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Amino-P Ligands from Iminosugars: New Readily Available and Modular Ligands for Enantioselective Pd-Catalyzed Allylic Substitutions

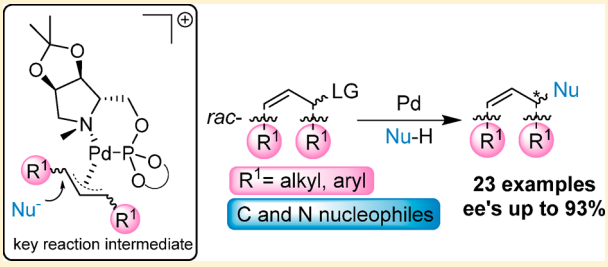
Carlota Borràs,[†] Pilar Elías-Rodríguez,[‡] Ana T. Carmona,[‡] Inmaculada Robina,*[,‡] Oscar Pàmies,*[,†] and Montserrat Diéguez*[,†]

[†]Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, Campus Sescelades, C/Marcel·lí Domingo, 1, 43007 Tarragona, Spain

[‡]Department of Organic Chemistry, University of Seville, C/ Prof. García González 1, 41012 Seville, Spain

Supporting Information

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 steric 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 give 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 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 formed chemical production because catalysts are used in the preparation of the majority of chemicals, resulting in a multibillion 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. Currently 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* influences of both types of functional groups that create an electronic differentiation between the two allylic terminal carbons and therefore favor 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 group more stable than oxazolines (such as 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 progress 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] that have wide substrate scope and are 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 manipulate), that are easy to prepare from simple starting materials, and that are good for several substrates and

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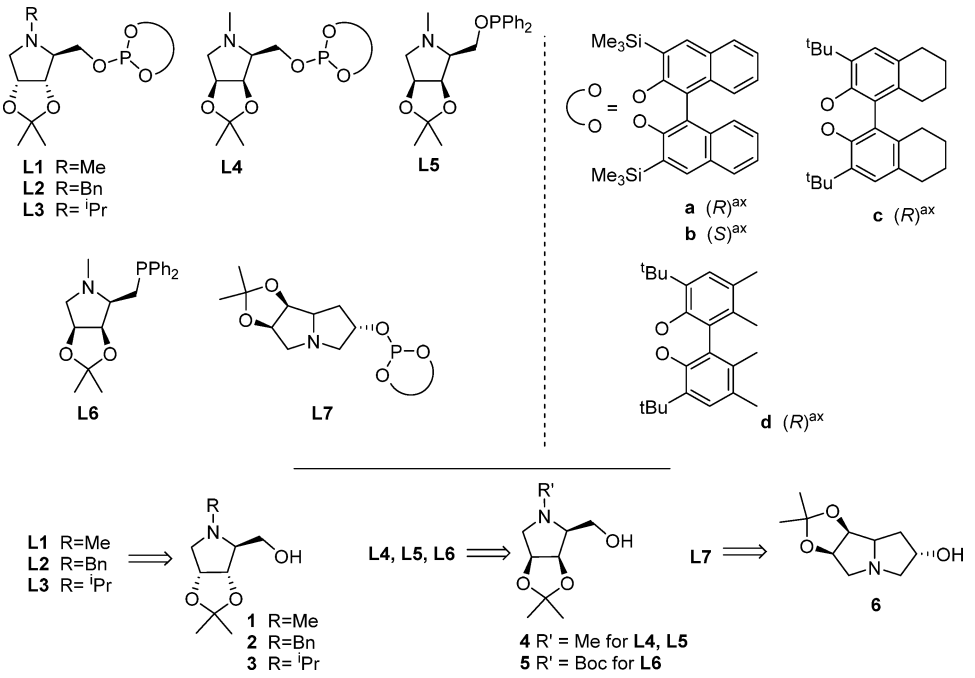
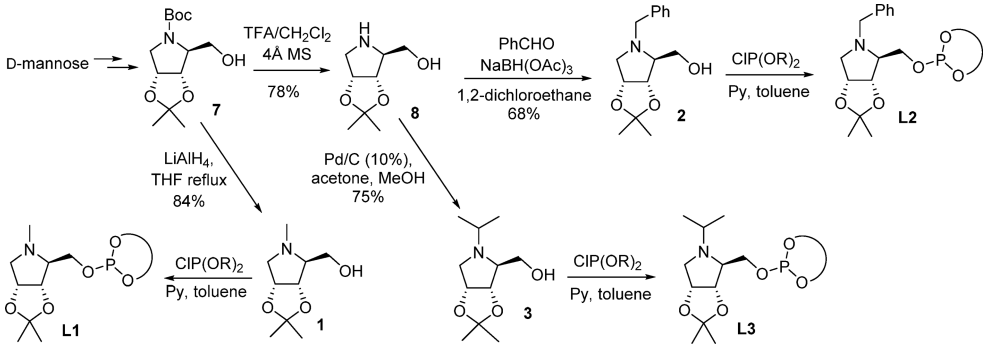


Figure 1. Amino-phosphite/phosphinite/phosphine ligands **L1a–d** through **L7a–d** and their starting products, cyclic amino-alcohols **1–6**.

Scheme 1. Synthesis of Ligands L1–L3



nucleophiles is a relevant topic in this reaction. Carbohydrates are particularly useful for preparing ligands because they are relatively abundant in an enantiomerically pure form, present a wide stereochemical diversity, and 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 for the optimal ligand for each type of substrate. Since the pioneering work of Pregosin,[11] among others,[12] on the use of carbohydrates as efficient ligands in allylic alkylations, many carbohydrates, mostly heterodonors, 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 (**L1a–d** through **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 in fixing 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 systematically 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**) group was also investigated. We have also performed the synthesis and elucidation of the appropriate Pd–allyl intermediates to elucidate the enantioselectivities obtained.

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 (Scheme 1).[14] Reduction of **7** with $LiAlH_4$ gave *N*-methylpyrrolidine 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*-isopropylhydroxypyrrolidine derivatives **2** and **3**, respectively.

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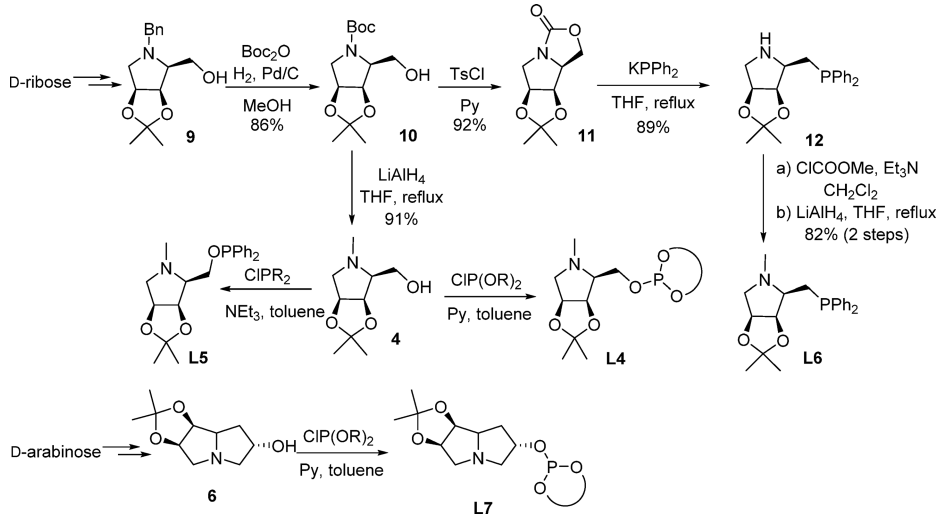
Scheme 2. Synthesis of Ligands L4−L7

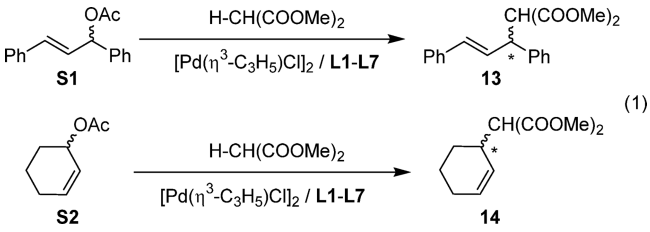


With these steps the appropriate variety in the steric and electronic proprieties of the amine part was reached. Finally, reaction of amino-alcohols **1**−**3** with the desired phosphorochloridite ($ClP(OR)_2$; OR = **a**−**d**) formed *in situ* gave access to amino-phosphite ligands **L1**−**L3** with the desired substituent/configurations of the biaryl phosphite group.

The preparation of ligands **L4**−**L6**, with a different configuration of the carbons bearing the isopropylidene group in comparison to **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*-methylpyrrolidine 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 (two 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**.

Advantageously, the amino-phosphite compounds are stable in air and are stable to hydrolysis; therefore, 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 bidimensional $^1H-^1H$ and $^1H-^{13}C$ spectra were performed. It 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 **L1a**−**d** throught **L7a**−**d** by applying them in the allylic alkylation of substrates **S1** and **S2**, which differ 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 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,d**, for cyclic substrate **S2** the best enantioselectivities in both product enantiomers were achieved using **L1a,b** and **L7a,b**.

Concerning the effect of the P functionality, we found that enantioselectivity decreased considerably by changing the

Table 1. Results for the Pd-Catalyzed Allylic Substitution of Substrates S1 and 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]Reaction conditions: 0.5 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$, ligand (0.011 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), BSA (3 equiv), dimethyl malonate (3 equiv), KOAc (pinch). [b]Conversion percentage determined by ^1H NMR. [c]Enantiomeric excesses measured by HPLC for **13** and by GC for **14**. Absolute configurations are shown in parentheses. [d]Reaction carried out at 0 °C.

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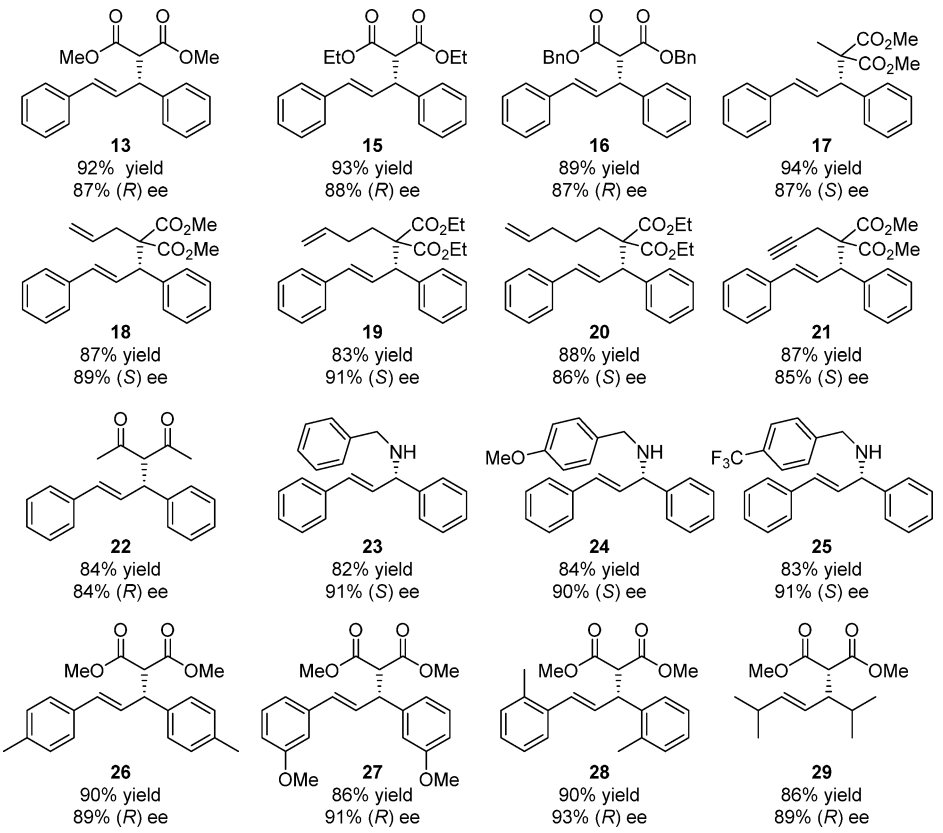

Figure 2. Pd-catalyzed allylic substitution of linear disubstituted symmetric substrates with C and N nucleophiles using the Pd-**L1a** catalytic system. Reactions were run at 0 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full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

phosphite (**L4**) for phosphinite or phosphine groups (ligands **L5** and **L6**) (Table 1; entry 9 vs entries 11 and 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 the biaryl phosphite moiety gave (*R*)-alkylated products, while ligands with an *S* configuration at the biaryl phosphite group gave (*S*)-alkylated products (e.g., entry 1 vs entry 2). In addition, for the linear substrate **S1** the enantioselectivity depends 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 entry 2). However, for the cyclic substrate the combination of both ligand parameters on enantioselectivity is less relevant. Therefore, by simply changing the configuration of the phosphite functionality both product 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 and 2 vs entries 3 and 4).

On comparison of 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 (Table 1; 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** (Table 1; entries 1 and 2 vs entries 13 and 14) it has little effect for substrate **S2** (entries 1 and 2 vs entries 13 and 14).

Finally, enantioselectivity can also be enhanced by changing the reaction parameters. Enantioselectivity was therefore further improved by decreasing the temperature to 0 °C (ee values up to 87% for **S1** and 81% for **S2**; Table 1, 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 Supporting Information).

Pd-Allylic Substitution of Other Substrates and with Other Nucleophiles: Scope and Limitations. The scope of Pd/**L1a**−**d** through **L7a**−**d** catalysts was then extended to other substrates and nucleophiles. As an example, Figures 2 and 3 show 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 of the steric nature of the ester groups of the malonate nucleophiles (products **13**, **15**, and **16**) and also of 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

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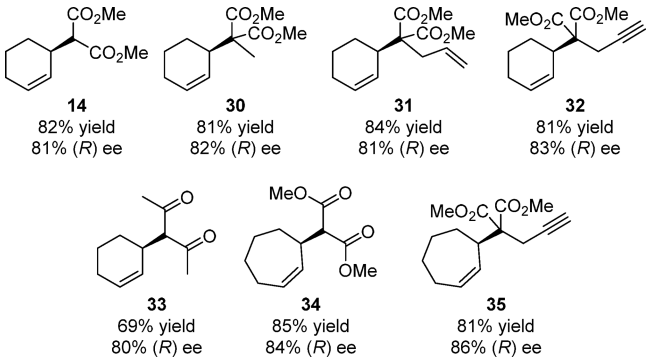

Figure 3. Pd-catalyzed allylic substitution of cyclic substrates with C nucleophiles using the Pd-**L1a** catalytic system. Reactions were run at 0 °C with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.5 mol %), CH_2Cl_2 as solvent, ligand (1.1 mol %), BSA (3 equiv), and KOAc. Full conversions were achieved after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

corresponding alkylated products **17**−**21** in enantioselectivities similar to those attained with dimethyl malonate (ee values 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 values 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 comparably high enantioselectivities in comparison with the case for **S1**.

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 values up to 83%, compounds **14** and **30**−**33**) were similar to those obtained when dimethyl malonate was used, even when acetylacetone was used as nucleophile. High yields and enantioselectivities were also reached when a seven-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.

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 values 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 values up to 93%, including the challenging sterically demanding compounds **28** and **29**), opens up the Pd−allylic alkylation reactions to novel types 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** $[Pd(\eta^3\text{-allyl})(P{-}N)]BF_4$ (*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

Scheme 3. Synthesis of $[Pd(\eta^3\text{-allyl})(P{-}N)]BF_4$ Complexes 36−39

complexes were confirmed by mass spectrometry and by NMR. For spectral assignments bidimensional $^1H-^1H$, $^1H-^{13}C$, $^{31}P-^1H$ and $^1H-^1H$ NOESY spectra were performed.

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 to −80 °C) indicated a mixture of two isomers, in equilibrium, in ratios 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* form, while the NOE indicated an *endo* disposition for the major isomer of **37** (Figure 4). Thus, varying the configuration of the phosphite functionality led to a different ratio of the isomers that provide both product enantiomers. For the major isomer of complex **36**, the NOE indicates an interaction between the hydrogen of the CH-N moiety and 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 *exo* and *endo* dispositions 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 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 these species, ^{13}C NMR shows 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 more quickly than the major isomer and that enantioselectivity is also controlled by the different reactivities of the isomers of complex **37** toward the nucleophile.

Finally, to evaluate the effect of the configuration of carbons bearing the isopropylidene group on the enantioselectivity

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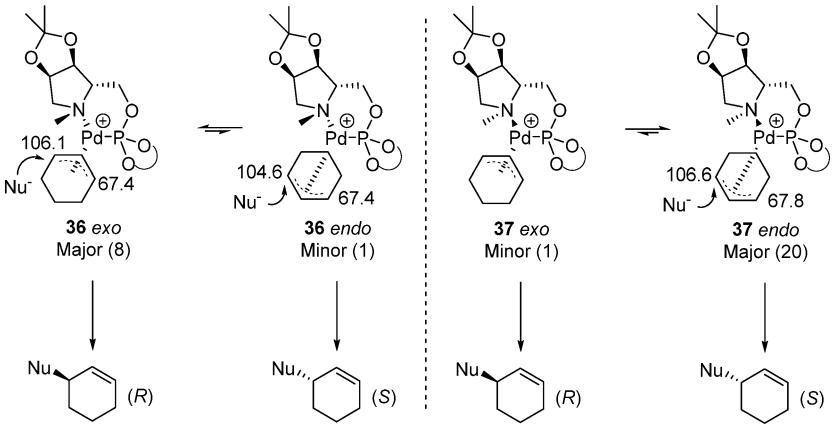
Scheme 4. Pd–η^3-Allyl Intermediates for Cyclic S2 Containing Ligands L1a (Isomers 36) and L1b (Isomers 37)[a]



[a]The ratio of each isomer is shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

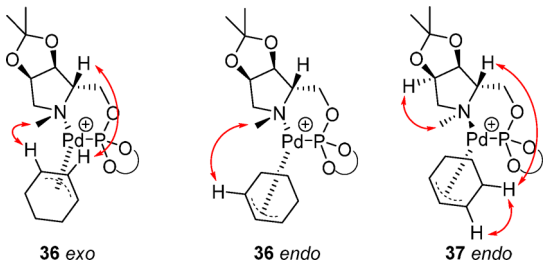
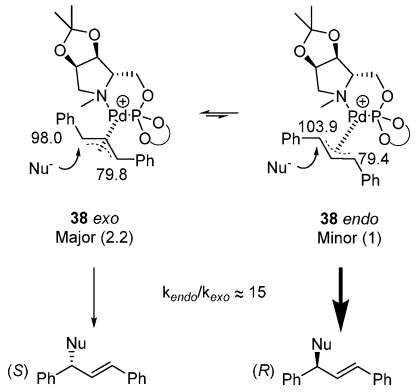


Figure 4. Selected NOE interactions from the NOESY spectra of Pd-η^3-allyl intermediates **36** and **37**.

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 (15% *R*).

The VT-NMR (+30 to −85 °C) 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 a NOE contact was also found between the hydrogen of the CH-N group and 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 isomer (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 values up to 80% *R*) is higher than the diastereoisomeric excesses of the Pd isomers (de = 37% *S*), the minor *endo* isomer should react more quickly than the *exo* isomer. To confirm this, we performed an *in situ* NMR study of the reactivity of both Pd isomers with dimethyl malonate at low temperature (Figure 5b). This experiment shows that the minor isomer (*endo*) reacts around 15 times faster with the nucleophile in comparison to 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

Scheme 5. Pd–η^3-Allyl Intermediates for Linear S1 Containing Ligand L1a (Isomers 38)[a]



[a]The ratio of each isomer is shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

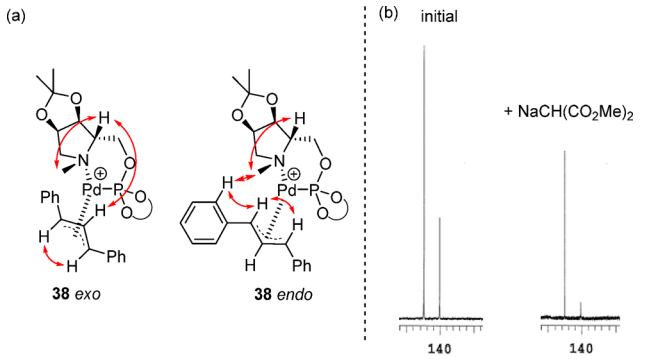


Figure 5. (a) Selected NOE interactions from the NOESY spectrum of Pd–η^3-allyl intermediates **38** (*exo* and *endo*). (b) Reactivity of intermediates **38** toward sodium dimethyl malonate at −80 °C: ^{31}P{^{1}H} NMR spectra before and after the addition of sodium dimethyl malonate in CD_2Cl_2.

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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 reactivities of the Pd isomers toward the nucleophile, rather than by the ratio of isomers, as was the case for substrate **S2** when the same ligand **L1a** was used.

In contrast to the previous study with ligand **L1a**, the VT-NMR (+30 to −85 °C) of Pd−allyl complexes **39** with **L4a** showed three compounds in equilibrium at a ratio of 3.2:1.7:1. The two major species were attributed to the *syn/syn endo* and *exo* isomers of **39** (see relevant NOE contacts in Figure 6),

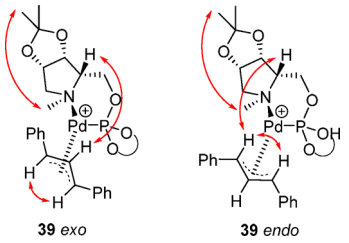
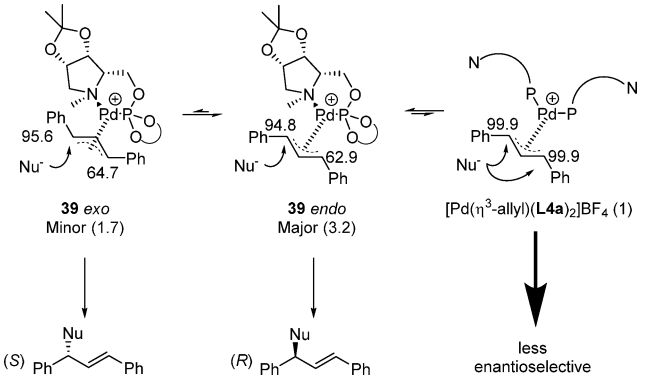


Figure 6. Selected NOE interactions from the NOESY spectrum of Pd−η^3-allyl intermediates **39** (*exo* and *endo*).

while the minor compound was assigned to a Pd−allyl complex ([Pd(η^3-allyl)(**L4a**)$_2$]BF$_4$) with two P−N ligands coordinated to the Pd in a monodentate fashion through the phosphite functionality (Scheme 6). Monodentate coordination of **L4a** in

Scheme 6. Pd−η^3-Allyl Intermediates for Linear S1 Containing Ligand L4a (Isomers 39 and [Pd(η^3-allyl)(L4a)$_2$]BF$_4$)[a]



[a]The ratio of each compound is shown in parentheses. The chemical shifts (in ppm) of the allylic terminal carbons are also shown.

the minor species [Pd(η^3-allyl)(**L4a**)$_2$]BF$_4$ is clearly disclosed because the signals of the methyl amine 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 in comparison to that with the Pd/**L1a** system could be due to the existence of [Pd(η^3-allyl)(**L4a**)$_2$]BF$_4$. This type of complex has been shown to provide higher conversion with lower enantioselectivity in comparison to their bidentate analogues because they have more degrees of freedom.[20]

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

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 that selectivities can be 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 values 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 depends 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 enantiomers can be attained by setting the configuration of the phosphite functionality. Additionally, for cyclic substrates, in contrast to linear substrates, enantioselectivity is also influenced by the substituent of the phosphite functionality and there is a slight effect of the configuration of carbons bearing the isopropylidene group and the rigidity of the ligand. In comparison with previous air-unstable 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 such as 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 substrates, 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 monodentate coordinated ligands. This study also indicates that the sugar backbone is able to control the

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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 synthesized 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 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 and AV500 and Varian Mercury-400 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. Coupling constants are reported in Hz. ^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) and 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*-isopropylidenepyrrolidine-3,4-diol (1). To a suspension of $LiAlH_4$ (420 mg, 10.9 mmol) in anhydrous THF (22 mL) at 0 °C was added a solution of **7**[14] (600 mg, 2.19 mmol) in anhydrous THF (22 mL). The mixture was heated at reflux for 2.5 h and then cooled at 0 °C. Diethyl ether and a saturated aqueous solution 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 a 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, $-C(CH_3)_2$), 1.51 (s, 3H, $-C(CH_3)_2$), 2.36 (s, 3H, $N-CH_3$), 2.51−2.57 (m, 2H, H-2, H-5a), 2.61 (br s, 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 ($-C(CH_3)_2$), 27.3 ($-C(CH_3)_2$), 40.0 ($N-CH_3$), 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*-isopropylidenepyrrolidine-3,4-diol (8). To a solution of **7**[14] (203 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (10 mL) with 4 Å MS at 0 °C was added anhydrous trifluoroacetic acid (1.9 mL). The mixture was stirred at room temperature 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 a 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). ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H, $-C(CH_3)_2$), 1.47 (s, 3H, $-C(CH_3)_2$), 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, $J_{2-1'b}$ = 4.2), 3.65 (dd, 1H, H-1′b), 4.50 (d, 1H, H-3, J_{3-4} = 5.4), 4.63 (br s, 2H, OH, NH), 4.76 (t, 1H, H-4). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 24.0 ($-C(CH_3)_2$), 26.3 ($-C(CH_3)_2$), 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*-isopropylidenepyrrolidine-3,4-diol (2). To a solution of **8** (125 mg, 0.72 mmol) in anhydrous 1,2-dichloroethane (7.5 mL) were successively added benzaldehyde (0.15 mL, 1.44 mmol) and $NaBH(OAc)_3$ (320 mg, 1.51 mmol). The mixture was stirred at room temperature for 3 h, and then a saturated aqueous solution 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 a 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). ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H,$-C(CH_3)_2$), 1.54 (s, 3H, $-C(CH_3)_2$), 2.39 (br s, 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, CH_2Ph, J_{H-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 ($-C(CH_3)_2$), 27.4 ($-C(CH_3)_2$), 58.3 (CH_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 (C_{arom}). 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*-isopropylidenepyrrolidine-3,4-diol (3). To a solution of compound **8** (121 mg, 0.70 mmol) in MeOH (1.5 mL) were added acetone (0.26 mL, 3.49 mmol) and Pd/C 10% (cat.). 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 a 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). ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, 3H, CH_3, J_{H-H} = 6.3), 1.09 (d, 3H, CH_3), 1.31 (s, 3H,$-C(CH_3)_2$), 1.50 (s, 3H, $C(CH_3)_2$), 2.32 (br s, 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, $(CH_3)_2CH$, 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 (CH_3), 22.3 (CH_3), 25.3 ($-C(CH_3)_2$), 27.6 ($-C(CH_3)_2$), 48.0 ($(CH_3)_2CH$), 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*-*tert*-Butoxycarbonyl-2-hydroxymethyl-3,4-*O*-isopropylidenepyrrolidine-3,4-diol (10). To a solution of compound **9**[15] (2.44 g, 9.28 mmol) in MeOH (70 mL) were added Boc_2O (2.02 g, 18.6 mmol) and Pd/C 10% (0.63 g). 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 colorless 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*-isopropylidenepyrrolidine-3,4-diol (4). To a suspension of $LiAlH_4$ (206 mg, 5.43 mmol) in anhydrous THF (11 mL) at 0 °C was added a solution of **10** (292.6 mg, 1.09 mmol) in anhydrous THF (11 mL). The mixture was heated at reflux for 2.5 h and then cooled at 0 °C. Diethyl ether and a saturated aqueous solution 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 a 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). ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H, $-C(CH_3)_2$), 1.51 (s, 3H, $-C(CH_3)_2$), 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, $N-CH_3$), 3.25 (d, 1H, H-5b), 3.42 (br s, 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_{4-3} =

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6.3), 4.70 (dd, 1H, H-3, J_{3-2} = 5.1). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 24.3 (−C(CH_3)$_2$), 25.9 (−C(CH_3)$_2$), 40.3 (N-CH_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*-Isopropylidenetetrahydropyrrolo[1,2-*c*]-oxazol-3-one-6,7-diol (11). To a solution of **10** (1.06 g, 3.89 mmol) in anhydrous pyridine (15 mL) at 0 °C was slowly added TsCl (1.89 g, 9.74 mmol). After the mixture was stirred at room temperature overnight, the solvent was evaporated and the residue was purified by a 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*-isopropylide-nepyrrolidine-3,4-diol (12). To a solution of **11** (147 mg, 0.74 mmol) in anhydrous THF (6.0 mL) at 0 °C was slowly added $KPPh_2$ (0.5 M in THF, 1.8 mL, 0.89 mmol). The mixture was heated at reflux for 2 h and then cooled to room temperature. 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 a chromatography column on silica gel (eluent: Et_2O/acetone 10/1, 1% Et_3N) to produce **12** (26 mg, 89%) as a colorless 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 (br s, 1H, NH), 2.37 (dd, 1H, H-1′a, $J_{1'a\text{-}1'b}$ = 13.2, $J_{1'a\text{-}2}$ = 8.1), 2.43 (dd, 1H, H-1′b, $J_{1'b\text{-}2}$ = 6.3), 2.50−2.62 (m, 2H, H-2, H-5a), 3.02 (d, 1H, H-5b, $J_{5b\text{-}5a}$ = 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(CH_3)$_2$), 26.0 (−C(CH_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 L1a−d, L2a, L3a, L4a,b, and L7a,b. The desired *in situ* prepared phosphorochloridite (1.1 equiv) was first dissolved in toluene (5 mL/mmol), and then pyridine (3.8 equiv) was added. After the corresponding alcohols **1**−**4** and **6** were azeotropically dried with toluene (3 × 1 mL), toluene (5 mL/mmol) and pyridine (3.8 equiv) were added. The solution was transferred slowly at 0 °C to a solution of the phosphorochloridite. The resulting reaction mixture was stirred overnight at 80 °C, 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 (C_{arom}). 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, $^2J_{H-H}$ = 9.6 Hz, $^3J_{H-H}$ = 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═, $^3J_{H-H}$ = 8.5 Hz), 7.33 (d, 1H, CH═, $^3J_{H-H}$ = 8.5 Hz), 7.69 (d, 2H, CH═, $^3J_{H-H}$ = 8.2 Hz), 8.10 (d, 2H, CH═, $^3J_{H-H}$ = 8.2 Hz). ^{13}C NMR (100.6 MHz, C_6D_6): δ −0.2 (CH_3, $SiMe_3$), −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 (C_{arom}). 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, $^2J_{H-H}$ = 9.5 Hz, $^3J_{H-H}$ = 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 (C_{arom}). 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, $^2J_{H-H}$ = 9.6 Hz, $^3J_{H-H}$ = 4.7 Hz), 2.58 (dd, 1H, CH, $^2J_{H-H}$ = 8.6 Hz, $^3J_{H-H}$ = 4.0 Hz), 2.93 (dd, 1H, CH_2−N, $^2J_{H-H}$ = 9.6 Hz, $^3J_{H-H}$ = 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 (C_{arom}). 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. ^{1}H 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 (C_{arom}). 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. ^{1}H 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),

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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 (C_{arom}). 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. ^{1}H 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, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 4.6 Hz), 1.87 (s, 3H, CH_3, NMe), 2.01 (m, 1H, CH), 2.88 (d, 1H, CH_2−N, $^2J_{H-H}$ = 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═, $^3J_{H-H}$ = 15.1 Hz, $^3J_{H-H}$ = 8.4 Hz), 7.68 (m, 2H, CH═), 8.12 (d, 2H, CH═, $^3J_{H-H}$ = 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 (C_{arom}). 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, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 4.6 Hz), 1.66 (s, 3H, CH_3, NMe), 2.00 (m, 1H, CH), 2.80 (d, $^2J_{H-H}$ = 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, $SiMe_3$), −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 (C_{arom}). 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, $^2J_{H-H}$ = 13.3 Hz, $^3J_{H-H}$ = 5.6 Hz), 2.78 (dd, 1H, CH_2, $^2J_{H-H}$ = 11.4 Hz, $^3J_{H-H}$ = 4.9 Hz) 2.90 (d, 1H, CH_2, $^2J_{H-H}$ = 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═, $^3J_{H-H}$ = 7.5 Hz), 7.30 (d, 1H, CH═, $^3J_{H-H}$ = 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 (C_{arom}). 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, $^2J_{H-H}$ = 13.1 Hz, $^3J_{H-H}$ = 5.8 Hz), 2.84 (m, 2H, CH_2, CH_2), 3.07 (t, 1H, CH, $^2J_{H-H}$ = 8.4 Hz), 3.18 (m, 1H, CH_2), 4.19 (d, 1H, CH−O, $^2J_{H-H}$ = 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═, $^3J_{H-H}$ = 8.5 Hz), 7.33 (d, 1H, CH═, $^3J_{H-H}$ = 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 (C_{arom}). 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, 0.5 mmol) 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 room temperature, followed by addition of the appropriate chlorodiphenylphosphine (0.55 mmol) via syringe. The reaction mixture was stirred for 1 h at room temperature. 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 (C_{arom}). 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*-isopropylidene-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 °C were successively added Et_3N (43 μL, 0.30 mmol) and $ClCO_2CH_3$ (24 μL, 0.30 mmol). The mixture was stirred at 0 °C 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 a saturated aqueous solution of $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated. The resulting crude product 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 °C. The reaction mixture was heated at reflux for 2 h and then cooled at 0 °C. Diethyl ether and a saturated aqueous solution 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 a chromatography column on silica gel (eluent: EtOAc/cyclohexane 1/2) to produce **L6** (81 mg, 82%) as a colorless 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(CH_3)$_2$), 1.59 (s, 3H,−C(CH_3)$_2$), 2.02 (s, 3H, N−CH_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_{4-3} = 6.0), 4.51 (dd, 1H, H-3, J_{3-2} = 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(CH_3)$_2$), 26.6 (−C(CH_3)$_2$), 26.7 (d, J_{C-P} = 13.9, C-1′), 39.6 (N-CH_3), 62.7 (C-5), 68.1 (d, J_{C-P} = 20.6, C-2), 78.3 (C-4), 81.5 (d, J_{C-P} = 3.6, C-3), 111.2 (-C(CH_3)$_2$), 128.4 (C_{arom}), 128.6 (d, J_{C-P} = 6.2, C_{arom}), 128.8 (d, J_{C-P} = 6.8, C_{arom}), 129.0 (C_{arom}), 132.9 (d, J_{C-P} = 18.1, C_{arom}), 133.6 (d, J_{C-P} = 19.8, C_{arom}), 139.7 (d, J_{C-P} = 15.0, C_{arom}−P), 140.4 (d, J_{C-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 room temperature under argon. After 30 min, $AgBF_4$ (9.8 mg, 0.05 mmol) was added, and the mixture was stirred for another 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: *m/z* found 832.2227, calcd for $C_{41}H_{53}NO_5PPdSi_2$ $(M - BF_4)^+$ 832.2229. Data for the major isomer (89%) are as follows. ^{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,

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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, $^2J_{H-H}$ = 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 (C_{arom}). Data for the minor isomer (11%) are as follows. ^{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 (C_{arom}).

*[Pd(η^3-1,3-cyclohexenyl)(**L1b**)]BF_4 (**37**).* Yield: 35 mg (76%). MS HR-ESI: m/z found 832.2233, calcd for $C_{41}H_{53}NO_5PPdSi_2$ $(M - BF_4)^+$ 832.2229. Data for the major isomer (96%) are as follows. ^{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═, $^3J_{H-H}$ = 8.4 Hz), 8.04 (d, 1H, CH═, $^3J_{H-H}$ = 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 (C_{arom}). Data for the minor isomer (4%) are as follows. ^{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: m/z found 944.2539, calcd for $C_{50}H_{57}NO_5PPdSi_2$ $(M - BF_4)^+$ 944.2542. Data for the major isomer (70%) are as follows. ^{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 (C_{arom}). Data for the minor isomer (30%) are as follows. ^{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 (C_{arom}).

*[Pd(η^3-1,3-diphenylallyl)(**L4a**)]BF_4 (**39**).* Yield: 44 mg (83%). MS HR-ESI: m/z found 944.2537, calcd for $C_{50}H_{57}NO_5PPdSi_2$ $(M - BF_4)^+$ 944.2542. Data for the major isomer (67%) are as follows. ^{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-P} = 35.7 Hz), 111.5 (d, CH allyl central, J_{C-P} = 11.4 Hz), 112.8 (CMe_2), 120.3–151.7 (C_{arom}). Data for the minor isomer (35%) are as follows. ^{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-P} = 36.5 Hz), 111.9 (d, CH allyl *central*, J_{C-P} = 11.4 Hz), 113.0 (CMe_2), 120.3–151.7 (C_{arom}). Data for [Pd(η^3-1,3-diphenylallyl)(**L4a**)$_2$]BF_4 (8%) are as follows. MS HR-ESI: m/z found 1589.5046, calcd for $C_{85}H_{101}N_2O_{10}P_2PdSi_4$ $(M - BF_4)^+$ 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 (C_{arom}).

Study of the Reactivity of [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 °C. 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 a capillary that contained a solution of triphenylphosphine in CD_2Cl_2 as the external standard.

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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, 0.03 mmol) was added. Then, the reaction mixture was stirred at room temperature during the time indicated in the text. The reaction mixture was subsequently quenched by adding Et_2O (5 mL) and saturated NH_4Cl(aq) (25 mL). The mixture was then extracted with Et_2O (3 × 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 (compounds **13**, **15**−**22**, and **26**−**28**), GC (compounds **14** and **30**−**35**), or ^1H NMR using $[Eu(hfc)_3]$ (compound **29**). For characterization and ee determination details see the 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 min, 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 mixture was stirred at room temperature for the time indicated in the text. The reaction mixture was subsequently quenched by adding Et_2O (5 mL) and saturated NH_4Cl(aq) (25 mL). The mixture was then extracted with Et_2O (3 × 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 the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00140.

$^{31}P\{^1H\}$ and ^1H and $^{13}C\{^1H\}$ NMR spectra of new ligands **L1a**−**d** through **L7a**−**d**, Pd intermediates **36**−**39**, and ligand intermediates **1**−**4**, **8**, **10**, and **12** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail for I.R.: robina@us.es.

*E-mail for O.P.: oscar.pamies@urv.cat.

*E-mail for M.D.: montserrat.dieguez@urv.cat.

ORCID

Montserrat Diéguez: 0000-0002-8450-0656

Notes

The authors declare no competing financial interest.

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