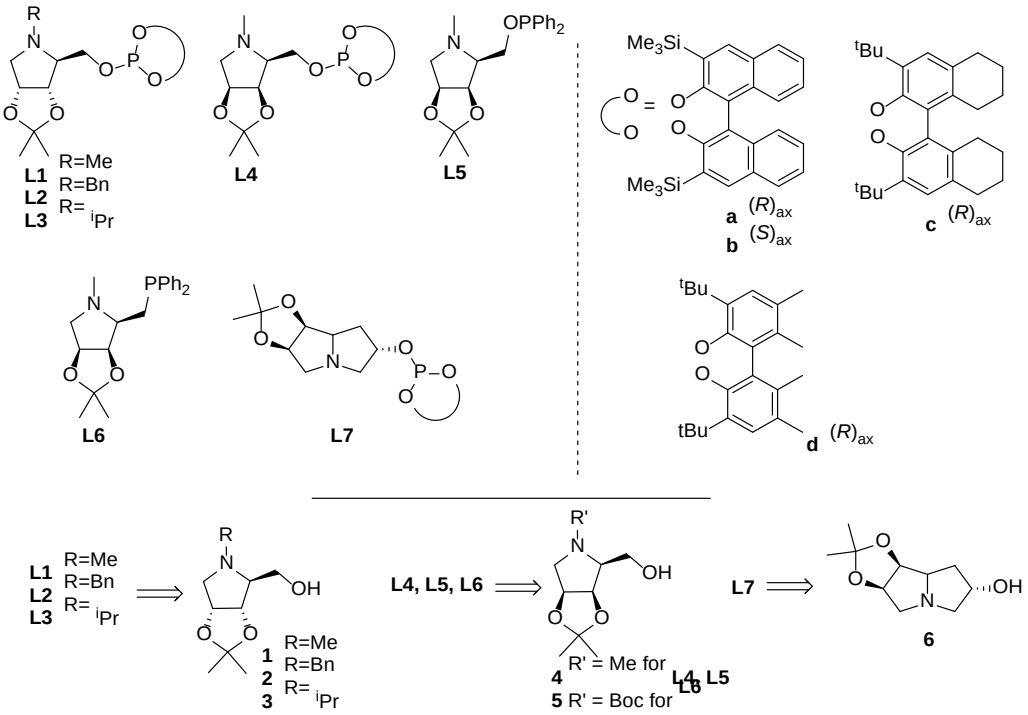
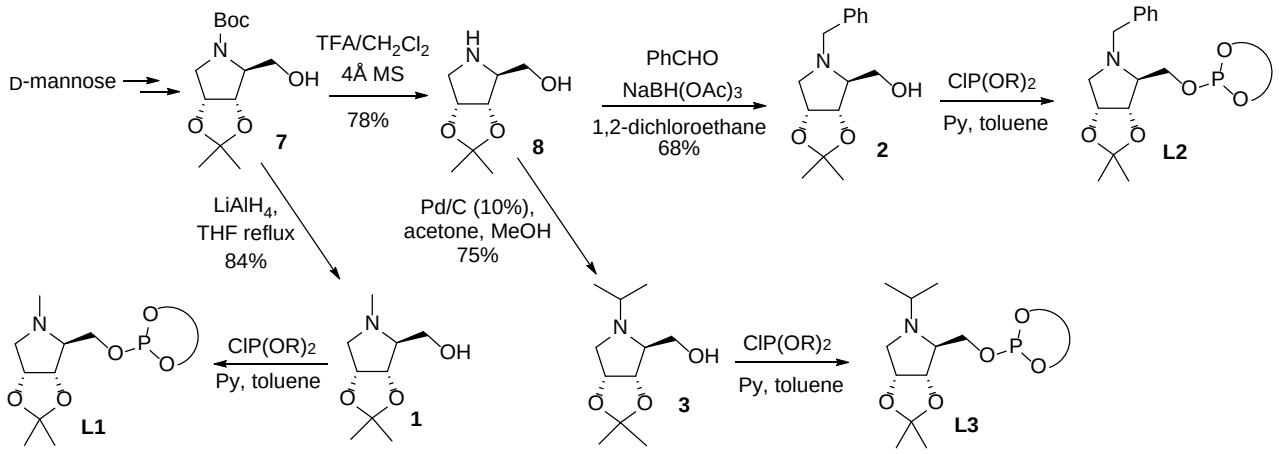


Figure 1. Amino-phosphite/phosphinite/phosphine ligands **L1**–**L7a**–**d** and their starting products, cyclic amino alcohols **1**–**6**.

Results and Discussion

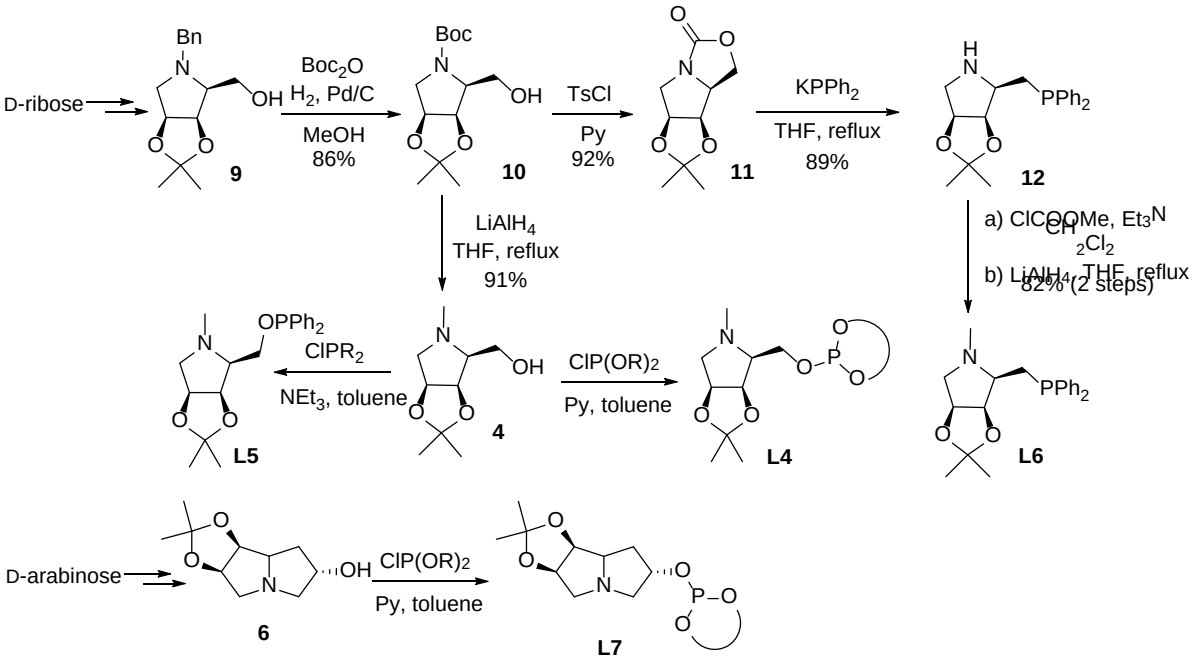
Preparation of ligands

The preparation of ligands **L1**–**L3** started from pyrrolidine alcohol **7**, easily obtained from D-mannose following the procedure recently reported by us.[14] Reduction of **7** with $LiAlH_4$ gave *N*-methyl pyrrolidine alcohol **1**. On its side, acidic deprotection of the Boc group of **7** followed by reductive amination with benzaldehyde and acetone afforded *N*-benzyl and *N*-isopropyl hydroxy pyrrolidine derivatives **2** and **3**, respectively. With these steps the appropriate variety in the steric and electronic proprieties of the amine part was reached. Finally, reaction of amino-alcohols **1**, **2** and **3** with the desired phosphorochloridite ($ClP(OR)_2$; OR= **a**–**d**) formed *in situ* gave access to amino-phosphite ligands **L1**–**L3** with the desired substituent/configurations of the biaryl phosphite group.



Scheme 1.Syntesis of ligands **L1**-**L3**.

The preparation of ligands **L4**–**L6**, with a different configuration of the carbons bearing the isopropylidene group than **L1**–**L3**, is outlined in Scheme 2. Alcohol **9** was prepared from D-ribose as previously reported.[15] Protecting group manipulation afforded *N*-Boc derivative **10** that after reduction with $LiAlH_4$ gave *N*-methyl pyrrolidine alcohol **4**. Its reaction with $ClP(OR)_2$ or $ClPR_2$ furnished the corresponding phosphite/phosphinite ligands **L4** and **L5**. Standard tosylation of **10** did not afford the corresponding tosylate derivative; instead, cyclic carbamate **11** was obtained as previously described for ***ent*-10**.[14] Nucleophilic ring opening of **11** by treatment with $KPPh_2$ in THF at reflux gave phosphine **12**. Reaction with methoxycarbonyl chloride gave the corresponding carbamate which, after reduction with $LiAlH_4$, gave amino-phosphine ligand **L6** in 82% yield (2 steps). On the other hand, starting from D-arabinose, pyrrolizidine-alcohol **6** was obtained (Scheme 2).[16] Subsequent reaction with $ClP(OR)_2$ afforded the corresponding amino-phosphites **L7**.

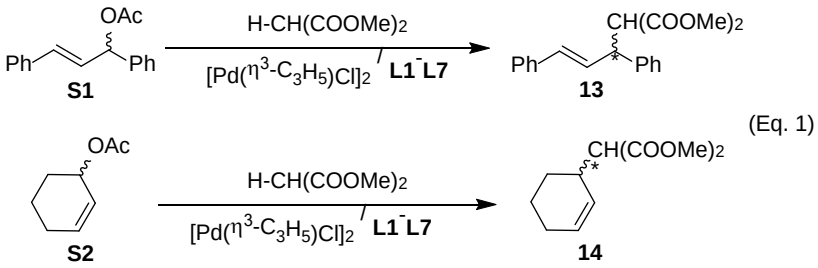


Scheme 2. Synthesis of ligands **L4**–**L7**.

Advantageously, the amino-phosphite compounds are stable in air and stable to hydrolysis, so they were further manipulated and stored in air. The phosphinite and phosphine analogues (**L5** and **L6**), however, were less stable in air and were stored under argon. The formation of the ligands was confirmed by NMR spectra and mass spectrometry. For spectral assignments bidimendional ^{1}H–^{1}H and ^{1}H–^{13}C spectra were performed. In should be noted that for all compounds only one isomer was observed.

Pd-allylic alkylation of disubstituted substrates S1 and S2 with dimethyl malonate

We initially tested the capacity of ligands **L1**–**L7a**–**d** by applying them in the allylic alkylation of substrates **S1** and **S2**, which differs in their steric properties, with dimethyl malonate as nucleophile (Eq 1). For substrate **S2** it is harder to control enantioselectivity, because of the lack of sterically hindered *anti* substituents, which are known to play a key role in the enantiodiscrimination. Enantioselectivities were found to depend on the ligand architecture and the substrate type (Table 1). While the best enantioselectivities for **S1** were achieved with ligands **L1a** and **L1d**, for cyclic substrate **S2** the best enantioselectivities in both product's enantiomers were achieved using **L1a**–**b** and **L7a**–**b**.



(Eq. 1)

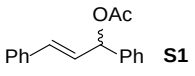
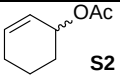
Concerning the effect of the P-functionality, we found that enantioselectivity decreased considerably by changing the phosphite (**L4**) by phosphinite or phosphine groups (ligands **L5** and **L6**) (Table 1; entry 9 vs 11–12). It was also found that the sense of enantioselectivity is controlled by the configuration of the biaryl phosphite functionality. Accordingly, ligands with *R* configuration at biaryl phosphite moiety, gave (*R*)-alkylated products, while ligands with *S* configuration at the biaryl phosphite group, gave (*S*)-alkylated products (e.g. entry 1 *vs* 2). In addition, for the linear substrate **S1** the enantioselectivity depend on the correct combination of the configuration of the biaryl phosphite moiety and the ligand backbone. The matched combination was therefore obtained with ligand **L1a**, containing an *R*-biaryl phosphite group (entry 1 vs 2). However, for the cyclic substrate the combination of both ligand parameters on enantioselectivity is less relevant. Therefore, by simple changing the configuration of the phosphite functionality both product's enantiomers can be obtained (entries 1 and 2). For the cyclic substrate **S2** enantioselectivity is also influenced by the substituents of the biaryl phosphite functionality. Enantioselectivities are therefore the highest when $SiMe_3$ groups are present at the *ortho* positions of the biaryl phosphite moiety (entries 1–2 *vs* 3–4).

Comparing the results with ligands **L1**−**L3**, it can be seen that the nature of the amine substituent has an effect on enantioselectivity, which increases with the presence of less sterically hindered substituents (entries 1, 5 and 6).

The effect of configuration of carbons bearing the isopropylidene group on enantioselectiviy was investigated, observing that is larger for substrate **S1** than **S2** (entries 1–2 vs 9–10).

We also studied the application of ligands **L7** with a more rigid ligand backbone since the nitrogen is constrained in a bicyclic structure. However, while the use of ligands **L7** has a negative effect on enantioselectivity for substrate **S1** (entries 1 and 2 vs 13 and 14) it has a little impact for substrate **S2** (entries 1 and 2 vs 13 and 14).

Table 1. Results for the Pd-catalyzed allylic substitution of substrates **S1**–**S2** using dimethyl malonate with P,N-ligands **L1–L7**.[a]

		 **S1**		 **S2**	
Entry	L	% Conv (h)[b]	% ee[c]	% Conv (h)[b]	% ee[c]
1	**L1a**	100 (6)	80 (*R*)	100 (12)	75 (*R*)
2	**L1b**	100 (6)	71 (*S*)	100 (12)	72 (*S*)
3	**L1c**	100 (6)	77 (*R*)	100 (12)	58 (*R*)
4	**L1d**	100 (6)	79 (*R*)	100 (12)	53 (*R*)
5	**L2a**	100 (6)	11 (*R*)	100 (12)	60 (*R*)
6	**L3a**	100 (6)	7 (*R*)	100 (12)	45 (*R*)
9	**L4a**	100 (6)	15 (*R*)	100 (12)	60 (*S*)
10	**L4b**	100 (6)	17 (*S*)	100 (12)	68 (*R*)
11	**L5**	100 (6)	6 (*S*)	100 (12)	38 (*S*)
12	**L6**	100 (24)	3 (*S*)	60 (24)	35 (*S*)
13	**L7a**	80 (6)	20 (*R*)	100 (12)	70 (*R*)
14	**L7b**	100 (6)	9 (*S*)	100 (12)	71 (*S*)
15[d]	**L1a**	100 (10)	87 (*R*)	100 (20)	81 (*R*)

[a] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 eq), dimethyl malonate (3 eq), KOAc (pinch). [b] Conversion percentage determined by ^{1}H-NMR. [c] Enantiomeric excesses measured by HPLC for **13** and by GC for **14**. Absolute configuration drawn in parentheses. [d] Reaction carried out at 0 °C.

Finally, enantioselectivity can also be enhanced by changing the reaction parameters. Enantioselectivity was therefore further improved by decreasing the temperature to 0 °C (ee's up to 87% for **S1** and 81% for **S2**, entry 15). We also tested the reaction using other base additives, since the literature indicated that in some cases the source of base can have a positive effect on the reaction,[17] but the activities and enantioselectivities did not improve further (the results of these experiments can be found in the S.I. section).

Pd-*allylic substitution of other substrates and with other nucleophiles. Scope and limitations*

The scope of Pd/**L1**–**L7a**–**d** catalysts was then extended to other substrates and nucleophiles. As an example, Figures 2 and 3 shows the results with ligand **L1a** which had delivered together with ligands **L1d** (for **S1**), and **L1b** and **L7a**–**b** (for **S2**) one of the best results.

We first performed the substitution of substrate **S1** with several nucleophiles. Advantageously, enantioselectivity was independent to the steric nature of the ester groups of the malonate nucleophiles (products **13**, **15**–**16**) and also to the replacement of the malonate by acetylacetone (product **22**) and benzylamine derivatives (products **23**–**25**). In addition, a broad range of substituted malonates, including those with unsaturated groups, reacted smoothly with **S1** to achieve the corresponding alkylated products **17**–**21** in enantioselectivities similar to those attained with dimethyl malonate (ee's up to 91%). These results are important because products **18**–**21** can been used as intermediates for preparing more complex chiral compounds.[18] Interestingly, enantioselectivities comparable to those achieved with **S1** were also achieved in the alkylation of other substrates (compounds **26**–**29**), including those more sterically demanding (compounds **28** and **29**, ee's up to 93% ee) than **S1**. These results show that the biaryl phosphite functionality in the Pd/**L1a** catalyst is able to adjust the chiral cavity to the steric and electronic demands of the substrate and therefore alkylate them with comparable high enantioselectivities than with **S1**.

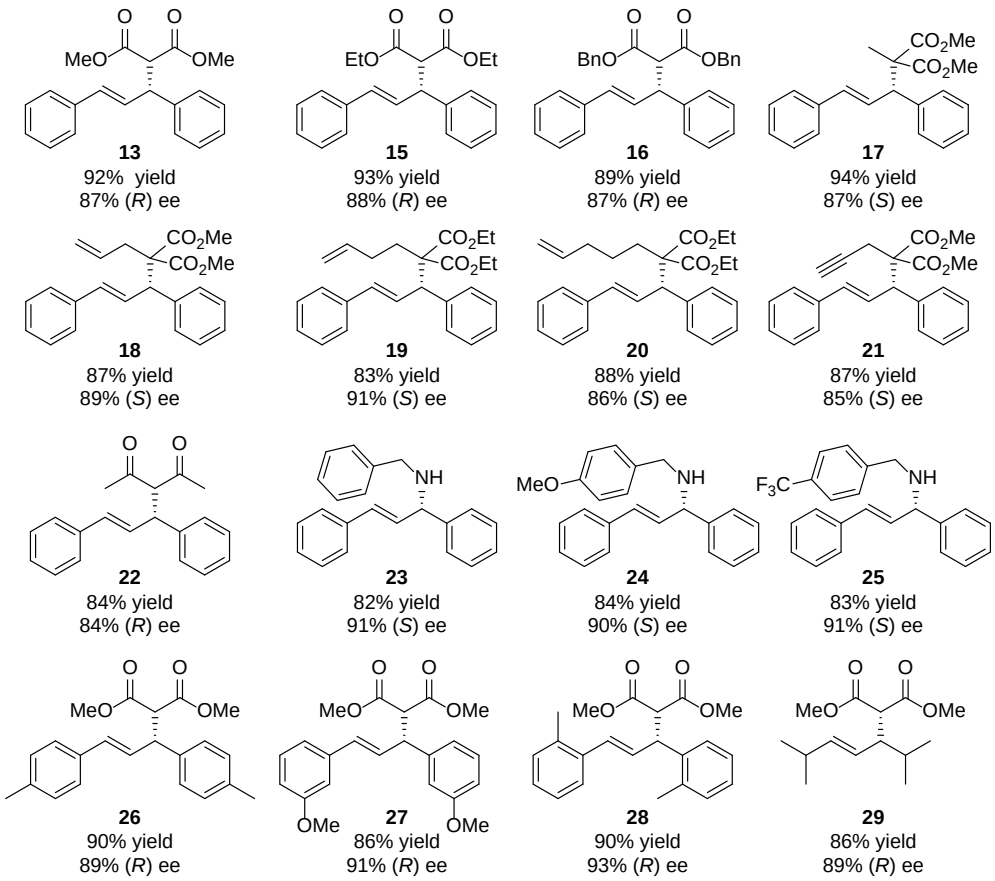


Figure 2. Pd-catalyzed allylic substitution of linear disubstituted symmetric substrates with C- and N- nucleophiles using Pd-**L1a** catalytic system. Reactions were run at 0 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions achieved after 12 h.

Encouraged by the high enantioselectivity reached for the challenging cyclic substrate **S2** (see Table 1) we then moved to the alkylation of cyclic substrates. For **S2**, several C-nucleophiles were used. In all cases, enantioselectivities (ee's up to 83%, compounds **14**, **30**–**33**) were similar to those obtained when using dimethyl malonate, even when acetylacetone was used as nucleophile. High yields and enantioselectivities were also reached when a 7-membered cyclic substrate was used with dimethyl and propargyl-malonates as nucleophiles (products **34** and **35**). Again, compounds **31**, **32** and **35** are relevant intermediates for the synthesis of chiral polycyclic compounds.[18a,d] These results are among the best reported for these substrates, even using synthetically valuable nucleophiles other than dimethyl malonate, for which few catalysts have afforded high catalytic performance.

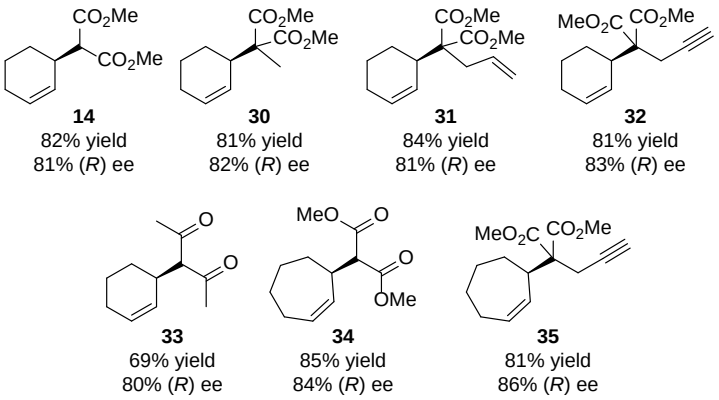


Figure 3. Pd-catalyzed allylic substitution of cyclic substrates with C-nucleophiles using Pd-**L1a** catalytic system. Reactions were run at 0 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions achieved after 24 h.

To sum up, the new sugar-based amino-phosphite ligands **L1a**,**d** and **L7a**–**b** have provided good results in different substrate types using several nucleophiles. The high catalytic performance (ee's up to 86%) reached with cyclic substrates are particularly encouraging. This fact, along with the promising results obtained for a number of linear substrates (ee's up to 93%; including the challenging sterically demanding compounds **28** and **29**), open up the Pd-allylic alkylation reactions to a novel type of readily available, solid, air stable and modular ligands.

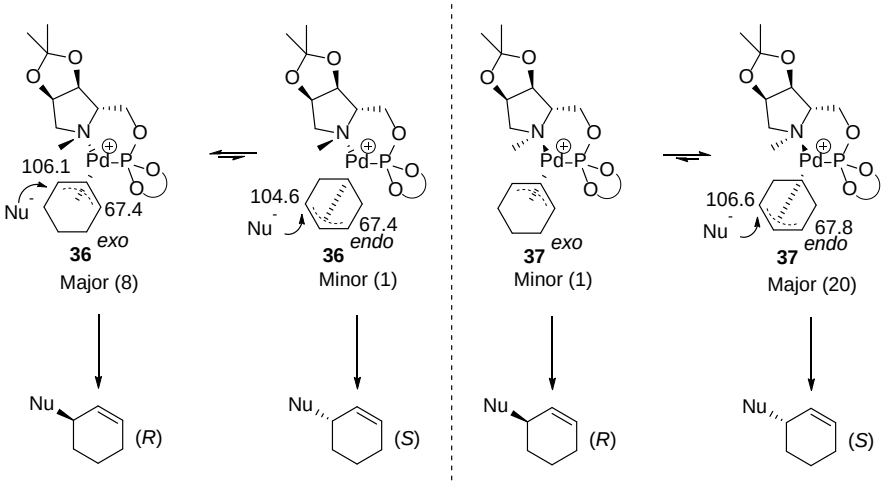
Mechanistic insights: investigation of the key Pd-π-allyl intermediates

In this process it has been proved that the enantioselectivity is controlled in the irreversible nucleophilic attack.[2] Therefore, studying the reactivity of the nucleophile with the Pd-π-allyl intermediates is crucial to explain the enantioselectivities achieved. We then prepared the Pd-π-allyl complexes **36**–**39** $[Pd(\eta^3\text{-allyl})(P\text{-}N)]BF_4$ (*P*-*N* = **L1a**, **L1b** and **L4a**), which contain cyclohexenyl- and 1,3-diphenylallyl groups, following a previously published method[19] from the $[PdCl(\eta^3\text{-allyl})]_2$ and the corresponding ligand with silver tetrafluoroborate (Scheme 3). The formation of the complexes were confirmed by mass spectrometry and by NMR. For spectral assignments bidimendional ^1H–^1H, ^1H–^{13}C, ^{31}P-^1H and ^1H-^1H NOESY spectra were performed.

Scheme 3. Synthesis of [Pd(η^3-allyl)(*P*-*N*)]BF_4 complexes **36**–**39**.

To understand the reversal in the sign of the enantioselectivity in the alkylation of cyclic substrates when varying the configuration of the phosphite functionality (moving from **a** to **b**), we studied the Pd-1,3-cyclohexenyl-allyl complex **36**, which has ligand **L1a** and compare it with the related Pd/**L1b** complex **37**. The VT-NMR study (30 ºC to –80 ºC) indicated a mixture of two isomers, in equilibrium, at a ratio of 1:8 and 20:1, respectively (Scheme 4). The major isomer of compound **36** was attributed by NOE to the Pd-η^3-*exo*, while the NOE indicated an *endo* disposition for major isomer of **37** (Figure 4). So, varying the configuration of the phosphite functionality lead to a different ratio of the isomers that provide both product's enantiomers. For the major isomer of complex **36**, the NOE indicates interaction between the hydrogen of the CH-N moiety with the central allyl proton, whereas for the major isomer of **37**, this NOE contact appears with one of the methylene groups of the cyclohexenyl moiety (Figure 4). These interactions are in agreement with an *exo* and an *endo* disposition of the major isomers of **36** and **37**, respectively. Moreover, the NOE also shows that for both isomers **36** the nitrogen adopts an *R*-configuration upon coordination, while for the major isomer of **37** it adopts an *S*-configuration. Thus, for isomers **36**, we found a NOE contact between the hydrogens of the methyl amine moiety with the terminal allylic proton *trans* to the phosphite moiety, whereas for the major isomer of **37** this NOE contact is found with the hydrogen of one of the CH-O groups of the sugar backbone (Figure 4). For all of them, the ^{13}C NMR show that the most electrophilic terminal allylic carbon is *trans* to the P-functionality (Scheme 4). If we assume that the nucleophilic attack is at the most electrophilic C, and since for complex **36** the enantioselectivity obtained experimentally (75% ee (*R*)) is similar to the diastereoisomeric excess of the Pd-isomers (de = 78% (*R*)) we can conclude that both isomers react at a similar rate. Therefore, for complex **36**, the enantioselectivity is mostly controlled by the ratio of the *exo* and *endo* compounds. However, for complex **37** the enantioselectivity obtained experimentally (72% (*S*)) is different from the diastereomeric excess (90% (*S*)) of the Pd-isomers. This indicates that the minor isomer should react slightly faster than the major one and that

enantioselectivity is also controlled by the different reactivity of the isomers of complex **37** towards the nucleophile.



Scheme 4. Pd-η^3-allyl intermediates for cyclic **S2** containing ligands **L1a** (isomers **36**) and **L1b** (isomers **37**). The ratio of each isomer is shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

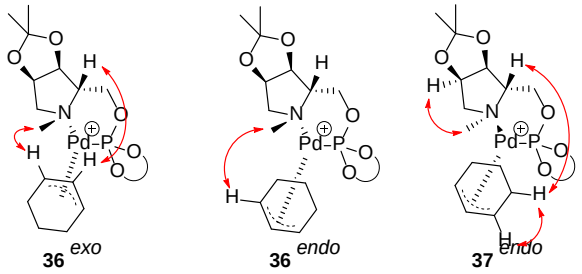
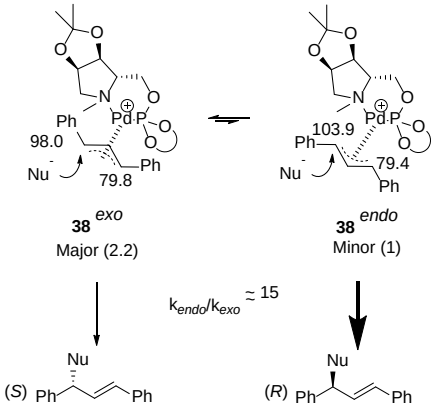


Figure 4. Selected NOE interactions from the NOESY spectra of Pd-η^3-allyl intermediates **36** and **37.**

Finally, to evaluate the effect of the configuration of carbons bearing the isopropylidene group on the enatioselectivity obtained in the allylic alkylation of **S1**, we studied the Pd allylic complexes with ligands **L1a** and **L4a** (**38** and **39**, respectively). Whereas ligand **L1a** provided high enantioselectivity (80% (*R*)), ligand **L4a** which differs in the configuration of the carbons bearing the isopropylidene group gave less enantioselectivity (17% (*S*)).

The VT-NMR (30 ºC to –85 ºC) investigation of Pd-allyl intermediate **38**, with ligand **L1a**, showed two isomers, in equilibrium, in a ratio of 2.2:1. They were

attributed by NMR to the two *syn*/*syn exo* and *endo* compounds (Scheme 5). For both the NOE experiment confirms a *syn*-*syn* disposition. Therefore, we found NOE contacts between the terminal protons of the allyl group (Figure 5a). In addition, the NOE also indicates that for both isomers the nitrogen adopts an *R*-configuration upon coordination. For the major isomer it was also found a NOE contact between the hydrogen of the CH-N group with the central allyl proton, whereas for the minor isomer there is a NOE contact of the methyl amine group with the hydrogen placed at the *ortho* position of one of the phenyl groups of the substrate. These interactions confirm an *exo* disposition for the major isomer of **38** and an *endo* disposition for the minor one (Figure 5a). The ^{13}C NMR shows that the most electrophilic terminal allylic C is again *trans* to the P-functionality. If we assume that the nucleophilic attack is at the most electrophilic terminal C and since the enantiomeric excess of the alkylation product (ee's up to 80% (*R*)) is higher than the diastereoisomeric excesses of the Pd-isomers (de= 37% (*S*)), the minor *endo* isomer should react faster than the *exo*. To confirm it we performed an *in situ* NMR study of the reactivity of both Pd-isomers with dimethyl malonate at low temperature (Figure 5b). This experiment evidences that the minor isomer (*endo*) reacts around 15 times faster with the nucleophile than the major isomer (*exo*). If we consider the ratio of each reacting isomer and their reactivity with dimethyl malonate, the theoretical ee should be 74% (*R*), which is in agreement with the experimental enantioselectivity (80% (*R*)). This is consistent with a nucleophilic attack mainly at the terminal C *trans* to the phosphite functionality of the minor *endo* isomer. Consequently, for substrate **S1** and ligand **L1a** the enantioselectivity seems to be controlled by the different reactivity of the Pd-isomers towards the nucleophile, rather than by the ratio of isomers, as was the case for substrate **S2** when the same ligand **L1a** was used.



Scheme 5. Pd-η^3-allyl intermediates for linear **S1** containing ligand **L1a** (isomers **38**). The ratio of each isomer is shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

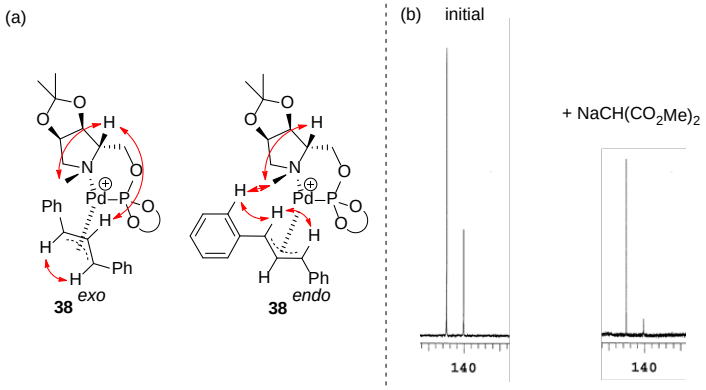
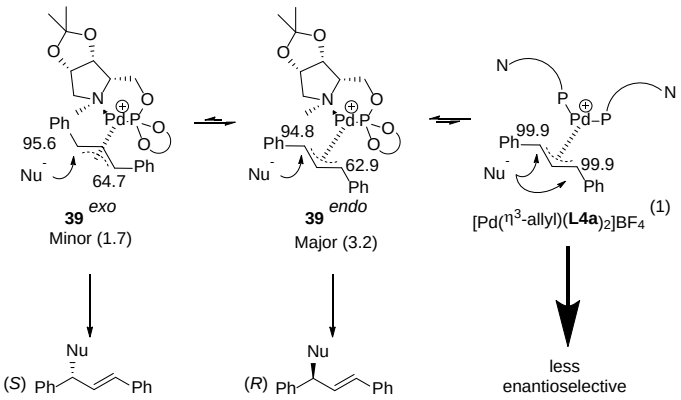


Figure 5. (a) Selected NOE interactions from the NOESY spectrum of Pd-η^3-allyl intermediates **38** *exo* and *endo*. (b) Reactivity of intermediates **38** towards sodium dimethyl malonate at –80 °C. ^{31}P-{^{1}H}NMR spectra before and after the addition of sodium dimethyl malonate in CD_2Cl_2.

In contrast to the previous study with ligand **L1a**, the VT-NMR (30 ºC to -85 ºC) of Pd-allyl complexes **39**, with **L4a**, showed three compounds in equilibrium at a ratio of 3.2:1.7:1. The two major ones were attributed to the *syn*/*syn endo* and *exo* isomers of **39** (see relevant NOE contacts in Figure 6), while the minor compound was assigned to Pd-allyl complex ([Pd(η^3-allyl)(**L4a**)$_2$]BF_4) with two P-N ligands coordinated to the Pd as a monodentate through the phosphite functionality (Scheme 6). Monodentate coordination of **L4a** in the minor species [Pd(η^3-allyl)(**L4a**)$_2$]BF_4 is clearly disclosed because the methyl amine's signals in the ^{1}H and ^{13}C NMR spectra are not shielded as is the case when the amino group coordinates to Pd. It should be pointed out that varying the configuration of carbons bearing the isopropylidene group also implied variations in the configuration of the nitrogen upon coordination to palladium from *R* (in isomers **38**) to *S* (in isomers **39**). Thus, for isomers **39**, we found NOE contacts between one of the methyl groups of the isopropylidene moiety with the methyl of the amino group (Figure 6). The lower enantioselectivity obtained with the Pd/**L4a** system than with the Pd/**L1a** one could be due to the existence of [Pd(η^3-allyl)(**L4a**)$_2$]BF_4. This type of complexes has shown to provide higher conversion with lower enantioselectivity than their bidentate analogues because they have more degrees of freedom.[20]

The elucidation of the Pd-1,3-diphenylallyl intermediates allows to conclude that for enantioselectivity to be high, a proper combination of the ligand components are required to avoid the formation of species with ligands coordinated in monodentated fashion.



Scheme 6. Pd-η^3-allyl intermediates for linear **S1** containing ligand **L4a** (isomers **39** and [Pd(η^3-allyl)(**L4a**)$_2$]BF_4). The ratio of each compound is shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

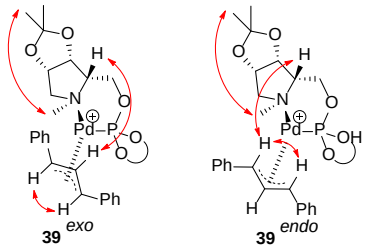


Figure 6. Selected NOE interactions from the NOESY spectrum of Pd-η^3-allyl intermediates **39** *exo* and *endo*.

Conclusions

A series of new iminosugar-phosphite/phosphinite/phosphine ligands have been screened in Pd allylic substitutions. These ligands are obtained in enantiomerically pure form from readily available sugars as starting materials. They thus contain the advantages of carbohydrates in terms of selection of the stereogenic carbons, polyfunctional groups able to modulate the electronic and sterical properties, and the general good stability of carbohydrate derivatives. Thus, several ligand parameters can be systematically varied so selectivities can been maximized for each substrate. By choosing the ligand components, we attained good results in a number of substrates

with several electronic and steric requirements and using C- and N-nucleophiles (23 compounds in total with ee's up to 93%). For both substrate types (linear and cyclic), biaryl phosphite groups in the ligand are needed for high enantioselectivity. This is advantageous because the iminosugar-phosphite ligands are air-stable solids in contrast to their amino-phosphinite/phosphine analogues. The influence of the remaining ligand components (amine substituent, the configuration of carbons bearing the isopropylidene group, the substituent/configuration of the phosphite functionality and the rigidity of the ligand) on the selectivity depend on each type of substrate. Particularly, for linear substrates we found that an *R*-configuration of the binaphthyl moiety is needed for high enantioselectivity. However, for cyclic substrates both product's enantiomers can be attained by setting the configuration of the phosphite functionality. Additionally, for cyclic substrates, in contrast to linear ones, enantioselectivity is also influenced by the substituent of the phosphite functionality and there is a little impact by the configuration of carbons bearing the isopropylidene group and the rigidity of the ligand. In comparison with previous air instable amino-P ligands[6] (P=phosphine, aminophosphine and phosphinite groups) found in the literature, the new amino-phosphite ligands gave a better substrate and nucleophile scope (i.e. including more challenging hindered linear and cyclic substrates, even with highly interesting nucleophiles like those α-substituted with unsaturated moieties). These results pave the way for the further development of modular amino-phosphite ligands, which are readily available and air stable, for the asymmetric Pd-allylic substitution of different substrates, including the more demanding cyclic ones, with a broad range of nucleophiles.

Finally, the elucidation of the Pd-π-allyl complexes allows us to explain the enantioselectivities obtained. It shows that for high enantioselectivities the ligand components need to be appropriately mixed to either enhance the difference in the ratio of the Pd-allyl isomers formed, or to enhance the reactivity of the nucleophile toward each Pd-allyl isomer, for cyclic substrates. However, for linear substrates the combination of ligand components has to suppress the formation of Pd-allyl complexes with monodentated coordinated ligands. This study also indicates that the sugar backbone is able to control the configuration of the amino group upon coordination, which in turn can be efficiently shifted from *R*- to *S*- by varying the configuration of the biaryl phosphite functionality.

Experimental Section

General considerations

All reactions were performed with standard Schlenk techniques using an argon atmosphere, except for the preparation of pyrrolidine alcohols and their precursors. Commercial chemicals were used as received. Solvents were dried by means of standard procedures and stored under argon. Phosphorochloridites were synthetized in one step from the appropriate biphenols and binols.[21] Racemic substrates **S1**, **S2**, 1,3-di-p-tolylallyl acetate, 1,3-bis(3-methoxyphenyl)allyl acetate, 1,3-di-o-tolylallyl acetate, 2,6-dimethylhept-4-en-3-yl acetate and cyclohept-2-en-1-yl acetate;[22] and Pd-allyl complexes $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-}C_3H_3)(\mu\text{-}Cl)]_2$[23] and $[Pd(\eta^3\text{-cyclohexenyl})(\mu\text{-}Cl)]_2$[24] were prepared as previously reported. TLC was performed on silica gel HF_{254} (Merck), with detection by UV light charring with H_2SO_4, *p*-anisaldehyde, vanillin, ninhydrin, $KMnO_4$, phosphomolybdic acid or with Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Silica gel 60 (Merck, 63–200 μm) was used for preparative chromatography. Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Jasco P-2000 spectropolarimeter. Infrared spectra were recorded with a Jasco FTIR-410 spectrophotometer. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were performed in Bruker, AV300, AV500 and Varian Mercury-400 MHz spectrometers for solutions in $CDCl_3$, C_6D_6 and DMSO-d_6 at room temperature, except when indicated. Chemical shifts are relative to that of $SiMe_4$ (^1H and $^{13}C\{^1H\}$) as an internal standard or H_3PO_4 (^{31}P) as an external standard. ^1H and ^{13}C assignments were confirmed by ^1H–^1H gCOSY, ^1H–^{13}C gHSQC and NOESY spectra. Mass spectra (CI and ESI) were recorded on Micromass AutoSpeQ and QTRAP (Applied Biosystems) y Orbitrap Elite spectrometers. NMR and mass spectra were registered in CITIUS (University of Seville) and in SRCiT (Universitat Rovira i Virgili).

(2*S*,3*S*,4*R*)-*N*-Methyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (1). To a suspension of $LiAlH_4$ (420 mg, 10.9 mmol) in anhydrous THF (22 mL) at 0 ºC, a solution of **7**[14] (600 mg, 2.19 mmol) in anhydrous THF (22 mL) was added. The mixture was heated at reflux for 2.5 h and then cooled at 0 ºC. Diethyl ether and sat. aq. sol. of Na_2SO_4 were successively added and the mixture was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/cyclohexane – 1/3) to produce **1** (345 mg, 84%) as a pale yellow oil. $[\alpha]_D^{24}$ - 19.9 (*c* 1.08, CH_2Cl_2). ^1H NMR (300 MHz,

$CDCl_3$), δ: 1.11 (s, 3H, -C(C*H*$_3$)$_2$), 1.51 (s, 3H, -C(C*H*$_3$)$_2$), 2.36 (s, 3H, N-C*H*$_3$), 2.51-2.57 (m, 2H, H-2, H-5a), 2.61 (brs, 1H, OH), 3.33-3.39 (m, 1H, H-5b), 3.63 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 11.4, $J_{1'a\text{-}2}$ = 2.7), 3.72 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 3.6), 4.56-4.63 (m, 2H, H-3, H-4). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 25.0 (-C(*C*H$_3$)$_2$), 27.3 (-C(*C*H$_3$)$_2$), 40.0 (N-*C*H$_3$), 59.3 (C-1'), 62.0 (C-5), 71.6 (C-2), 77.8, 82.2 (C-3, C-4), 113.1 (-*C*(CH$_3$)$_2$). HRMS (ESI) *m/z:* calcd for $C_9H_{18}NO_3$: 188.1281 $[M+H]^+$; found 188.1276.

(2*S*,3*S*,4*R*)-2-Hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (8). To a solution of **7**[14] (203 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (10 mL) with 4Å MS at 0 ºC, was added anhydrous trifluoroacetic acid (1.9 mL). The mixture was stirred at r.t. for 1 h and then was filtered and the solvent was evaporated. The residue was dissolved in anhydrous CH_2Cl_2 and Ambersep 900 was added. The resulting mixture was filtered and the solvent was evaporated. The residue was purified by chromatography column on silica gel (eluent: CH_2Cl_2/MeOH – 10/1, 1% Et_3N) to produce **8** (101 mg, 78%) as a pale yellow oil. $[\alpha]_D^{27}$ - 26.2 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.30 (s, 3H, -C(C*H*$_3$)$_2$), 1.47 (s, 3H, -C(C*H*$_3$)$_2$), 3.08 (dd, 1H, H-5a, $J_{5a\text{-}5b}$ = 13.5, $J_{5a\text{-}4}$ = 4.2), 3.19 (d, 1H, H-5b), 3.39 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 11.1, $J_{1'a\text{-}2}$ = 8.7), 3.49 (dd, 1H, H-2, $J_{2\text{-}1'b}$ = 4.2), 3.65 (dd, 1H, H-1'b), 4.50 (d, 1H, H-3, $J_{3\text{-}4}$ = 5.4), 4.63 (brs, 2H, OH, NH), 4.76 (t, 1H, H-4). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 24.0 (-C(*C*H$_3$)$_2$), 26.3 (-C(*C*H$_3$)$_2$), 51.3 (C-5), 59.5 (C-1'), 66.5 (C-2), 81.0 (C-4), 82.7 (C-3), 111.6 (-*C*(CH$_3$)$_2$). HRMS (ESI) *m/z:* calcd for $C_8H_{16}NO_3$: 174.1125 $[M+H]^+$; found 174.1121.

(2*S*,3*S*,4*R*)-*N*-Benzyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (2). To a solution of **8** (125 mg, 0.72 mmol) in anhydrous 1,2-dichloroethane (7.5 mL), benzaldehyde (0.15 mL, 1.44 mmol) and $NaBH(OAc)_3$ (320 mg, 1.51 mmol) were successively added. The mixture was stirred at r.t. for 3 h and then, sat. aq. sol. of $NaHCO_3$ (15 mL) was added. The aqueous phase was extracted (× 4) with EtOAc. The organic layers were dried with Na_2SO_4, filtered and evaporated. The residue was purified by chromatography column on silica gel (eluent: Et_2O/cyclohexane – 3/1→Et_2O) to produce **2** (128 mg, 68%) as a pale yellow oil. $[\alpha]_D^{28}$ + 41.3 (*c* 0.94, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.32 (s, 3H,-C(C*H*$_3$)$_2$), 1.54 (s, 3H, -C(C*H*$_3$)$_2$), 2.39 (brs, 1H, OH), 2.61-2.66 (m, 1H, H-5a), 2.94-2.97 (m, 1H, H-2), 3.17-3.23 (m, 1H, H-5b), 3.57 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 11.1, $J_{1'a\text{-}2}$ = 3.6), 3.60 (d, 1H, C*H*$_2$Ph, $J_{H\text{-}H}$ =

12.9), 3.65 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 3.9), 3.98 (d, 1H, CH_2Ph), 4.56-4.63 (m, 2H, H-3, H-4), 7.23-7.36 (m, 5H, H-arom.). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 25.0 (-C(*C*H_3)$_2$), 27.4 (-C(*C*H_3)$_2$), 58.3 (*C*H_2Ph), 58.6 (C-5), 59.6 (C-1'), 70.1 (C-2), 78.6, 82.7 (C-3, C-4), 112.9 (-*C*(CH$_3$)$_2$), 127.5, 128.6, 128.9, 138.5 (aromatic carbons). HRMS (ESI) *m/z:* calcd for $C_{15}H_{22}NO_3$: 264.1594 $[M+H]^+$; found 264.1594.

(2*S*,3*S*,4*R*)-*N*-Isopropyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (3). To a solution of compound **8** (121 mg, 0.70 mmol) in MeOH (1.5 mL), acetone (0.26 mL, 3.49 mmol) and Pd/C 10% (cat.) were added. The reaction mixture was stirred under H_2 overnight. The catalyst was filtered through celite and washed with MeOH. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: CH_2Cl_2/MeOH – 30/1→20/1) to produce **3** (113 mg, 75%) as a pale yellow oil. $[\alpha]_D^{27}$ + 13.3 (*c* 0.79, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.00 (d, 3H, C*H*$_3$, $J_{H\text{-}H}$ = 6.3), 1.09 (d, 3H, C*H*$_3$), 1.31 (s, 3H,-C(C*H*$_3$)$_2$), 1.50 (s, 3H, C(C*H*$_3$)$_2$), 2.32 (brs, 1H, OH), 2.77 (dd, 1H, H-5a, $J_{5a\text{-}5b}$ = 10.2, $J_{5a\text{-}4}$ = 4.8), 2.97-3.06 (m, 2H, (CH$_3$)$_2$C*H*, H-2), 3.18 (dd, 1H, H-5b, $J_{5b\text{-}4}$ = 6.0), 3.52 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 10.8, $J_{1'a\text{-}2}$ = 2.7), 3.63 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 3.6), 4.52 (dd, 1H, H-3, *J* = 6.6, *J* = 3.0), 4.56-4.62 (m, 1H, H-4). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 15.7 (*C*H$_3$), 22.3 (*C*H$_3$), 25.3 (-C(*C*H$_3$)$_2$), 27.6 (-C(*C*H$_3$)$_2$), 48.0 ((CH$_3$)$_2$*C*H), 51.6 (C-5), 59.6 (C-1'), 65.8 (C-2), 78.4 (C-4), 83.0 (C-3), 112.5 (-*C*(CH$_3$)$_2$). HRMS (ESI) *m/z:* calcd for $C_{11}H_{22}NO_3$: 216.1594 $[M+H]^+$; found 216.1589.

(2*S*,3*R*,4*S*)-*N*-*terc*-Butoxycarbonyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (10). To a solution of compound **9**[15] (2.44 g, 9.28 mmol) in MeOH (70 mL), Boc_2O (2.02 g, 18.6 mmol) and Pd/C 10% (0.63 g) were added. The reaction mixture was stirred under H_2 for 3 h. The catalyst was filtered through celite and washed with MeOH. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/cyclohexane – 1/2) to give **10** (2.18 g, 86%) as a colourless oil. $[\alpha]_D^{24}$ +41.8 (*c* 1.00, CH_2Cl_2). NMR and IR data are in accordance with those of its enantiomer.[14] HRMS (ESI) *m/z:* calcd for $C_{13}H_{23}NO_5Na$: 296.1468 $[M+Na]^+$; found 296.1465.

(2*S*,3*R*,4*S*)-*N*-Methyl-2-hydroxymethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (4). To a suspension of $LiAlH_4$ (206 mg, 5.43 mmol) in anhydrous THF (11 mL) at 0 ºC, a solution of **10** (292.6 mg, 1.09 mmol) in anhydrous THF (11 mL) was added. The mixture was heated at reflux for 2.5 h and then cooled at 0 ºC. Diethyl ether and sat. aq. sol. of Na_2SO_4 were successively added and the mixture was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/MeOH– 7/1→5:1) to produce **4** (184.2 mg, 91%) as a pale yellow solid. $[\alpha]_D^{27}$ + 72.5 (*c* 0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.30 (s, 3H, -C(C*H*$_3$)$_2$), 1.51 (s, 3H, -C(C*H*$_3$)$_2$), 2.06-2.13 (m, 1H, H-2), 2.19 (dd, 1H, H-5a, $J_{5a\text{-}5b}$ = 11.4, $J_{5a\text{-}4}$ = 4.5), 2.32 (s, 3H, N-C*H*$_3$), 3.25 (d, 1H, H-5b), 3.42 (brs, 1H, OH), 3.84 (dd, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 11.7, $J_{1'a\text{-}2}$ = 6.0), 3.91 (dd, 1H, H-1'b, $J_{1'b\text{-}2}$ = 3.6), 4.61 (dd, 1H, H-4, $J_{4\text{-}3}$ = 6.3), 4.70 (dd, 1H, H-3, $J_{3\text{-}2}$ = 5.1). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 24.3 (-C(*C*H$_3$)$_2$), 25.9 (-C(*C*H$_3$)$_2$), 40.3 (N-*C*H$_3$), 59.7 (C-1'), 61.7 (C-5), 69.7 (C-2), 78.0 (C-4), 81.8 (C-3), 111.3 (-*C*(CH$_3$)$_2$). HRMS (ESI) *m/z:* calcd for $C_9H_{18}NO_3$: 188.1281 $[M+H]^+$; found 188.1277.

(6*S*,7*R*,7a*S*)-6,7-O-Isopropyliden-tetrahydropyrrolo[1,2-c]-oxazol-3-ona-6,7-diol (11). To a solution of **10** (1.06 g, 3.89 mmol) in anhydrous pyridine (15 mL) at 0 ºC, TsCl (1.89 g, 9.74 mmol) was slowly added. After stirring at r.t. overnight, the solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/cyclohexane – 1/1→2/1) to produce **11** (713 mg, 92%) as a white solid. $[\alpha]_D^{22}$ +25.6 (c 0.82, CH_2Cl_2). HRMS (ESI) *m/z:* calcd for $C_9H_{13}NO_4Na$: 222.0737 $[M+Na]^+$; found 222.0735. NMR and IR data are in accordance with those of its enantiomer.[14]

(2*S*,3*R*,4*S*)-2-Diphenylphosphinomethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (12). To a solution of **11** (147 mg, 0.74 mmol) in anhydrous THF (6.0 mL) at 0 ºC, $KPPh_2$ (0.5 M in THF, 1.8 mL, 0.89 mmol) was slowly added. The mixture was heated at reflux for 2 h and then cooled to r.t. IRA-120H$^+$ was added and the resulting mixture was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: Et_2O/acetone – 10/1, 1% Et_3N) to produce **12** (26 mg, 89%) as a colourless oil. $[\alpha]_D^{22}$ +63.2 (*c* 0.57, CH_2Cl_2). ^{31}P NMR (121.5 MHz, $CDCl_3$), δ: -20.9. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.31

(s, 3H, -C(CH_3)$_2$), 1.46 (s, 3H, -C(CH_3)$_2$), 1.95 (brs, 1H, NH), 2.37 (dd, 1H, H-1'a, $J_{1'a-1'b}$ = 13.2, $J_{1'a-2}$ = 8.1), 2.43 (dd, 1H, H-1'b, $J_{1'b-2}$ = 6.3), 2.50-2.62 (m, 2H, H-2, H-5a), 3.02 (d, 1H, H-5b, J_{5b-5a} = 13.5), 4.57 (dd, 1H, H-3, J_{3-4} = 5.7, J_{3-2} = 3.9), 4.61-4.64 (m, 1H, H-4), 7.29-7.35 (m, 6H, H-arom.), 7.42-7.53 (m, 4H, H-arom.). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ: 24.1 (-C(*C*H_3)$_2$), 26.0 (-C(*C*H_3)$_2$), 27.3 (d, J_{C-P} = 13.2, C-1'), 53.2 (C-5), 61.5 (d, J_{C-P} = 16.3, C-2), 81.8 (d, J_{C-P} = 4.5, C-3), 82.2 (C-4), 110.6 (-*C*(CH$_3$)$_2$), 128.4 (C-arom.), 128.5 (d, J_{C-P} = 8.4, C-arom.), 128.6 (d, J_{C-P} = 6.7, C-arom.), 128.9 (C-arom.), 132.8 (d, J_{C-P} = 19.1, C-arom.), 133.1 (d, J_{C-P} = 19.3, C-arom.), 138.6 (d, J_{C-P}= 13.0, C_{arom}-P), 138.9 (d, J_{C-P} = 13.0, C_{arom}-P). HRMS (ESI) *m/z:* calcd for $C_{20}H_{25}NO_2P$: 342.1617 $[M+H]^+$; found 342.1609.

General procedure for the synthesis of the amino-phosphite ligands L1–L4a–d and L7a–b. The desired in situ prepared phosphorochloridite (1.1 eq) was first dissolved in toluene (5 mL/mmol) and then pyridine (3.8 eq) was added. After azeotropically drying the corresponding alcohols **1**–**4** and **6**, with toluene (3x1 mL), toluene (5 mL/mmol) and pyridine (3.8 eq) was added. The solution was transferred slowly at 0 ºC to the solution of the phosphorochloridite. The resulting reaction mixture was stirred overnight at 80 ºC, and then the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography in alumina (eluent: toluene/triethylamine – 100/1) to produce the corresponding ligand as a white solid.

L1a: Yield: 72.5 mg (56%, reaction carried out using 0.20 mmol of **1**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 132.9. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.52 (s, 9H, CH_3, $SiMe_3$), 0.54 (s, 9H, CH_3, $SiMe_3$), 1.17 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.96 (s, 3H, CH_3, NMe) 2.37 (dd, 1H, CH_2-N, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =4.8 Hz), 2.47 (m, 1H, CH), 2.89 (dd, 1H, CH_2-N, $^2J_{H-H}$ =9.6 Hz, $^3J_{H-H}$ =6.1 Hz), 3.45 (m, 1H, CH_2-OP), 4.11 (m, 1H, CH_2-OP), 4.33 (m, 1H, CH-O), 4.53 (m, 1H, CH-O), 6.85 (m, 2H, CH=), 7.01 (m, 1H, CH=), 7.04-7.13 (m, 1H, CH=), 7.24 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.36 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.69 (d, 2H, CH=, $^3J_{H-H}$ =8.5 Hz), 8.12 (d, 2H, CH=, $^3J_{H-H}$ =8.5 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 24.9 (CH_3), 27.2 (CH_3), 39.3 (CH_3, NMe), 61.8 (CH_2-N), 62.3 (CH_2-OP), 70.1 (CH), 77.8 (CH-O), 82.3 (CH-O), 112.5 (C), 122.5 – 153.1 (Aromatic Carbons). Anal. calcd. (%) for $C_{35}H_{44}NO_5PSi_2$: C 65.09, H 6.87, N 2.17; found: C 65.30, H 6.87, N 2.15. TOF-MS (ESI+): *m/z:* calcd for $C_{35}H_{44}NO_5PSi_2$: 668.2388 $[M+Na]^+$; found 668.2390.

L1b: Yield: 100.0 mg (60%, reaction carried out using 0.25 mmol of **1**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 136.5. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.50 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 1.10 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.02 (s, 3H, CH_3, NMe) 2.42 (dd, 1H, CH_2-N, $^{2}J_{H-H}$ =9.6 Hz, $^{3}J_{H-H}$ =4.6 Hz), 2.61 (m, 1H, CH), 2.95 (m, 1H, CH_2-N), 3.53 (m, 1H, CH_2-OP), 4.09 (m, 1H, CH_2-OP), 4.24 (m, 1H, CH-O), 4.32 (m, 1H, CH-O), 6.86 (m, 2H, CH=), 7.02 (m, 1H, CH=), 7.12 (m, 1H, CH=), 7.24 (d, 1H, CH=, $^{3}J_{H-H}$ =8.5 Hz), 7.33 (d, 1H, CH=, $^{3}J_{H-H}$ =8.5 Hz), 7.69 (d, 2H, CH=, $^{3}J_{H-H}$ =8.2 Hz), 8.10 (d, 2H, CH=, $^{3}J_{H-H}$ =8.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, SiMe3), -0.2 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 24.9 (CH_3), 27.2 (CH_3), 39.5 (CH_3, NMe), 61.9 (CH_2-N), 64.1 (CH_2-OP), 70.3 (CH), 77.9 (CH-O), 82.4 (CH-O), 112.6 (C), 122.3 – 152.9 (Aromatic Carbons). Anal. calcd. (%) for $C_{35}H_{44}NO_5PSi_2$: C 65.09, H 6.87, N 2.17; found: C 65.69, H 6.89, N 2.12. TOF-MS (ESI+): *m/z:* calcd for $C_{35}H_{44}NO_5PSi_2$: 668.2388 $[M+Na]^+$; found 668.2387.

L1c: Yield: 71.5 mg (44%, reaction carried out using 0.25 mmol of **1**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 129.6. ^{1}H NMR (400 MHz, C_6D_6), δ: 1.98 (s, 3H, CH_3), 2.11 (m, 2H, CH_2), 2.28 (s, 3H, CH_3) 2.31 (m, 6H, CH_2), 2.38 (s, 18H, CH_3, ^{t}Bu), 2.92 (s, 3H, CH_3, NMe), 3.07 (m, 1H, CH_2), 3.35 (m, 9H, CH_2, CH, CH_2-N), 3.77 (dd, 1H, CH_2-N, $^{2}J_{H-H}$ =9.5 Hz, $^{3}J_{H-H}$ =6.1 Hz), 4.31 (m, 1H, CH_2-OP), 4.86 (m, 1H, CH_2-OP), 5.18 (m, 1H, CH-O), 5.34 (m, 1H, CH-O), 7.96 (m, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: 23.6 (CH_2), 23.8 (CH_2), 23.9 (CH_2), 25.7 (CH_2), 28.0 (CH_2), 28.1 (CH_2), 28.3 (CH_3), 30.3 (CH_3), 30.4 (CH_2), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.3 (C, ^{t}Bu), 35.4 (C, ^{t}Bu), 40.2 (CH_3, NMe), 62.7 (CH_2-N), 63.5 (CH_2-OP), 71.0 (CH), 78.9 (CH-O), 83.3 (CH-O), 113.3 (C), 126.1 – 139.3 (Aromatic Carbons). Anal. calcd. (%) for $C_{37}H_{52}NO_5P$: C 71.47, H 8.43, N 2.25; found: C 71.69, H 8.42, N 2.23. TOF-MS (ESI+): *m/z:* calcd for $C_{37}H_{52}NO_5P$: 644.3475 $[M+Na]^+$; found 644.3479.

L1d: Yield: 118.4 mg (61%, reaction carried out using 0.35 mmol of **1**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 127.5. ^{1}H NMR (400 MHz, C_6D_6), δ: 1.14 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.54 (s, 18H, CH_3, ^{t}Bu) 1.64 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.07 (s, 3H, CH_3, NMe), 2.43 (dd, 1H, CH_2-N, $^{2}J_{H-H}$ =9.6 Hz, $^{3}J_{H-H}$ =4.7 Hz), 2.58 (dd, 1H, CH, $^{2}J_{H-H}$ =8.6 Hz, $^{3}J_{H-H}$ =4.0 Hz), 2.93 (dd, 1H, CH_2-N, $^{2}J_{H-H}$ =9.6 Hz, $^{3}J_{H-H}$ =6.1 Hz), 3.49 (m, 1H, CH_2-OP), 4.10 (m, 1H, CH_2-OP), 4.34 (m, 1H, CH-O), 4.53 (m, 1H, CH-O), 7.17 (m, 1H, CH=), 7.18 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: 16.2 (CH_3), 16.4 (CH_3), 20.0 (CH_3), 20.1 (CH_3), 24.9 (CH_3), 27.2 (CH_3), 29.8 (CH_3), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 34.6 (C, ^{t}Bu), 34.7 (C, ^{t}Bu),

39.3 (CH_3, NMe), 61.9 (CH_2-N), 62.4 (CH_2-OP), 70.3 (CH), 77.9 (CH-O), 82.5 (CH-O), 112.4 (C), 125.3 – 146.2 (Aromatic Carbons). Anal. calcd. (%) for $C_{33}H_{48}NO_5P$: C 69.57, H 8.49, N 2.46; found: C 69.70, H 8.50, N 2.44. TOF-MS (ESI+): *m/z:* calcd for $C_{33}H_{48}NO_5P$: 592.3162 $[M+Na]^+$; found 592.3165.

L2a: Yield: 167.2 mg (50%, reaction carried out using 0.46 mmol of **2**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 133.6. ^1H NMR (400 MHz, C_6D_6), δ: 0.47 (s, 9H, CH_3, $SiMe_3$), 0.48 (s, 9H, CH_3, $SiMe_3$), 1.16 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.51 (dd, 1H, CH_2-N, $^2J_{H-H}$ =10.3 Hz, $^3J_{H-H}$ =3.6 Hz), 2.76 (dd, 1H, CH_2-N, $^2J_{H-H}$ =10.3 Hz, $^3J_{H-H}$ =3.6 Hz) 2.92 (m, 1H, CH), 3.22 (d, 1H, CH_2Ph, $^2J_{H-H}$ =13.3 Hz), 3.36 (m, 1H, CH_2-OP), 3.64 (d, 1H, CH_2Ph, $^2J_{H-H}$ =13.3 Hz), 4.07 (m, 1H, CH_2-OP), 4.27 (m, 1H, CH-O), 4.59 (dd, 1H, CH-O, $^2J_{H-H}$ =6.6 Hz, $^3J_{H-H}$ =2.6 Hz), 6.84 (m, 2H, CH=), 7.03 (m, 7H, CH=), 7.20 (d, 1H, CH=, $^3J_{H-H}$ =8.6 Hz), 7.32 (d, 1H, CH=, $^3J_{H-H}$ =8.6 Hz), 7.65 (d, 2H, CH=, $^3J_{H-H}$ =8.4 Hz), 8.07 (d, 2H, CH=, $^3J_{H-H}$ =4.7 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.4 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 24.9 (CH_3), 27.2 (CH_3), 56.9 (CH_2Ph), 58.5 (CH_2-N), 62.8 (CH_2-OP), 67.9 (CH), 78.6 (CH-O), 82.7 (CH-O), 112.1 (C), 122.4 – 153.0 (Aromatic Carbons). Anal. calcd. (%) for $C_{41}H_{48}NO_5PSi_2$: C 68.21, H 6.70, N 1.94; found: C 68.60, H 6.76, N 1.90. TOF-MS (ESI+): *m/z:* calcd for $C_{41}H_{48}NO_5PSi_2$: 744.2701 $[M+Na]^+$; found 744.2703.

L3a: Yield: 148.9 mg (70%, reaction carried out using 0.30 mmol of **3**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 134.24. ^1H NMR (400 MHz, C_6D_6), δ: 0.49 (s, 9H, CH_3, $SiMe_3$), 0.51 (s, 9H, CH_3, $SiMe_3$), 0.69 (d, 3H, CH_3, ^{i}Pr, $^2J_{H-H}$ =6.3 Hz) 0.78 (d, 3H, CH_3, ^{i}Pr, $^2J_{H-H}$ =6.3 Hz), 1.21 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.63 (m, 3H, CH_2-N, CH, ^{i}Pr), 3.11 (m, 1H, CH), 3.38 (m, 1H, CH_2-OP), 3.97 (m, 1H, CH_2-OP), 4.35 (m, 1H, CH-O), 4.60 (dd, 1H, CH-O, $^2J_{H-H}$ =6.5 Hz, $^3J_{H-H}$ =1.2 Hz), 6.82 (t, 2H, CH=, $^3J_{H-H}$ =11.3 Hz), 7.08 (m, 2H, CH=), 7.19 (d, 1H, CH=, $^3J_{H-H}$ =8.6 Hz), 7.29 (d, 1H, CH=, $^3J_{H-H}$ =8.5 Hz), 7.65 (m, 2H, CH=), 8.08 (d, 2H, CH=, $^3J_{H-H}$ =9.3 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.3 (CH_3, $SiMe_3$), -0.2 (CH_3, $SiMe_3$), -0.1 (CH_3, $SiMe_3$), 17.0 (CH_3, ^{i}Pr), 21.8 (CH_3, ^{i}Pr), 25.2 (CH_3), 27.3 (CH_3), 47.9 (CH, ^{i}Pr), 52.8 (CH_2-N), 62.8 (CH_2-OP), 64.6 (CH), 78.5 (CH-O), 82.7 (CH-O), 111.7 (C), 122.4 – 153.0 (Aromatic Carbons). Anal. calcd. (%) for $C_{37}H_{48}NO_5PSi_2$: C 65.94, H 7.18, N 2.08; found: C 66.03, H 7.23, N 2.07. TOF-MS (ESI+): *m/z:* calcd for $C_{37}H_{48}NO_5PSi_2$: 696.2701 $[M+Na]^+$; found 696.2700.

L4a: Yield: 71 mg (54%, reaction carried out using 0.20 mmol of **4**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 135.6. ^1H NMR (400 MHz, C_6D_6), δ: 0.55 (s, 9H, CH_3, $SiMe_3$), 0.57 (s, 9H, CH_3, $SiMe_3$), 1.14 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.55 (dd, 1H, CH_2-N,

$^{2}J_{H\text{-}H}$ =10.8 Hz, $^{3}J_{H\text{-}H}$ =4.6 Hz), 1.87 (s, 3H, CH_3, NMe), 2.01 (m, 1H, CH), 2.88 (d, 1H, CH_2-N, $^{2}J_{H\text{-}H}$ =10.8 Hz), 3.59 (m, 1H, CH_2-OP), 4.07 (m, 1H, CH-O), 4.28 (m, 1H, CH-O), 4.52 (m, 1H, CH_2-OP), 6.84 (m, 2H, CH=), 7.04 (m, 2H, CH=), 7.29 (dd, 2H, CH=, $^{3}J_{H\text{-}H}$ =15.1 Hz, $^{3}J_{H\text{-}H}$ =8.4 Hz), 7.68 (m, 2H, CH=), 8.12 (d, 2H, CH=, $^{3}J_{H\text{-}H}$ =5.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, SiMe3), -0.1 (CH_3, $SiMe_3$), 1.1 (CH_3, $SiMe_3$), 25.1 (CH_3), 26.0 (CH_3), 40.2 (CH_3, NMe), 62.5 (CH_2-N), 62.7 (CH_2-OP), 69.4 (CH), 77.9 (CH-O), 80.2 (CH-O), 110.8 (C), 122.3 – 153.3 (Aromatic Carbons). Anal. calcd. (%) for $C_{35}H_{44}NO_5PSi_2$: C 65.09, H 6.87, N 2.17; found: C 65.24, H 6.87, N 2.15. TOF-MS (ESI+): *m/z:* calcd for $C_{35}H_{44}NO_5PSi_2$: 668.2388 $[M+Na]^+$; found 668.2390.

L4b: Yield: 112.9 mg (43%, reaction carried out using 0.40 mmol of **4**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 137.7. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.54 (s, 9H, CH_3, $SiMe_3$), 0.55 (s, 9H, CH_3, $SiMe_3$), 1.14 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.50 (dd, 1H, CH_2-N, $^{2}J_{H\text{-}H}$ =10.8 Hz, $^{3}J_{H\text{-}H}$ =4.6 Hz), 1.66 (s, 3H, CH_3, NMe), 2.00 (m, 1H, CH), 2.80 (d, $^{2}J_{H\text{-}H}$ =10.8 Hz, 1H, CH_2-N), 4.03 (m, 3H, CH_2-OP, CH-O), 4.36 (m, 1H, CH-O), 6.83 (m, 2H, CH=), 7.08 (m, 2H, CH=), 7.25 (m, 2H, CH=), 7.65 (m, 2H, CH=), 8.06 (s, 2H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, SiMe3), -0.1 (CH_3, $SiMe_3$), 0.00 (CH_3, $SiMe_3$), 1.0 (CH_3, $SiMe_3$), 25.1 (CH_3), 25.9 (CH_3), 39.8 (CH_3, NMe), 62.2 (CH_2-N), 62.6 (CH_2-OP), 69.8 (CH), 77.9 (CH-O), 80.1 (CH-O), 110.8 (C), 122.2 – 153.0 (Aromatic Carbons). Anal. calcd. (%) for $C_{35}H_{44}NO_5PSi_2$: C 65.09, H 6.87, N 2.17; found: C 65.27, H 6.88, N 2.15. TOF-MS (ESI+): *m/z:* calcd for $C_{35}H_{44}NO_5PSi_2$: 668.2388 $[M+Na]^+$; found 668.2386.

L7a: Yield: 51.9 mg (40%, reaction carried out using 0.20 mmol of **6**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 142.2. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.43 (s, 3H, CH_3, $SiMe_3$), 0.46 (s, 15H, CH_3, $SiMe_3$), 1.09 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.57 (m, 2H, CH_2-CHOP), 2.67 (dd, 1H, CH_2, $^{2}J_{H\text{-}H}$ =13.3 Hz, $^{3}J_{H\text{-}H}$ =5.6 Hz), 2.78 (dd, 1H, CH_2, $^{2}J_{H\text{-}H}$ =11.4 Hz, $^{3}J_{H\text{-}H}$ =4.9 Hz) 2.90 (d, 1H, CH_2, $^{2}J_{H\text{-}H}$ =13.3 Hz), 3.15 (m, 2H, CH_2, CH), 4.21 (m, 2H, CH-O), 4.37 (m, 1H, CH-OP), 6.81 (m, 2H, CH=), 7.03 (m, 2H, CH=), 7.18 (d, 1H, CH=, $^{3}J_{H\text{-}H}$ =7.5 Hz), 7.30 (d, 1H, CH=, $^{3}J_{H\text{-}H}$ =10.3 Hz), 7.66 (m, 2H, CH=), 8.06 (s, 1H, CH=), 8.08 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 25.1 (CH_3), 26.8 (CH_3), 37.0 (CH_2-CHOP), 59.5 (CH_2), 61.3 (CH_2), 70.5 (CH), 78.5 (CH-OP), 81.1 (CH-O), 84.9 (CH-O), 111.2 (C), 122.3 – 157.2 (Aromatic Carbons). Anal. calcd. (%) for $C_{36}H_{44}NO_5PSi_2$: C 65.72, H 6.74, N 2.13; found: C 65.88, H 6.75, N 2.11. TOF-MS (ESI+): *m/z:* calcd for $C_{36}H_{44}NO_5PSi_2$: 680.2388 $[M+Na]^+$; found 680.2389.

L7b: Yield: 53.2 mg (40%, reaction carried out using 0.20 mmol of **6**). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 141.0. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.45 (s, 9H, CH_3, $SiMe_3$), 0.47 (s, 9H, CH_3, $SiMe_3$), 1.15 (s, 3H, CH_3), 1.51 (m, 4H, CH_3, CH_2-CHOP), 1.68 (m, 1H, CH_2-CHOP), 2.65 (dd, 1H, CH_2, $^{2}J_{H-H}$ =13.1 Hz, $^{3}J_{H-H}$ =5.8 Hz), 2.84 (m, 2H, CH_2, CH_2), 3.07 (t, 1H, CH, $^{2}J_{H-H}$ =8.4 Hz), 3.18 (m, 1H, CH_2), 4.19 (d, 1H, CH-O, $^{2}J_{H-H}$ =6.2 Hz), 4.30 (m, 1H, CH-O), 4.39 (m, 1H, CH-OP), 6.82 (m, 2H, CH=), 7.03 (m, 2H, CH=), 7.21 (d, 1H, CH=, $^{3}J_{H-H}$ =8.5 Hz), 7.33 (d, 1H, CH=, $^{3}J_{H-H}$ =8.5 Hz), 7.65 (m, 2H, CH=), 8.07 (s, 1H, CH=), 8.08 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: -0.2 (CH_3, $SiMe_3$), 0.0 (CH_3, $SiMe_3$), 25.2 (CH_3), 26.8 (CH_3), 37.8 (CH_2-CHOP), 59.5 (CH_2), 60.4 (CH_2), 70.6 (CH), 78.4 (CH-OP), 81.2 (CH-O), 84.9 (CH-O), 111.2 (C), 122.3 – 152.3 (Aromatic Carbons). Anal. calcd. (%) for $C_{36}H_{44}NO_5PSi_2$: C 65.72, H 6.74, N 2.13; found: C 65.84, H 6.76, N 2.12. TOF-MS (ESI+): *m/z:* calcd for $C_{36}H_{44}NO_5PSi_2$: 680.2388 $[M+Na]^+$; found 680.2391.

Procedure for the preparation of the amino-phosphinite ligand L5. Pyrrolidine-hydroxyl compound **4** (93.1 mg, 0.5mmol) and DMAP (6.7 mg, 0.055 mmol) were first dissolved in toluene (1 mL). Then triethylamine was added (0.09 mL, 0.65 mmol) at r.t, followed by addition of the appropriate chlorophosphine (0.55 mmol) via syringe. The reaction was stirred for 1 h at r.t. The solvent was then removed and the product was purified by flash chromatography on alumina (toluene/NEt_3 = 100/1) to produce the corresponding ligand as an oil. Yield: 30 mg (15%). ^{31}P NMR (161.9 MHz, C_6D_6), δ: 116.1. ^{1}H NMR (400 MHz, C_6D_6), δ: 1.00 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.97 (s, 3H, CH_3-N), 2.34 (m, 1H, CH_2-N), 2.60 (m, 1H, CH-N), 2.79 (m, 1H, CH_2-N), 3.67 (m, 2H, CH_2-O), 4.12 (m, 1H, CH-O), 4.32 (m, 1H, CH-O), 6.86 (m, 7H, CH=), 7.41 (m, 2H, CH=), 7.83 (m, 1H, CH=). ^{13}C NMR (100.6 MHz, C_6D_6), δ: 24.0 (CH_3), 26.4 (CH_3), 38.6 (CH_3-N), 58.3 (CH_2-O), 61.1 (CH_2-N), 70.9 (CH-N), 77.0 (CH-O), 81.5 (CH-O), 111.8 (CMe_2), 126.6 – 130.9 (Aromatic Carbons). TOF-MS (ESI+): *m/z:* calcd for $C_{21}H_{26}NO_3P$: 394.1543 $[M+Na]^+$; found 394.1538.

Preparation of the amino-phosphine ligand (2*S*,3*R*,4*S*)-*N*-Methyl-2-diphenylphosphinomethyl-3,4-*O*-isopropyliden-pyrrolidine-3,4-diol (L6). To a solution of **12** (94 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (1.5 mL) at 0 ºC, Et_3N (43 µL, 0.30 mmol) and $ClCO_2CH_3$ (24 µL, 0.30 mmol) were successively added. The mixture was stirred at 0 ºC for 3 h. HCl (0.1 M) (6 mL) was added and the aqueous phase was

extracted (× 3) with CH_2Cl_2. The organic layers were washed with sat. aq. sol. of $NaHCO_3$, dried with Na_2SO_4, filtered and evaporated. The resulting crude was dissolved in anhydrous THF (2 mL) and added to a suspension of $LiAlH_4$ (32 mg, 0.83 mmol) in anhydrous THF (1.0 mL) at 0 ºC. The reaction mixture was heated at reflux for 2 h and then cooled at 0 ºC. Diethyl ether and sat. aq. sol. of Na_2SO_4 were successively added and the mixture was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated and the residue was purified by chromatography column on silica gel (eluent: EtOAc/cyclohexane – 1/2) to produce **L6** (81 mg, 82%) as a colourless oil. $[\alpha]_D^{24}$ +167.5 (0.58, CH_2Cl_2). ^{31}P NMR (202 MHz, C_6D_6), δ: -21.1. ^{1}H NMR (500 MHz, C_6D_6), δ: 1.27 (s, 3H, -C(C*H*$_3$)$_2$), 1.59 (s, 3H,-C(C*H*$_3$)$_2$), 2.02 (s, 3H, N-C*H*$_3$), 1.54 (dd, 1H, H-5a, $J_{5a\text{-}5b}$ = 10.5, $J_{5a\text{-}4}$ = 5.0), 1.71-1.76 (m, 1H, H-2), 2.44 (dt, 1H, H-1'a, $J_{1'a\text{-}1'b}$ = 13.5, $J_{1'a\text{-}2}$ = $J_{1'a\text{-}P}$ = 2.5), 2.72-2.77 (m, 1H, H-1'b), 3.03 (d, H-5b, 1H,), 4.18 (dd, 1H, H-4, $J_{4\text{-}3}$ = 6.0), 4.51 (dd, 1H, H-3, $J_{3\text{-}2}$ = 4.5), 7.01-7.13 (m, 6H, H-arom.), 7.49-7.52 (m, 2H, H-arom.), 7.54-7.57 (m, 2H, H-arom.). ^{13}C NMR (125.7 MHz, C_6D_6), δ: 25.7 (-C(*C*H$_3$)$_2$), 26.6 (-C(*C*H$_3$)$_2$), 26.7 (d, $J_{C\text{-}P}$ = 13.9, C-1'), 39.6 (N-*C*H$_3$), 62.7 (C-5), 68.1 (d, $J_{C\text{-}P}$ = 20.6, C-2), 78.3 (C-4), 81.5 (d, $J_{C\text{-}P}$ = 3.6, C-3), 111.2 (-*C*(CH$_3$)$_2$), 128.4 (C-arom.), 128.6 (d, $J_{C\text{-}P}$ = 6.2, C-arom.), 128.8 (d, $J_{C\text{-}P}$ = 6.8, C-arom.), 129.0 (C-arom.), 132.9 (d, $J_{C\text{-}P}$ = 18.1, C-arom.), 133.6 (d, $J_{C\text{-}P}$ = 19.8, C-arom.), 139.7 (d, $J_{C\text{-}P}$ = 15.0, C_{arom}-P), 140.4 (d, $J_{C\text{-}P}$ = 13.4, C_{arom}-P). HRMS (ESI) *m/z:* calcd for $C_{21}H_{27}NO_2P$: 356.1774 $[M+H]^+$; found 356.1768.

General procedure for the preparation of [Pd(η^3-allyl)(P-N)]BF$_4$ (36–39). The 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 rt under argon. After 30 min, $AgBF_4$ (9.8 mg, 0.05 mmol) was added, and the mixture was stirred for other 30 min. The mixture was then filtered through Celite under argon, and the resulting solutions were analyzed by NMR spectroscopy. The complexes were precipitated as pale yellow solids by adding hexane.

[Pd(η^3-1,3-cyclohexenyl)(L1a)]BF$_4$ (36). Yield: 37.7 mg (82%). MS HR-ESI [found 832.2227, $C_{41}H_{53}NO_5PPdSi_2$ $(M\text{-}BF_4)^+$ requires 832.2229]. Major isomer (89%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 140.7 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.51 (s, 9H, CH_3, CH_3-Si), 0.53 (s, 9H, CH_3, CH_3-Si), 0.88-2.21 (m, 6H, CH_2), 1.41 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.12 (s, 3H, CH_3-N), 3.17 (m, 1H, CH), 3.37 (b, 1H, CH allyl *trans* to N), 3.44 (bd, 1H, CH_2-N, *J*= 12.4 Hz), 3.99 (dd, 1H, CH_2-N, $^2J_{H\text{-}}$

$_H$= 12.4 Hz, $^3J_{H-H}$= 3.6 Hz), 4.42-4.49 (b, 2H, CH_2-O), 5.02 (m, 2H, CH-O), 5.41 (m, 1H, CH allyl *central*), 6.05 (m, 1H, CH allyl *trans* to P), 6.92 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.12 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.24 (m, 1H, CH=), 7.31 (m, 1H, CH=), 7.47 (m, 1H, CH=), 7.55 (m, 1H, CH=), 7.98 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.04 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.19 (s, 1H, CH=), 8.22 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: -0.1 (CH_3-Si), 0.5 (CH_3-Si), 19.9 (CH_2), 24.4 (CH_3), 26.0 (CH_3), 27.0 (CH_2), 28.2 (b, CH_2), 51.4 (CH_3-N), 65.5 (d, CH_2-O, J_{C-P}= 6.1 Hz), 67.4 (d, CH allyl *trans* to N, J_{C-P}= 8.4 Hz), 68.7 (CH_2-N,), 75.2 (d, CH, J_{C-P}= 2.3 Hz), 77.9 (CH-O), 79.8 (CH-O), 106.1 (d, CH allyl *trans* to P, J_{C-P}= 39.4 Hz), 113.6 (d, CH allyl *central*, J_{C-P}= 6 Hz), 114.7 (CMe_2), 120.6-151.5 (aromatic carbons). Minor isomer (11%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 142.7 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.46 (s, 9H, CH_3, CH_3-Si), 0.59 (s, 9H, CH_3, CH_3-Si), 0.88-2.21 (m, 6H, CH_2), 1.36 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.17 (m, 1H, CH), 3.22 (s, 3H, CH_3-N), 3.37 (b, 1H, CH allyl *trans* to N), 3.44 (bd, 1H, CH_2-N, *J*= 12.4 Hz), 3.92 (dd, 1H, CH_2-N, $^2J_{H-H}$= 12.6 Hz, $^3J_{H-H}$= 4.0 Hz), 4.42-4.51 (b, 2H, CH_2-O), 5.02 (m, 2H, CH-O), 5.83 (m, 1H, CH allyl *central*), 6.28 (m, 1H, CH allyl *trans* to P), 6.98 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.10 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 7.24 (m, 1H, CH=), 7.28 (m, 1H, CH=), 7.48 (m, 1H, CH=), 7.51 (m, 1H, CH=), 7.98 (m, 1H, CH=), 8.03 (d, 1H, CH=, $^3J_{H-H}$= 8.0 Hz), 8.16 (s, 1H, CH=), 8.20 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.0 (CH_3-Si), 0.5 (CH_3-Si), 19.3 (CH_2), 24.3 (CH_3), 25.9 (CH_3), 26.9 (CH_2), 29.6 (CH_2), 50.9 (CH_3-N), 65.3 (d, CH_2-O, J_{C-P}= 10.2 Hz), 66.5 (b, CH allyl *trans* to N), 69.6 (CH_2-N,), 75.02 (b, CH), 79.3 (CH-O), 80.8 (CH-O), 104.6 (d, CH allyl *trans* to P, J_{C-P}= 42.6 Hz), 113.9 (d, CH allyl *central*, J_{C-P}= 8 Hz), 116.1 (CMe_2), 120.6-151.5 (aromatic carbons).

[Pd(η^3-1,3-cyclohexenyl)(L1b)]BF_4 (37). Yield: 35 mg (76%). MS HR-ESI [found 832.2233, $C_{41}H_{53}NO_5PPdSi_2$ $(M\text{-}BF_4)^+$ requires 832.2229]. Major isomer (96%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 142.5 (s, 1P). ^{1}H NMR(400 MHz, CD_2Cl_2, 298 K), δ: 0.47 (s, 9H, CH_3, CH_3-Si), 0.55 (s, 9H, CH_3, CH_3-Si), 0.88-1.17 (m, 3H, CH_2), 1.35 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.59 (m, 1H, CH_2), 1.82 (m, 1H, CH_2), 2.12 (m, 1H, CH_2), 3.34 (s, 3H, CH_3-N), 3.48 (m, 1H, CH), 3.59 (bd, 1H, CH_2-N, *J*= 13.6 Hz), 3.67 (m, 1H, CH allyl *trans* to N), 3.75 (dd, 1H, CH_2-N, $^2J_{H-H}$= 13.6 Hz, $^3J_{H-H}$= 5.6 Hz), 4.15 (m, 1H, CH_2-O), 4.45 (m, 1H, CH_2-O), 4.71 (m, 1H, CH-O), 4.96 (m, 1H, CH-O), 5.49 (m, 1H, CH allyl *central*), 6.14 (m, 1H, CH allyl *trans* to P), 6.94 (d, 1H, CH=, $^3J_{H-H}$= 8.8 Hz), 7.13 (d, 1H, CH=, $^3J_{H-H}$= 8.4 Hz), 7.22 (m, 1H, CH=), 7.32 (m, 1H, CH=),

7.47 (m, 1H, CH=), 7.56 (m, 1H, CH=), 7.99 (d, 1H, CH=, $^{3}J_{H-H}$= 8.4 Hz), 8.04 (d, 1H, CH=, $^{3}J_{H-H}$= 8.0 Hz), 8.20 (s, 1H, CH=), 8.23 (s, 1H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.8 (CH_3-Si), 20.7 (CH_2), 23.8 (CH_3), 26.4 (CH_3), 27.4 (CH_2), 28.5 (CH_2), 53.4 (CH_3-N), 66.4 (d, CH_2-O, J_{C-P}= 6.8 Hz), 67.2 (d, CH_2-N, J_{C-P}= 8.3 Hz), 67.8 (b, CH allyl *trans* to N), 75.9 (CH), 80.0 (CH-O), 81.2 (CH-O), 106.6 (d, CH allyl *trans* to P, J_{C-P}= 38.7 Hz), 113.4 (d, CH allyl *central*, J_{C-P}= 10.7 Hz), 114.2 (CMe_2), 121.3-151.9 (aromatic carbons). Minor isomer (4%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 141.8 (s, 1P).

[Pd(η^3-1,3-diphenylallyl)(L1a)]BF_4 (38). Yield: 40 mg (78%). MS HR-ESI [found 944.2539, $C_{50}H_{57}NO_5PPdSi_2$ $(M\text{-}BF_4)^+$ requires 944.2542]. Major isomer (70%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 145.0 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.64 (s, 9H, CH_3, CH_3-Si), 0.67 (s, 9H, CH_3, CH_3-Si), 1.27 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.57 (s, 3H, CH_3-N), 3.01 (bd, 1H, CH_2-N, *J*= 13.6 Hz), 3.18 (m, 1H, CH), 4.09 (bd, 1H, CH_2-N, *J*= 13.6 Hz), 4.59 (m, 1H, CH_2-O), 4.93 (m, 1H, CH_2-O), 5.22 (m, 1H, CH allyl *trans* to N), 5.30 (m, 1H, CH-O), 5.31 (m, 1H, CH-O), 5.78 (m, 1H, CH allyl *trans* to P), 5.8 (m,1H, CH=), 6.62 (m, 1H, CH allyl *central*), 6.2 – 8.3 (m, 19H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.5 (CH_3-Si), 0.8 (CH_3-Si), 23.0 (CH_3), 25.7 (CH_3), 50.1 (CH_3-N), 63.7 (CH_2-N), 67.4 (d, CH_2-O, J_{C-P}= 4.0 Hz), 77.0 (CH), 78.4 (CH-O), 78.5 (CH-O), 79.8 (CH allyl *trans* to N), 98.0 (d, CH allyl *trans* to P, J_{C-P}= 35.7 Hz), 111.5 (d, CH allyl *central*, J_{C-P}= 6.2 Hz), 113.2 (CMe_2), 120.4-151.9 (aromatic carbons). Minor isomer (30%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 140.2 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.52 (s, 9H, CH_3, CH_3-Si), 0.76 (s, 9H, CH_3, CH_3-Si), 1.27 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.83 (m, 1H, CH), 2.84 (bd, 1H, CH_2-N, *J*= 13.2 Hz), 2.57 (s, 3H, CH_3-N), 4.08 (bd, 1H, CH_2-N, *J*= 13.2 Hz), 4.56 (m, 1H, CH allyl *trans* to N), 4.75 (m, 1H, CH_2-O), 4.81 (m, 1H, CH_2-O), 5.30 (m, 1H, CH-O), 5.35 (m, 1H, CH-O), 5.59 (m, 1H, CH allyl *trans* to P), 6.82 (m, 1H, CH allyl *central*), 6.2 – 8.3 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.6 (CH_3-Si), 0.7 (CH_3-Si), 23.90 (CH_3), 26.0 (CH_3), 49.8 (CH_3-N), 61.0 (CH_2-N), 64.4 (b, CH_2-O), 75.4 (CH), 78.4 (CH-O), 78.5 (CH-O), 79.4 (CH allyl *trans* to N), 103.9 (d, CH allyl *trans* to P, J_{C-P}= 32.7 Hz), 114.4 (d, CH allyl *central*, J_{C-P}= 12.2 Hz), 114.5 (CMe_2), 120.4-151.9 (aromatic carbons).

[Pd(η^3-1,3-diphenylallyl)(L4a)]BF_4 (39). Yield: 44 mg (83%). MS HR-ESI [found 944.2537, $C_{50}H_{57}NO_5PPdSi_2$ $(M\text{-}BF_4)^+$ requires 944.2542]. Major isomer (67%): ^{31}P

NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 135.0 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.45 (s, 9H, CH_3, CH_3-Si), 0.75 (s, 9H, CH_3, CH_3-Si), 1.21 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.70 (s, 3H, CH_3-N), 3.22 (m, 1H, CH), 3.36 (dd, 1H, CH_2-N, *J*= 14.0 Hz, *J*= 5.6 Hz), 3.72 (m, 1H, CH_2-N), 4.50-4.64 (m, 2H, CH-O), 4.70 (m, 1H, CH_2-O), 4.82 (m, 1H, CH allyl *trans* to N), 4.86 (m, 1H, CH_2-O), 5.32 (m, 1H, CH allyl *trans* to P), 6.57-6.67 (m, 1H, CH allyl *central*), 5.8 – 8.3 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: 0.3 (CH_3-Si), 0.7 (CH_3-Si), 22.9 (CH_3), 25.5 (CH_3), 53.1 (CH_3-N), 63.7 (CH_2-O), 64.1 (CH_2-N), 64.7 (CH allyl *trans* to N), 76.0 (CH), 80.5 (CH-O), 80.8 (CH-O), 95.6 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 35.7 Hz), 111.5 (d, CH allyl *central*, $J_{C\text{-}P}$= 11.4 Hz), 112.8 (CMe_2), 120.3-151.7 (aromatic carbons). Minor isomer (35%): ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 137.7 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.51 (s, 9H, CH_3, CH_3-Si), 0.66 (s, 9H, CH_3, CH_3-Si), 1.22 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.22 (m, 1H, CH_3-N), 3.71 (m, 1H, CH_2-N), 3.80 (m, 1H, CH_2-N), 4.01 (m, 1H, CH), 4.50-4.64 (m, 2H, CH-O), 4.69 (m, 1H, CH_2-O), 4.82 (m, 1H, CH_2-O), 5.09 (m, 1H, CH allyl *trans* to N), 5.54 (m, 1H, CH allyl *trans* to P), 6.57-6.67 (m, 1H, CH allyl *central*), 5.8 – 8.3 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: -0.2 (CH_3-Si), 0.5 (CH_3-Si), 22.4 (CH_3), 24.0 (CH_3), 48.6 (CH_3-N), 61.7 (CH_2-N), 63.7 (CH_2-O), 62.9 (CH allyl *trans* to N), 77.8 (CH), 80.5 (CH-O), 80.2 (CH-O), 94.8 (d, CH allyl *trans* to P, $J_{C\text{-}P}$= 36.5 Hz), 111.9 (d, CH allyl *central*, $J_{C\text{-}P}$= 11.4 Hz), 113.0 (CMe_2), 120.3-151.7 (aromatic carbons). [Pd(η^3-1,3-diphenylallyl)(**L4a**)$_2$]BF_4 (8%): MS HR-ESI [found 1589.5046, $C_{85}H_{101}N_2O_{10}P_2PdSi_4$ $(M\text{-}BF_4)^+$ requires 1589.5038]. ^{31}P NMR (161.9 MHz, CD_2Cl_2, 298 K), δ: 137.7 (s, 1P). ^{1}H NMR (400 MHz, CD_2Cl_2, 298 K), δ: 0.55 (s, 9H, CH_3, CH_3-Si), 0.63 (s, 9H, CH_3, CH_3-Si), 1.18 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.81 (m, 1H, CH_3-N), 2.52 (m, 1H, CH), 2.87 (b, 2H, CH_2-N), 4.50-4.64 (m, 2H; CH-O), 4.57 (m, 1H, CH_2-O), 4.90 (m, 1H, CH_2-O), 5.85 (m, 2H, CH allyl *terminal*), 6.57-6.67 (m, 1H, CH allyl *central*), 5.8 – 8.3 (m, 20H, CH=). ^{13}C NMR (100.6 MHz, CD_2Cl_2, 298 K), δ: -0.1 (CH_3-Si), 0.0 (CH_3-Si), 23.1 (CH_3), 24.5 (CH_3), 42.5(CH_3-N), 60.7 (b, CH_2-N), 69 (b, CH_2-O), 76.9-77.1 (CH-O), 77.6-77.8 (CH), 99.9 (m, CH allyl *terminal*), 112.0 (b, CH allyl *central*), 112.3 (CMe_2), 120.3-151.7 (aromatic carbons).

Study of the reactivity of the [Pd(η^3-allyl)(L)]BF_4 with sodium malonate by in situ NMR spectroscopy.[25] A solution of in situ prepared [Pd(η^3-allyl)(L)]BF_4 (L=amino-

phosphite, 0.05 mmol) in CD_2Cl_2 (1 ml) was cooled in the NMR spectrometer to -80 ºC. At this temperature, a solution of cooled sodium malonate (0.1 mmol) was added. The reaction was then followed by ^{31}P NMR spectroscopy. The relative reaction rates were calculated using capillary that contained a solution of triphenylphosphine in CD_2Cl_2 as the external standard.

Typical procedure for the allylic alkylation of disubstituted linear and cyclic substrates. A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the desired ligand (0.0055 mmol) in CH_2Cl_2 (0.5 mL) was prepared. After 30 min, a solution of the appropriated substrate (0.5 mmol) in CH_2Cl_2 (1.5 mL), nucleophile (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (3 mg, 003 mmol) was added. Then, the reaction was stirred at room temperature during the time indicated in the manuscript. Then, the reaction was quenched by adding Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL). The mixture was then extracted with Et_2O (3 x 10 mL) and the collected organic phases were dried over $MgSO_4$. Conversions were measured by ^1H NMR and enantiomeric excesses were determined either by HPLC (compounds **13**, **15**–**22** and **26**–**28**) or by GC (compounds **14** and **30**–**35**) or by ^1H NMR using $[Eu(hfc)_3]$ (compound **29**). For characterization and ee determination details see Supporting Information.

Typical procedure for the allylic amination of disubstituted linear substrate S1. A solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the desired ligand (0.0055 mmol) in CH_2Cl_2 (0.5 mL) was prepared. After 30 minutes, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) (0.5 mmol) in CH_2Cl_2 (1.5 mL), the desired amine (1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (3 mg, 0.03 mmol) were added. Then, the reaction was stirred at room temperature during the time indicated in the manuscript. Then, the reaction was quenched by adding Et_2O (5 mL) and saturated NH_4Cl (aq) (25 mL). The mixture was then extracted with Et_2O (3 x 10 mL) and the collected organic phases were dried over $MgSO_4$. Conversions were measured by ^1H NMR and enantiomeric excesses were determined by HPLC. For characterization and ee determination details see Supporting Information.

Associated content

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:.

Copies of $^{31}P\{^{1}H\}$ and ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of new ligands **L1**–**L7a–d**, and Pd-intermediates **36**−**39** and of ligand intermediates **1**–**4**, **8**, **10** and **12**.

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Notes

The authors declare no competing financial interests.

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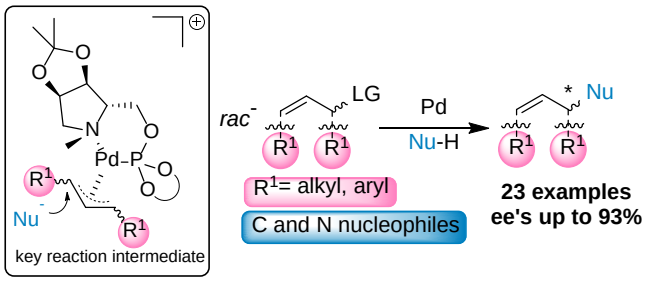
TOC Graphic


key reaction intermediate
rac-
LG
Pd
Nu-H
Nu
R1= alkyl, aryl
C and N nucleophiles
23 examples
ee's up to 93%

.