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Sugar-Based Diphosphoroamidite as a Promising New Class of Ligands in Pd-Catalyzed Asymmetric Allylic Alkylation Reactions

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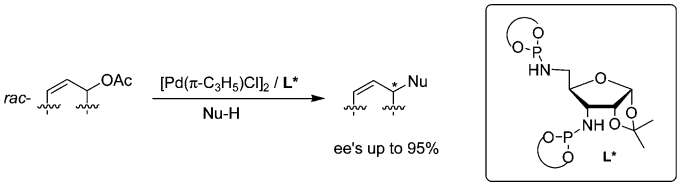

We have designed a new family of readily available modular diphosphoroamidite ligands from D-xylose for Pd-catalyzed asymmetric allylic alkylation reactions. This constitutes the first example of diphosphoroamidite ligands applied to this process. Good-to-excellent activities (TOFs up to 850 mol substrate $\times$ (mol Pd $\times$ h)$^{-1}$) and enantioselectivities (ee's up to 95%) have been obtained for several substrates with different electronic and steric properties. The results indicate that catalytic performance is highly affected by the substituents and the axial chirality of the biaryl moieties of the ligand. We also discuss the synthesis and characterization of the Pd$-\pi$-allyl intermediates to get more insight into the origin of enantioselectivity using these catalytic systems.

Introduction

The development of methods for enantioselective carbon−carbon bond formation is one of the key issues in organic synthesis. A versatile method for achieving this is the palladium-catalyzed asymmetric allylic substitution with carbon nucleophiles.[1] A large number of chiral ligands, mainly P− and N− ligands, which possess either C_2 or C_1 symmetry, have provided high enantiomeric excesses.[1] Most of the chiral ligands developed for asymmetric allylic substitution are mixed bidentate donor ligands (such as P−N, P−S, and S−N).[1,2] The efficiency of this type of hard−soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms. However, homodonor ligands (e.g., diphosphine,[3] dithioether,[4] and bisoxazoline[5] ligands) have, though to a lesser extent, also demonstrated their potential usefulness in this process mainly based on the chiral discrimination induced by C_2 or C_1 backbone symmetry. Recently, a group of less electron-rich phosphorus compounds—biaryl diphosphite ligands—have also demonstrated their potential utility by overcoming the most common limitations of this process, such as low reaction rates and high substrate specificity.[6] Therefore, these ligand systems have provided excellent enantioselectivities and activities in different substrate types.[6] The use of biaryl phosphites was beneficial because (1) the reaction rates increased due to the larger

(1) For recent reviews, see: (a) Tsuji, J. Palladium Reagents and Catalysis. *Innovations in Organic Synthesis*; Wiley: New York, 1995. (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 24. (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(2) Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159.

(3) See, for example: (a) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057. (b) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089. (c) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520. (d) Dierkes, P.; Randechul, S.; Barloy, L.; De Cian, A.; Fischer, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3116.

(4) See, for example: (a) Fernández, F.; Gómez, M.; Jansat, S.; Muller, G.; Martín, E.; Flores-Santos, L.; Garcia, P. X.; Acosta, A.; Aghmiz, A.; Gimenéz-Pedros, M.; Masdeu-Bultó, A. M.; Diéguez, M.; Claver, C.; Maesro, M. A. *Organometallics* **2005**, *24*, 3946. (b) Khiar, N.; Araujo, C. S.; Suárez, B.; Fernández, I. *Eur. J. Org. Chem.* **2006**, 1685. (c) Jansat, S.; Gómez, M.; Muller, G.; Diéguez, M.; Aghmiz, A.; Claver, C.; Masdeu-Bulto, A. M.; Flores-Santos, L.; Martín, E.; Maestro, M. A.; Mahía, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1469.

(5) See, for instance: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (c) Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164.

(6) (a) Diéguez, M.; Jansat, S.; Gomez, M.; Ruiz, A.; Muller, G.; Claver, C. *Chem. Commun.* **2001**, 1132. (b) Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1257. (c) Diéguez, M.; Pàmies, O.; Claver, C. *J. Org. Chem.* **2005**, *70*, 3363.

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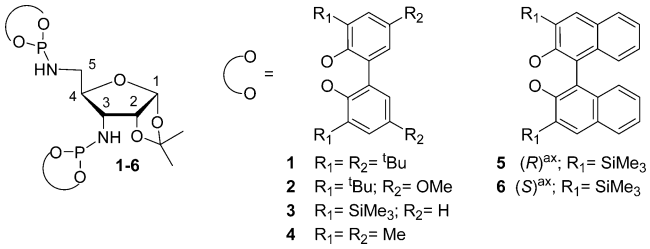

FIGURE 1. Diphosphoroamidite ligands **1**−**6**.

π-acceptor ability of the phosphite moiety[7] and (2) enantioselectivity increased because the chiral pocket (the chiral cavity where the allyl is embedded) created is flexible enough to allow the perfect coordination of hindered and unhindered substrates (which decreases the substrate specificity).[8]

Following our interest in highly modular, versatile π-acceptor ligands, and encouraged by the success of the phosphoroamidite ligands in asymmetric catalysis,[9] we report here the synthesis of a new family of furanoside diphosphoroamidite ligands (**1**−**6**, Figure 1) for the enantioselective Pd-catalyzed allylic alkylation reactions. We also discuss the synthesis and characterization of the Pd−π-allyl intermediates to get more insight into the origin of the enantioselectivity using these catalytic systems.

These diphosphoroamidite ligands are derived from natural D-(+)-xylose, so they also have the advantage of carbohydrates, such as availability at a low price and facile modular construction, which makes the tedious optical resolution procedure unnecessary.[10] The modular construction of these ligands allows sufficient flexibility to fine tune the steric and electronic properties of the biaryl moieties to explore how they affect catalytic performance (activity and selectivity). In this way, we studied how attaching different groups to the ortho and para positions of the biphenyl moieties affects the catalytic performance with ligands **1**−**4**. To further investigate how enantioselectivity was influenced by the configuration of the biaryl moieties, ligands **5** and **6** containing different enantiomerically pure binapthyl moieties were also tested. As a result, the optimal combination for maximum activity and selectivity for different substrates types were reached.

To the best of our knowledge this is the first example of diphosphoroamidite ligands applied to the enantioselective Pd-catalyzed allylic substitution reactions.

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(8) The flexibility that offers the biphenyl moiety can be used to fine tune the chiral pocket formed upon complexation. See: (a) ref 7b. (b) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Adv. Synth. Catal.* **2005**, *347*, 1943.

(9) See, for instance: (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (b) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (c) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426. (d) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Angew. Chem., Int. Ed.* **2006**, *12*, 3596. (e) Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Chem. Eur. J.* **2004**, *10*, 6232. (f) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2232. (g) Alejakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262. (h) Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Commun.* **2001**, 2702. (i) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49.

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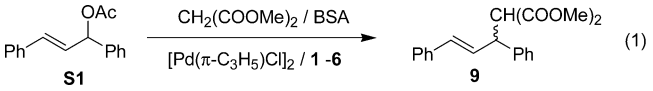
Results and Discussion

Ligand Synthesis. The new diphosphoroamidite ligands **1**−**6** were synthesized very efficiently from diamine **8** by reacting 2 equiv of the desired in-situ-formed phosphorochloridite[11] in the presence of pyridine. 3,5-Dideoxy-3,5-diamino-1,2-*O*-isopropylidene-ribofuranose **8** was easily prepared on a large scale from inexpensive D-(+)-xylose. All the ligands were stable during purification on neutral alumina under an atmosphere of argon and isolated in moderate yields as white solids. The ^{1}H, ^{31}P, and ^{13}C NMR spectra were as expected for these C_1 ligands (see the Experimental Section and Scheme 1).

Asymmetric Allylic Alkylation Reactions. We first investigated the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1**, which is widely used as a model substrate, with dimethyl malonate using the chiral diphosphoroamidite ligands **1**−**6** (eq 1).



(1)

The catalysts were generated in situ from 0.5 mol % of π-allyl−palladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand, and a catalytic amount of KOAc. The nucleophile was generated from dimethyl malonate in the presence of *N*,*O*-bis-(trimethylsilyl)acetamide (BSA).

We determined the optimal reaction conditions by conducting a series of experiments in which the solvent and the ligand-to-palladium ratio were varied. We first studied the effect of four solvents with ligand **1** (Table 1, entries 1−4). The best activity and enantioselectivity was achieved with dichloromethane as solvent (entry 1). We next studied the effect of varying the ligand-to-palladium ratio (Table 1, entries 1, 5, and 6). The results show that an excess of ligand is not needed for good activities and enantioselectivities.

For comparative purposes, the rest of the ligands were tested under conditions that provided the optimum tradeoff between enantioselectivities and reaction rates, i.e., a ligand-to-palladium ratio of 1.1 and dichloromethane as a solvent. The results, shown in Table 2, indicate that catalytic performance (activities and enantioselectivities) is highly affected by the substituents and the axial chirality of the biaryl moieties. In general, good activity (TOFs up to 850 mol **S1** × (mol Pd × h)$^{-1}$)[13] and enantioselectivity (ee's up to 75%) were obtained in the alkylation of **S1**.

The effect of the biphenyl substituents was investigated with ligands **1**−**4** (Table 2, entries 1−4). We found that these moieties affect both activity and enantioselectivity. Substituents in the para positions of the biphenyl moieties are required for good enantioselectivity (Table 2, entries 1, 2, and 4 vs 3). Thus, ligands **1**, **2**, and **4** with substituents at para positions of the biphenyl moieties provided higher enantioselectivities than ligand **3**, without substituents in these positions. However, the type of substituents in the para positions is also important. Therefore, the presence of the methoxy group in the biphenyl

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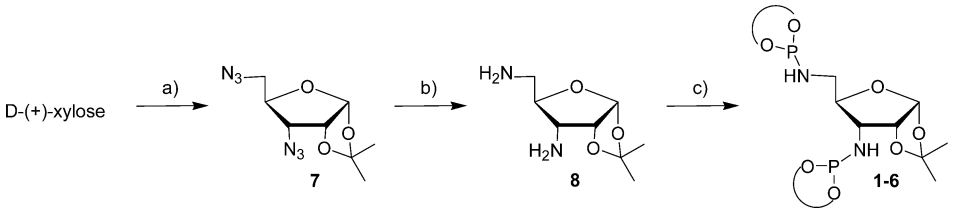
(13) TOF measured at around 30% conversion.

SCHEME 1. Synthesis of the New Diphosphoroamidite Ligands 1−6[a]



[a] (a) Ref 12. (b) PPh_3, THF/H_2O. (c) $ClP(OR)_2$, Py, toluene.

TABLE 1. Pd-Catalyzed Allylic Alkylation of S1 Using Ligand 1: Effect of the Solvent and Ligand-to-Palladium Ratio[a]

entry	solvent	ratio of **1**/Pd	% conversion (min)[b]	% ee[c]
1	CH_2Cl_2	1.1	100 (15)	66 (*R*)
2	DMF	1.1	90 (15)	53 (*R*)
3	toluene	1.1	10 (15)	58 (*R*)
4	THF	1.1	20 (15)	54 (*R*)
5	CH_2Cl_2	0.8	62 (15)	67 (*R*)
6	CH_2Cl_2	2	100 (15)	62 (*R*)

[a] Conditions: 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel-OD). Absolute configuration shown in parentheses.

TABLE 2. Pd-Catalyzed Allylic Alkylation of S1 with Ligands 1−6[a]

entry	ligand	% conversion (min)[b]	% ee[c]
1	**1**	100 (15)	66 (*R*)
2	**2**	33 (15)	59 (*R*)
3	**3**	11 (15)	13 (*S*)
4	**4**	87 (15)	63 (*R*)
5	**5**	78 (30)	75 (*R*)
6	**6**	85 (30)	30 (*R*)
7[d]	**1**	98 (60)	66 (*R*)
8[d]	**5**	24 (150)	74 (*R*)

[a] Conditions: 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel-OD). Absolute configuration shown in parentheses. [d] Reaction carried out at 0.1 mol % of $[Pd(\pi\text{-}C_3H_5)Cl]_2$.

moieties has a negative effect on both activity and enantioselectivity (Table 2, entry 1 vs 2). Moreover, the substituents in the ortho positions of the biphenyl moieties have a slight but important effect on both activity and enantioselectivity (Table 2, entries 1 vs 4). Activities and enantioselectitivies are therefore highest when *tert*-butyl groups are present at both ortho and para positions of the biphenyl moieties.

To further investigate how enantioselectivity was influenced by the groups attached to the biaryl moieties, ligands **5** and **6** containing different enantiomerically pure binapthyl moieties were also tested (Table 2, entries 5 and 6). Ligand **5** containing *R*-binaphtyl moieties produced the *R*-**9** product in 75% ee, while ligand **6** containing *S*-binaphtyls produced the *R*-**9** product in lower enantioselectivity (30% ee). These results indicate that there is a cooperative effect between the configuration of the biaryl moieties and the configurations of the ligand backbone that results in a matched combination for ligand **5**. Note that this cooperative effect is highly advantageous, allowing us to increase enantioselectivity up to 75% ee (entry 5).

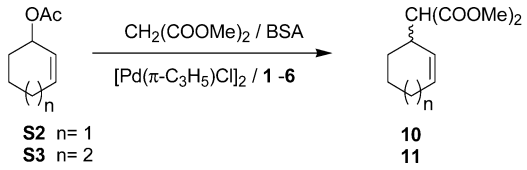
We also performed the reaction at a low catalyst concentration (**S1**/Pd = 500) using ligands **1** and **5** (entries 7 and 8). Good enantioselectivity (ee's up to 74% (*R*)) and high activity (TOFs up to >560 mol **S1** × (mol Pd × h)$^{-1}$) were obtained.

TABLE 3. Pd-Catalyzed Allylic Alkylation of S2 Using Ligand 1: Effect of the Solvent and Ligand-to-Palladium Ratio[a]

entry	solvent	ratio of **1**/Pd	% conversion (min)[b]	% ee[c]
1	CH_2Cl_2	1.1	100 (120)	82 (*S*)
2	DMF	1.1	100 (120)	75 (*S*)
3	toluene	1.1	56 (120)	79 (*S*)
4	THF	1.1	100 (120)	88 (*S*)
5	THF	0.8	95 (120)	88 (*S*)
6	THF	2	100 (120)	86 (*S*)

[a] Conditions: 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by GC. Reaction time in minutes shown in parentheses. [c] Determined by GC. Absolute configuration shown in parentheses.

We next tested this new family of ligands in the Pd-catalyzed asymmetric allylic alkylation of cyclic substrates (eq 2).



(2)

Enantioselectivity in cyclic substrates is usually more difficult to control, mainly because of the presence of less sterically demanding syn substituents, which play a crucial role in the enantioselection observed with acyclic substrates in the corresponding Pd−allyl intermediate.[1] Therefore, few catalytic systems have provided good enantioselectivities.[3b,d,7b,14]

We first tested the efficiency of the chiral diphosphoroamidite ligands **1**−**6** in the Pd-catalyzed allylic alkylation of *rac*-3-acetoxycyclohexene **S2** (eq 2), which is usually used as a model cyclic substrate.

The preliminary investigations into the solvent effect and the ligand-to-palladium ratio using ligand **1** provided a different trend for the solvent effect than those into the previously tested substrate **S1**. Therefore, the best enantioselectivities and reaction rates were obtained when THF was used as solvent and the ligand-to-palladium ratio was 1.1 (Table 3).

The results of using ligands **1**−**6** under the optimized conditions are shown in Table 4. In general, high enantioselectivity (ee's up to 88%) with good activity were obtained in the alkylation of **S2**. Again, enantioselectivity was affected by the substituents at the biaryl moieties and the cooperative effect between stereocenters. However, the effect of these parameters was different from those observed in the alkylation of **S1**.

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TABLE 4. Pd-Catalyzed Allylic Alkylation of S2 and S3 with Ligands 1−6[a]

entry	ligand	substrate	% conversion (min)[b]	% ee[c]
1	**1**	**S2**	100 (120)	88 (*S*)
2	**2**	**S2**	100 (120)	76 (*S*)
3	**3**	**S2**	90 (120)	17 (*S*)
4	**4**	**S2**	32 (120)	5 (*S*)
5	**5**	**S2**	19 (120)	56 (*R*)
6	**6**	**S2**	42 (120)	72 (*S*)
7	**1**	**S3**	51 (360)	95 (*S*)

[a] Conditions: 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, room temperature. [b] Conversion percentage of acetates **10** and **11** determined by GC. Reaction time in minutes shown in parentheses. [c] Enantiomeric excesses determined by GC. Absolute configuration shown in parentheses.

Therefore, enantioselectivity was best with ligand **1** (88% (*S*) ee). These results clearly show the importance of using modular scaffolds in the ligand design.

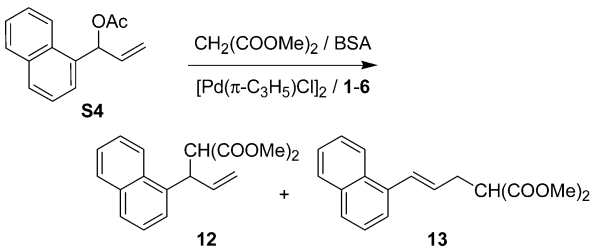
Regarding the effect of the substituents in the biphenyl moieties, again substituents in the para position are necessary for high ee's (entries 1 and 2 vs 3). However, in contrast to the alkylation of **S1**, the effect of the type of substituent in ortho positions is more significant. Therefore, enantioselectivities and activities are higher when more sterically demanding substituents are present (i.e., ^{t}Bu > Me).

Concerning the effect of the configuration of the biaryl moieties, the cooperative effect previously reported with substrate **S1** also showed a different tendency and the matched combination was therefore observed for ligand **6** (entries 5 and 6).

Encouraged by the excellent results obtained in the alkylation of cyclic substrate **S2**, we examined the stereoselective allylic alkylation of the seven-membered cyclic substrate **S3** using ligand **1** (Table 4, entry 7). Interestingly, for this sterically undemanding substrate, high enantioselectivities (ee's up to 95%) were also obtained.

In summary the results obtained with cyclic substrates are among the best reported so far.[3b,d,7b,14]

To further study the potential of these readily available ligands, we also tested them in the allylic alkylation of the monosubstituted linear substrate 1-(1-naphthyl)allyl acetate **S4** (eq 3).



(3)

For this substrate, as well as controlling the enantioselectivity of the process, the regioselectivity is also a problem, because a mixture of regioisomers may be obtained. Most Pd catalysts developed to date favor the formation of the achiral linear product **13** rather than the desired branched isomer **12**.[1] Therefore, the development of highly regio- and enantioselective Pd catalysts is still a challenge.[15] The results are summarized in Table 5. Interestingly, under nonoptimized conditions, the catalytic system containing ligand **1** produced the desired branched isomer as the major product with high activity and enantioselectivity (ee's up to 83% (*S*)). The results indicate that enantioselectivities are highly affected by the substituents in the para position of the biphenyl moieties (Table 5, entries 1−4). However, regioselectivity is mainly governed by the substituents at the ortho positions (Table 5, entries 1−4). It should be note that the cooperative effect previously observed with substrates **S1** and **S2** has the main effect on regioselectivity (Table 5, entries 5 and 6). These results are among the best reported so far,[15] and it is clear that they represent a major improvement over other Pd−homodonor bidentate catalytic systems[16] that predominantly provide the linear achiral product as the major one.

TABLE 5. Selected Results for the Pd-Catalyzed Allylic Alkylation of S5[a]

entry	ligand	% conversion (min)[b]	**12**/**13**[c]	% ee[d]
1	**1**	100 (30)	65/35	76 (*S*)
2	**2**	100 (30)	65/35	22 (*R*)
3	**3**	100 (30)	60/40	13 (*S*)
4	**4**	100 (30)	40/60	72 (*S*)
5	**5**	100 (30)	65/35	33 (*R*)
6	**6**	100 (30)	80/20	20 (*S*)
7[e]	**1**	100 (120)	65/35	83 (*S*)

[a] Conditions: 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol % ligand, room temperature. [b] Conversion percentage measured by ^{1}H NMR. Reaction time in minutes shown in parentheses. [c] Branched to linear ratio determined by ^{1}H NMR. [d] Enantiomeric excesses determined by HPLC. Absolute configuration shown in parentheses. [e] $T = 0$ °C.

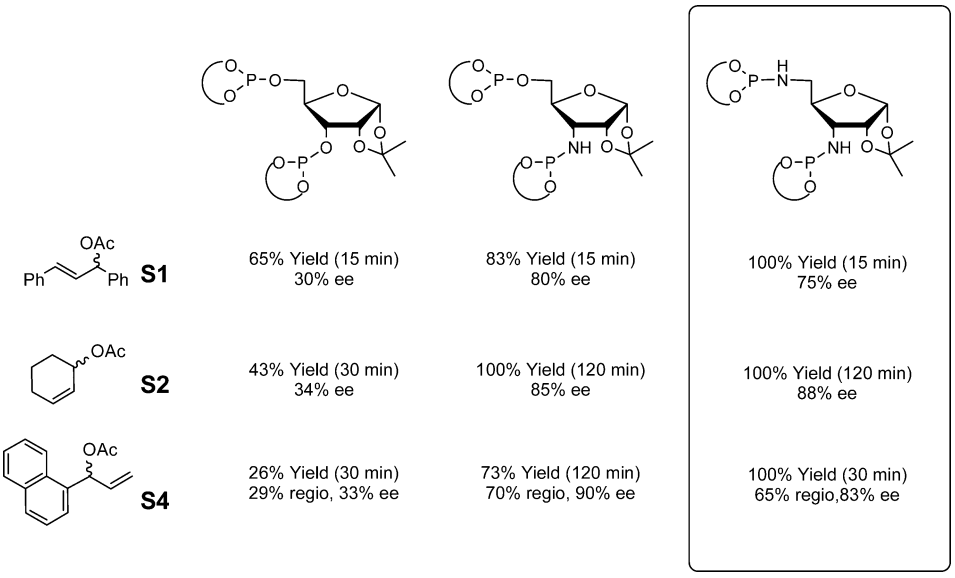
To sum up, these diphosphoroamidite ligands have provided good results in different substrates types. The high activities and enantioselectivities (ee's up to 95%) obtained for cyclic substrates are particularly noteworthy as is the combination of high regio- and enantioselectivitities (regioselectivities up to 65% and ee's up 83%) for monosubstituted substrate **S4**. These facts, along with the promising results obtained for substrate **S1**, open up the Pd-catalyzed allylic alkylation reactions to a new class of ligands—the diphosphoroamidites. The efficiency of the ligand design is also corroborated by the fact that these Pd−diphosphoroamidite catalysts provide higher activities, regio-, and enantioselectivities than their Pd−diphosphite analogues[6b] (Scheme 2). In addition, these ligands provide comparable results to those with related heterodonor phosphite−phosphoroamidite ligands recently described for this process.[9i]

Origin of Enantioselectivity: Study of the Pd-π-allyl Intermediates. In order to get more insight into the effect of the ligand parameters on catalytic performance, we performed a study of the Pd−π-allyl compounds **14**−**17**, $[Pd(\pi\text{-allyl})(L)]BF_4$ (L = diphosphoroamidite ligands), since they are key intermediates in the studied allylic alkylation reactions (Scheme 3).[1] These ionic palladium complexes containing 1,3-diphenyl and cyclohexenyl groups were prepared from the corresponding palladium allyl dimer and the appropriate ligand in the presence of silver tetrafluoroborate, following the previously described

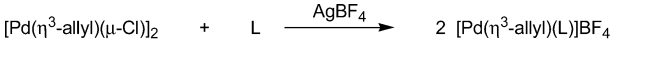
(15) For successful applications of Pd catalysts, see: (a) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (b) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814. (c) You, S. L.; Zhu, X. Z.; Luo, Y. M.; Hou, X. L.; Dai, L. X. *J. Am. Chem. Soc.* **2001**, *123*, 7471.

(16) See, for example: (a) Laurenti, D.; Feuerstein, M.; Pèpe, G.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 1633. (b) Canal, J. M.; Gómez, M.; Jiménez, F.; Rocamora, M.; Muller, G.; Duñach, E.; Franco, D.; Jiménez, A.; Cano, F. H. *Organometallics* **2000**, *19*, 966. (c) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 585−662.

SCHEME 2



SCHEME 3. Preparation of Pd−Allyl Intermediates 14−17



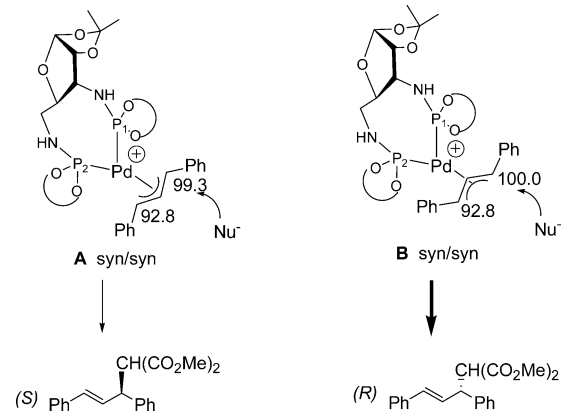
14 allyl = 1,3-Ph_2-C_3H_3; L = **2**
15 allyl = 1,3-Ph_2-C_3H_3; L = **3**
16 allyl = *cyclo*-C_6H_9; L = **1**
17 allyl = *cyclo*-C_6H_9; L = **4**

methodology (Scheme 3).[17] The complexes were characterized in solution using ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The spectral assignments (see the Experimental Section) were based on information from ^{1}H−^{1}H, ^{31}P−^{1}H, and ^{13}C−^{1}H correlation measurements in combination with ^{1}H−^{1}H NOESY experiments.

A. 1,3-Diphenyl Allyl Palladium Complexes. To understand the differences in catalytic performance observed in the alkylation of **S1** using ligands **1**−**6**, we decided to study the 1,3-diphenylallyl palladium complexes containing ligand **2** (which provided product (*R*)-**9** in good enantioselectivity) and ligand **3** without substituents on the para positions of the biphenyl moieties (which provided low enantioselectivity in the reversed enantiomer). In addition, this study allowed us to explain the important effect of the para substituents of the biphenyl groups on catalytic performance (see above).

The NMR study of the Pd−allyl intermediate containing ligand **2**, [Pd(η^3-1,3-diphenylallyl)(**2**)]BF_4 (**14**), showed a mixture of two isomers in a ratio of 1:1 (see the Experimental Section). No changes were observed down to −80 °C. Both isomers could be unambiguously assigned by NOE to the two syn/syn isomers (Scheme 4). The carbon NMR chemical shifts indicate for both isomers that the most electrophilic allyl carbon terminus is trans to the phosphorus at the C-5 position (P_2). Assuming that the nucleophilic attack takes place at the more electrophilic carbon terminus[18] and based on the observed stereochemical outcome of the reaction, 59% (*R*) in product **9**,

SCHEME 4. Diastereoisomer Pd−Allyl Intermediates 14[a]



[a] P_1: Phosphorus atom next to C-3. P_2: Phosphorus atom next to C-5 (assigned by ^{31}P−^{1}H HMBC correlation experiment).

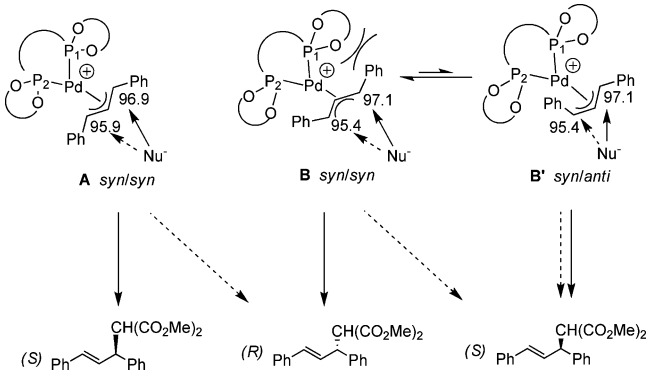
and the fact that enantiomeric excess of **9** is higher than the diastereoisomeric excess of the Pd intermediates, the **B** isomer must react faster than the **A** isomer. This is consistent with the fact that for both isomers, the most electrophilic allylic terminal carbon atom is the one trans to the phosphorus at C-5 (P_2) in the **B** isomer.

The NMR study of the Pd−allyl intermediate containing ligand **3**, [Pd(η^3-1,3-diphenylallyl)(**3**)]BF_4 (**15**), showed a mixture of two isomers in a ratio of 1:1 (see the Experimental Section). One of the isomers could be unambiguously assigned by NOE experiment to a syn/syn isomer **A** (Scheme 5). However, for the other isomer and in contrast to **14**, the VT-^{31}P NMR spectra indicated a fluxional behavior for the phosphorus next to C-3 (P_1) in isomer **B** (assigned by ^{31}P−^{1}H HMBC correlation experiment) that could not be frozen out until −80 C. This fluxionability can be attributed to an equilibrium between syn/syn and syn/anti isomers (Scheme 5) or to the fluxional behavior of the biphenyl moieties. However, the study of the models suggested that the absence of the para substituents in the biphenyl moieties in ligand **3** caused a different orientation of the biphenyl moieties in the Pd−π-allyl intermediate than for complex **14** which resulted in a new steric repulsion between one of the biphenyl moieties and one of the phenyl substituents

(17) Deerenberg, S.; Schrekker, H. S.; van Strijdonck, G. P. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. *J. Org. Chem.* **2000**, *65*, 4810.

(18) It is well-known that the enantioselectivity in the palladium-catalyzed allylic alkylation with soft reagents is controlled by the nucleophilic attack to the more electrophilic terminal carbon of the allyl ligand in the Pd(II) intermediates such as **14**. See ref 1.

SCHEME 5. Diastereoisomer Pd−Allyl Intermediates 15[a]



[a] P_1: Phosphorus atom next to C-3. P_2: Phosphorus atom next to C-5 (assigned by $^{31}P-^{1}H$ HMBC correlation experiment).

of **S1** in this isomer (Scheme 5). The formation of the anti isomer minimized this new steric repulsion. It should be noted that this syn/anti isomerism is observed at the most electrophilic allylic terminal carbon (the one exhibiting the highest ^{13}C chemical shifts). Assuming that the nucleophilic attack takes place at the most electrophilic carbon atom, the attack at syn/syn isomer **B** will lead to the formation of (*R*)-**9**, while the attack in syn/anti isomer **B′** will lead to the formation of the opposite enantiomer of product **9**.

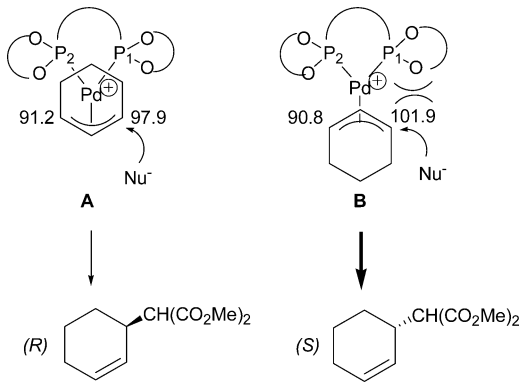
Another important difference between complexes **14** and **15** was found in the ^{13}C NMR spectra. For each isomer of complex **15** the electronic differences between both allylic terminal carbons ($\Delta(\delta^{13}C) \approx 1$ ppm) decreased considerably compared to those of isomers of **14** ($\Delta(\delta^{13}C) \approx 8$ ppm). Therefore, the electrophilicity of the allylic terminal carbons for **15** decreased.

In summary, the notable decrease in enantioselectivity observed using the Pd/**3** catalyst in comparison with the Pd/**2** catalyst system may be due to either the presence of a syn/syn and syn/anti equilibrium or the possibility that the nucleophile attacks at both allylic terminal carbons in each isomer, due to their low electronic differentiation ($\Delta(\delta^{13}C) \approx 1$ ppm), or a combination of both. However, the fact that the allylic terminal carbons in complex **14** are more electrophilic may explain the higher activities obtained with the Pd/**2** catalytic system (Table 2, entries 2 vs 3).

B. Cyclohexenyl Allyl Palladium Complexes. In order to elucidate the difference in catalytic performance observed with ligands **1**−**6** in the alkylation of cyclic substrates (**S2** and **S3**), we next studied the ionic palladium complexes containing the cyclohexenyl groups. In contrast to the alkylation of **S1**, the substituents in the ortho positions of the biaryl moieties also have a considerable effect on catalytic performance. For this reason, we decided to study the cyclohexenyl allyl−palladium complexes containing ligand **1** (which provided the best enantioselectivity) and ligand **4** (which provided the lowest enantioselectivity).

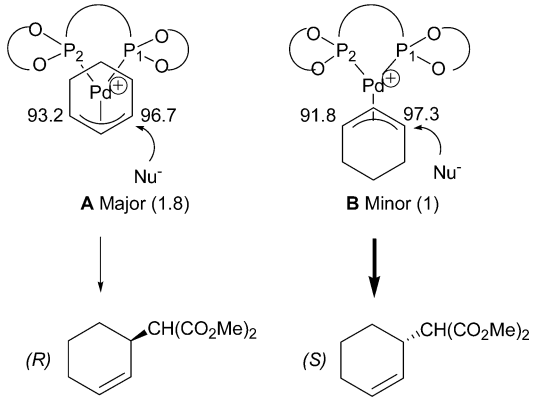
The NMR study of the Pd−allyl intermediate containing ligand **1**, [Pd(η^3-*cyclo*-C_6H_9)(**2**)]BF_4 (**16**), showed a mixture of two isomers in a ratio of 1:1 (see the Experimental Section). Both isomers could be assigned by NOE to the two syn/syn isomers (Scheme 6). The carbon NMR chemical shifts indicated for both isomers that the most electrophilic allylic terminus carbon is trans to the phosphorus at the C-5 position (P_2). Assuming that the nucleophilic attack takes place at the most electrophilic allylic carbon terminus and based on the observed

SCHEME 6. Diastereoisomer Pd−Allyl Intermediates 16[a]



[a] P_1: Phosphorus atom next to C-3. P_2: Phosphorus atom next to C-5 (assigned by $^{31}P-^{1}H$ HMBC correlation experiment).

SCHEME 7. Diastereoisomer Pd−Allyl Intermediates 17[a]



[a] P_1: Phosphorus atom next to C-3. P_2: Phosphorus atom next to C-5 (assigned by $^{31}P-^{1}H$ HMBC correlation experiment).

stereochemical outcome of the reaction, 88% (*S*) in product **10**, and the fact that enantiomeric excess of **10** is higher than the diastereoisomeric excesses of the Pd intermediates, the **B** isomer must react faster than the **A** isomer. This is consistent with the fact that for both isomers the most electrophilic allylic carbon atom is the one trans to the phosphorus at C-5 in the **B** isomer.

In contrast to complex **16**, the NMR study of the Pd−allyl intermediate containing ligand **4**, [Pd(η^3-*cyclo*-C_3H_9)(**4**)]BF_4 (**17**), revealed the presence of one isomer in excess 1.8:1 (see the Experimental Section). Both isomers could be assigned by NOE to the two syn/syn isomers (Scheme 7). Another important difference between complexes **16** and **17** is the lower electronic differentiation between the more electrophilic allylic terminus carbon atoms of both isomers (**A** and **B**) in complex **17** ($\Delta(\delta^{13}C) \approx 0.6$ ppm) than in complex **16** ($\Delta(\delta^{13}C) \approx 4$ ppm). This low electronic differentiation suggests that the nucleophile can attack both isomers at a similar rate. However, the difference between the diastereoisomeric ratio and enantioselectivity observed in the alkylation of **S2** (de = 28% vs ee = 5%) indicates that the nucleophile reacts faster with the minor isomer, but the relative reaction rates between both isomers is much lower than in complex **16**. The lower activity observed with Pd/**4** catalytic system may be due to fact that the allylic terminal carbons in complex **17** are less electrophilic than with complex **16** (Table 4, entries 1 vs 4).

Conclusion

In summary, we have described the first application of diphosphoroamidite ligands for the Pd-catalyzed asymmetric allylic substitution reactions of several substrate types. These ligands have the advantage of being easily prepared in a few steps from commercial D-xylose, an inexpensive natural chiral feedstock. In addition, they can be easily tuned so the effect of different substituents and configurations of the biaryl moieties on catalytic performance can be explored. By carefully selecting the ligand components, we obtained good results in different substrate types. Particularly, for the hindered disubstituted linear substrate **S1**, we found that substituents in the para positions of the biphenyl moieties are needed for good enantioselectivity. However, for cyclic substrates **S2** and **S3**, in addition to the presence of para substituents, the presence of bulky substituents in the ortho positions are necessary for high enantioselectivity. For the monosubstituted linear substrate **S5**, the results indicate that enantioselectivities are highly affected by the substituents in the para position of the biphenyl moieties. However, regioselectivity is mainly governed by the substituents at the ortho positions. Therefore, the presence of substituents in the para positions combined with bulky substituents in the ortho positions of the biaryl moieties are necessary to obtain the optimum tradeoff between regio- and enantioselectivities. The study of the 1,3-diphenyl and cyclohexenyl Pd−π-allyl intermediates by NMR spectroscopy allows the understanding of the catalytic behavior observed. This study indicates that the nucleophilic attack takes place predominantly at the allylic terminal carbon atom located trans to the phosphoroamidite moiety attached to C-5.

The high activities and enantioselectivities (ee's up to 95%) obtained for cyclic substrates **S2** and **S3** are particularly noteworthy as is the combination of high regio- and enantioselectivitities (regioselectivities up to 65% and ee's up 83%) for monosubstituted substrate **S4**. These facts together with the promising results obtained for substrate **S1** open up the Pd-catalyzed allylic alkylation reactions to a new class of ligands—the diphosphoroamidites.

Experimental Section

General Considerations. All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. 3,5-Dideoxy-3,5-diazido-1,2-*O*-isopropylidene-ribofuranose **7**[12] and phosphorochloridite[11] were prepared as previously described. ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard.

3,5-Dideoxy-3,5-diamino-1,2-*O*-isopropylidene-ribofuranose (8). 3,5-Dideoxy-3,5-diazido-1,2-*O*-isopropylidene-ribofuranose **7** (2.0 g, 4.1 mmol) was dissolved in a THF/H_2O (90 mL, 4:1), and triphenylphosphine (5.0 g, 19.1 mmol) was added. The reaction mixture was stirred overnight at room temperature, and the THF was evaporated under vacuum. The residue was extracted with ether (3 × 20 mL). Evaporation of the aqueous solution gave the product as a yellow oil. Yield: 1.2 g, 77%. ^{1}H NMR, δ: 1.34 (s, 3H; CH_3), 1.53 (s, 3H; CH_3), 1.62 (b, 4H, NH_2), 2.83 (dd, 1H, H-5′, $^2J_{5'}$-5 = 13.6 Hz, $^3J_{5'}$-4 = 6 Hz), 3.02 (m, 1H, H-3), 3.07 (dd, 1H, H-5, $^2J_5$-5′ = 13.6 Hz, $^3J_5$-4 = 3.2 Hz), 3.66 (m, 1H, H-4), 4.46 (t, 1H, H-2, $^3J_2$-1 = $^3J_2$-3 = 4 Hz), 5.77 (d, 1H, H-1, $^3J_1$-2 = 4 Hz). ^{13}C NMR, δ: 26.6 (CH_3), 26.8 (CH_3), 42.9 (C-5), 56.4 (C-3), 81.0 (C-2), 82.4 (C-4), 104.3 (C-1), 112.1 (CMe_2). Anal. Calcd (%) for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.57; N, 14.88. Found: C, 51.12; H, 8.64; N, 14.97.

3,5-Bis[(3,3′,5,5′-tetra-t-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]-3,5-diamine-3,5-dideoxy-1,2-*O*-isopropylidene-ribofuranose (1). Phosphorochloridite (2.2 mmol) produced in situ was dissolved in toluene (5 mL), and pyridine (0.36 mL, 4.6 mmol) was added. **8** (189 mg, 1 mmol) was azeotropically dried with toluene (3 × 2 mL) and then dissolved in toluene (10 mL), to which pyridine (0.36 mL, 4.6 mmol) was added. The phosphorochloridite solution was transferred slowly over 5 min at room temperature to the solution of **8**. The reaction mixture was stirred overnight at 80 °C, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography over neutral alumina (toluene/NEt_3 = 100/2) to produce a white powder. Yield: 0.55 g, 52%. ^{31}P NMR, δ (C_6D_6): 149.4 (d, 1P, J_P-P = 4 Hz), 150.7 (d, 1P, J_P-P = 4 Hz). ^{1}H NMR, δ (C_6D_6): 1.12 (s, 3H, CH_3), 1.24 (s, 9H, CH_3, ^{t}Bu), 1.25 (s, 9H, CH_3, ^{t}Bu), 1.32 (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 3H, CH_3), 1.58 (s, 9H, CH_3, ^{t}Bu), 1.62 (s, 9H, CH_3, ^{t}Bu), 1.63 (s, 18H, CH_3, ^{t}Bu), 3.04 (m, 1H, H-5′), 3.26 (m, 1H, NH−C-3), 3.35 (m, 1H, H-3), 3.40 (m, 1H, NH−C-5), 3.56 (m, 1H, H-5), 3.62 (m, 1H, H-4), 3.68 (m, 1H, H-2), 5.33 (d, 1H, H-1, $^3J_1$-2 = 4 Hz), 7.0−7.6 (m, 8H, CH═). ^{13}C NMR, δ (C_6D_6): 26.7 (CH_3), 27.0 (CH_3), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 32.1 (CH_3, ^{t}Bu), 32.3 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 36.0 (C, ^{t}Bu), 36.1 (C, ^{t}Bu), 42.6 (d, CH_2, J_C-P = 24.2 Hz), 55.7 (d, CH_2, J_C-P = 15.9 Hz), 80.8 (C-2), 81.9 (C-4), 104.3 (C-1), 112.2 (CMe_2), 124.4 (CH═), 124.5 (CH═), 124.7 (CH═), 124.9 (CH═), 126.9 (CH═), 127.1 (CH═), 127.2 (CH═), 127.3 (CH═), 127.6 (CH═), 134.2 (C), 134.4 (C), 134.5 (C), 134.7 (C), 141.2 (C), 141.3 (C), 146.6 (C), 146.7 (C), 146.8 (C), 147.0 (C). Anal. Calcd (%) for $C_{64}H_{94}N_2O_7P_2$: C, 72.15; H, 8.89; N, 2.63. Found: C, 72.45; H, 8.59; N, 2.49.

3,5-Bis[(3,3′-bis-t-butyl-5,5′-bis-methoxy-1,1′-biphenyl-2,2′-diyl)phosphite]-3,5-diamine-3,5-dideoxy-1,2-*O*-isopropylidene-ribofuranose (2). Treatment of the corresponding phosphrochloridite (2.2 mmol) produced in situ and **8** (189 mg, 1 mmol), as described for compound **1**, afforded diphosphoroamidite **2**, which was purified by flash chromatography (toluene/NEt_3 = 100/2) to produce a white powder. Yield: 0.41 g, 43%. ^{31}P NMR, δ (C_6D_6): 148.5 (s, 1P), 151.4 (s, 1P). ^{1}H NMR, δ (C_6D_6): 1.10 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.54 (s, 9H, CH_3, ^{t}Bu), 1.55 (s, 9H, CH_3, ^{t}Bu), 1.58 (s, 9H, CH_3, ^{t}Bu), 3.15 (m, 1H, H-5′), 3.26 (s, 3H; OCH_3), 3.31 (s, 3H; OCH_3), 3.32 (b, 2H, NH), 3.34 (s, 3H; OCH_3), 3.39 (s, 3H; OCH_3), 3.40 (m, 1H, H-3), 3.50 (m, 1H, H-5), 3.63 (m, 1H, H-4), 3.86 (m, 1H, H-2), 5.39 (d, 1H, H-1, $^3J_1$-2 = 4 Hz), 6.6−7.2 (m, 8H, CH═). ^{13}C NMR, δ (C_6D_6): 26.7 (CH_3), 27.0 (CH_3), 31.7 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 32.0 (CH_3, ^{t}Bu), 35.9 (C, ^{t}Bu), 41.8 (d, C-5, J_C-P = 22 Hz), 55.1 (d, C-3, J_C-P = 15 Hz), 55.4, 55.5 (OCH_3), 80.2 (C-2), 82.1 (C-4), 104.4 (C-1), 112.3 (CMe_2), 113.3 (CH═), 113.4 (CH═), 113.8 (CH═), 114.8 (CH═), 114.9 (CH═),115.2 (CH═),128.8 (CH═),129.6 (CH═), 134.9 (C), 135.1 (C), 135.3 (C), 156.3 (C), 156.4 (C), 156.5 (C), 156.7 (C). Anal. Calcd (%) for $C_{52}H_{70}N_2O_{11}P_2$: C, 64.99; H, 7.34; N, 2.91. Found: C, 65.01; H, 7.41; N, 2.79.

3,5-Bis[(3,3′-bis-trimethylsilyl-1,1′-biphenyl-2,2′-diyl)phosphite]-3,5-diamine-3,5-dideoxy-1,2-*O*-isopropylidene-ribofuranose (3). Treatment of the corresponding phosphrochloridite (2.2 mmol) produced in situ and **8** (189 mg, 1 mmol), as described for compound **1**, afforded diphosphoroamidite **3**, which was purified by flash chromatography (toluene/NEt_3 = 100/2) to produce a white powder. Yield: 0.46 g, 51%. ^{31}P NMR, δ (C_6D_6): 148.0 (s, 1P), 154.3 (s, 1P). ^{1}H NMR, δ (C_6D_6): −0.32 (s, 9H, CH_3−Si), 0.38 (s, 9H, CH_3−Si), 0.4 (s, 18H, CH_3−Si), 1.13 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.92 (m, 1H, H-5′), 3.06 (m, 1H, H-3), 3.14 (m, 1H, NH−C-5), 3.29 (s, 1H, NH−C-3), 3.45 (m, 1H, H-5), 3.56 (m, 1H, H-4), 3.79 (m, 1H, H-2), 5.47 (d, 1H, H-1, $^3J_1$-2 = 4 Hz), 6.9−7.4 (m, 12H, CH═). ^{13}C NMR, δ (C_6D_6): 0.56 (CH_3−Si), 0.59 (CH_3−Si), 0.63 (CH_3−Si), 0.68 (CH_3−Si), 0.82 (CH_3−Si), 0.86 (CH_3−Si), 26.8 (CH_3), 27.1 (CH_3), 42.6 (d, C-5, J_C-P = 20 Hz), 54.4 (C-3), 80.7 (C-2), 82.1 (C-4), 104.3 (C-1), 112.1 (CMe_2), 124.8 (CH═), 125.2 (CH═), 125.4 (CH═), 126.0 (CH═), 132.2

(C), 132.3 (C), 132.4 (CH═), 132.5 (CH═), 132.6 (CH═), 132.5 (CH═), 135.7 (CH═), 138.1 (C), 156.4 (C), 155.5 (C), 156.0 (C). Anal. Calcd (%) for $C_{44}H_{62}N_2O_7P_2Si_4$: C, 58.38; H, 6.90; N, 3.09. Found: C, 58.31; H, 6.84 N, 3.01.

3,5-Bis[(3,3′,5,5′-tetramethyl-1,1′-biphenyl-2,2′-diyl)phosphite]-3,5-diamine-3,5-dideoxy-1,2-*O*-isopropylidene-ribofuranose (4). Treatment of the corresponding phosphrochloridite (2.2 mmol) produced in situ and **8** (189 mg, 1 mmol), as described for compound **1**, afforded diphosphoroamidite **4**, which was purified by flash chromatography (toluene/NEt_3 = 100/2) to produce a white powder. Yield: 0.23 g, 32%. ^{31}P NMR, δ (C_6D_6): 141.8 (s, 1P), 148.0 (s, 1P). ^{1}H NMR, δ (C_6D_6): 1.29 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.14 (m, 1H, H-5′), 3.28 (m, 2H, NH), 3.37 (m, 1H, H-3), 3.42 (m, 2H, H-5, H-4), 4.16 (m, 1H, H-2), 5.52 (d, 1H, H-1, $^3J_1$-2 = 4 Hz), 6.9−7.4 (m, 8H, CH═). ^{13}C NMR, δ (C_6D_6): 16.9 (CH_3), 17.1 (CH_3), 17.3 (CH_3), 17.5 (CH_3), 20.9 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 40.3 (d, C-5, J_C-P = 20 Hz), 54.0 (d, C-3, J_C-P = 12 Hz), 81.1 (C-2), 81.6 (C-4), 104.6 (C-1), 112.2 (CMe_2), 128.5 (CH═), 128.6 (CH═), 128.8 (CH═), 129.6 (CH═), 130.2 (C), 131.4 (CH═), 131.5 (CH═), 131.6 (CH═), 131.7 (CH═), 132.3 (C), 132.7 (C), 133.4 (C), 133.6 (C), 134.0 (C), 147.0 (C), 147.1 (C), 147.8 (C), 147.98 (C). Anal. Calcd (%) for $C_{40}H_{46}N_2O_7P_2$: C, 65.92; H, 6.36; N, 3.84. Found: C, 65.99; H, 6.42; N, 3.89.

3,5-Bis[((*R*)-3,3′-bis-trimethylsilyl-1,1′-binaphthyl-2,2′-diyl)-phosphite]-3,5-diamine-3,5-dideoxy-1,2-*O*-isopropylidene-ribofuranose (5). Treatment of the corresponding phosphrochloridite (2.2 mmol) produced in situ and **8** (189 mg, 1 mmol), as described for compound **1**, afforded diphosphoroamidite **5**, which was purified by flash chromatography (toluene/NEt_3 = 100/2) to produce a white powder. Yield: 0.33 g, 30%. ^{31}P NMR, δ (C_6D_6): 147.2 (s, 1P), 151.2 (s, 1P). ^{1}H NMR, δ (C_6D_6): 0.43 (s, 9H, CH_3−Si), 0.45 (s, 9H, CH_3−Si), 0.52 (s, 9H, CH_3−Si), 0.57 (s, 9H, CH_3−Si), 1.12 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.79 (m, 2H, H-5′, NH−C-3), 3.08 (m, 1H, H-3), 3.23 (m, 1H, NH−C-5), 3.38 (m, 1H, H-2), 4.41 (m, 1H, H-4), 5.03 (d, 1H, H-1, $^3J_1$-2 = 4 Hz), 6.8−8.2 (m, 20H, CH═). ^{13}C NMR, δ (C_6D_6): 0.6 (CH_3−Si), 0.7 (CH_3−Si), 1.0 (CH_3−Si), 1.1 (CH_3−Si), 1.1 (CH_3−Si), 26.5 (CH_3), 27.1 (CH_3), 42.7 (d, C-5, J_C-P = 16 Hz), 54.4 (C-3), 80.5 (C-2), 81.5 (C-4), 104.1 (C-1), 111.9 (CMe_2), 125.0 (CH═), 125.1 (CH═), 125.4 (CH═), 127.1 (CH═), 127.4 (CH═), 127.5 (CH═), 127.6 (CH═), 127.8 (CH═), 128.2 (CH═), 128.6 (CH═), 128.8 (CH═), 129.1 (CH═), 129.2 (CH═), 129.6 (CH═), 131.2 (CH═), 131.8 (CH═), 132.7 (C), 133.0 (C), 133.4 (C), 133.6 (C), 134.7 (C), 135.0 (C), 136.6 (CH═), 136.9 (CH═), 137.7 (CH═), 137.9 (CH═), 153.0 (C), 153.9 (C), 154.5 (C). Anal. Calcd (%) for $C_{60}H_{70}N_2O_7P_2Si_4$: C, 65.19; H, 6.38; N, 2.53. Found: C, 65.25; H, 6.29; N, 2.39.

3,5-Bis[((*S*)-3,3′-bis-trimethylsilyl-1,1′-binaphthyl-2,2′-diyl)-phosphite]-3,5-diamine-3,5-dideoxy-1,2-*O*-isopropylidene-ribofuranose (6). Treatment of the corresponding phosphrochloridite (2.2 mmol) produced in situ and **8** (189 mg, 1 mmol), as described for compound **1**, afforded diphosphoroamidite **6**, which was purified by flash chromatography (toluene/NEt_3 = 100/2) to produce a white powder. Yield: 0.24 g, 22%. ^{31}P NMR, δ (C_6D_6): 153.5 (s, 1P), 154.6 (s, 1P). ^{1}H NMR, δ (C_6D_6): 0.54 (s, 9H, CH_3−Si), 0.56 (s, 9H, CH_3−Si), 0.62 (s, 9H, CH_3−Si), 0.67 (s, 9H, CH_3−Si), 1.00 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 3.32 (m, 3H, H-3, H-5′, NH), 3.48 (m, 1H, NH), 3.60 (m, 1H, H-5), 3.67 (m, 1H, H-4), 4.32 (m, 1H, H-2), 5.05 (d, 1H, H-1, $^3J_1$-2 = 3.6 Hz), 6.8−8.2 (m, 20H, CH═). ^{13}C NMR, δ (C_6D_6): 0.7 (CH_3−Si), 0.8 (CH_3−Si), 0.9 (CH_3−Si), 1.1 (CH_3−Si), 1.2 (CH_3−Si), 26.7 (CH_3), 26.9 (CH_3), 43.0 (d, C-5, J_C-P = 28 Hz), 56.3 (d, C-3, J_C-P = 22 Hz), 80.5 (d, C-2, J_C-P = 5.2 Hz), 82.2 (d, C-4, J_C-P = 6.4 Hz), 104.4 (C-1), 112.3 (CMe_2), 125.1 (CH═), 125.3 (CH═), 126.0 (CH═), 127.1 (CH═), 127.2 (CH═), 127.4 (CH═), 127.5 (CH═), 127.7 (CH═), 128.2 (CH═), 128.6 (CH═), 128.8 (CH═), 129.0 (CH═), 131.4 (CH═), 131.8 (CH═), 132.4 (C), 132.7 (C), 132.9 (C), 133.1 (C), 137.0 (CH═), 137.2 (CH═), 137.7 (CH═), 137.9 (CH═), 151.8 (C), 151.9 (C), 154.3 (C), 154.4 (C). Anal. Calcd (%) for $C_{60}H_{70}N_2O_7P_2Si_4$: C, 65.19; H, 6.38; N, 2.53. Found: C, 65.07; H, 6.42; N, 2.58.

Preparation of [Pd((η^3-1,3-diphenylallyl)(2)]BF_4. Ligand **2** (48.1 mg, 0.05 mmol) and the complex of [Pd(μ-Cl)(η^3-1,3-diphenylallyl)]$_2$ (17.3 mg, 0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.5 mmol) was added after 30 min, and the mixture was stirred for 30 min. The mixture was then filtered over Celite under argon, and the resulting solution was analyzed by NMR.

Isomer 14B: ^{31}P NMR (CD_2Cl_2), δ: 145.0 (d, 1P, P next to C-3, J_P-P = 116 Hz), 148.1 (d, 1P, P next to C-5, J_P-P = 116 Hz). ^{1}H NMR (CD_2Cl_2), δ: 1.2−1.7 (m, 42H, CH_3, CH_3 *t*-Bu), 2.81 (m, 1H, NH), 3.52 (m, 2H, H-5, H-5′), 3.71 (m, 1H, H-4), 3.8−4.0 (m, 14H, H-3, N−H, OCH_3), 4.57 (m, 1H, H-2), 5.20 (m, 1H, CH terminal), 5.26 (m, 1H, CH terminal), 5.66 (d, 1H, H-1, $^3J_1$-2 = 3.2 Hz), 6.24 (m, 2H, CH═), 6.44 (m, 1H, CH central), 6.5−7.2 (m, 16 H, CH═). ^{13}C NMR (CD_2Cl_2), δ: 26.3 (CH_3), 26.6 (CH_3), 31−33 (m, CH_3, *t*-Bu), 35−36 (m, C, *t*-Bu), 38.7 (m, C-5), 53.4 (m, C-3), 56.0 (OCH_3), 56.2 (OCH_3), 56.4 (OCH_3), 78.4 (m, C-2), 79.9 (m, C-4), 92.8 (m, CH terminal), 100.0 (m, CH terminal), 104.9 (C-1), 113.3 (m, CH central), 114.3 (CMe_2), 114.5−157.0 (aromatic carbons).

Isomer 14A: ^{31}P NMR (CD_2Cl_2), δ: 144.7 (d, 1P, P next to C-3, J_P-P = 115 Hz), 148.0 (d, 1P, P next to C-5, J_P-P = 115 Hz). ^{1}H NMR (CD_2Cl_2), δ: 1.2−1.7 (m, 42H, CH_3, CH_3 *t*-Bu), 2.81 (m, 1H, NH), 3.52 (m, 2H, H-5, H-5′), 3.71 (m, 1H, H-4), 3.8−4.0 (m, 14H, H-3, N−H, OCH_3), 4.66 (m, 1H, H-2), 5.18 (m, 1H, CH terminal), 5.24 (m, 1H, CH terminal), 5.72 (d, 1H, H-1, $^3J_1$-2 = 3.6 Hz), 6.24 (m, 2H, CH═), 6.44 (m, 1H, CH central), 6.5−7.2 (m, 16 H, CH═). ^{13}C NMR (CD_2Cl_2), δ: 26.3 (CH_3), 26.6 (CH_3), 31−33 (m, CH_3, *t*-Bu), 35−36 (m, C, *t*-Bu), 38.7 (m, C-5), 53.4 (m, C-3), 56.0 (OCH_3), 56.2 (OCH_3), 56.4 (OCH_3), 78.4 (m, C-2), 79.9 (m, C-4), 92.8 (m, CH terminal), 99.3 (m, CH terminal), 104.9 (C-1), 113.3 (m, CH central), 114.3 (CMe_2), 114.5−157.0 (aromatic carbons).

Preparation of [Pd((η^3-1,3-diphenylallyl)(3)]BF_4. Ligand **3** (45.2 mg, 0.05 mmol) and the complex of [Pd(μ-Cl)(η^3-1,3-diphenylallyl)]$_2$ (17.3 mg, 0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.5 mmol) was added after 30 min, and the mixture was stirred for 30 min. The mixture was then filtered over Celite under argon, and the resulting solution was analyzed by NMR.

Isomer 15B: ^{31}P NMR (CD_2Cl_2), δ: 145.2 (d, 1P, P next to C-3, J_P-P = 97 Hz), 148.5 (d, 1P, P next to C-5, J_P-P = 97 Hz). ^{1}H NMR (CD_2Cl_2), δ: 0.3−0.7 (m, 36H, CH_3−Si), 1.2−1.3 (m, 6H, CH_3), 2.9 (m, 1H, NH), 3.4−3.9 (m, 5H, H-3, H-4, H-5, H-5′, NH), 4.63 (m, 1H, H-2), 5.48 (m, 1H, CH terminal), 5.52 (m, 1H, CH terminal), 5.66 (d, 1H, H-1, $^3J_1$-2 = 3.6 Hz), 6.52 (m, 1H, CH central), 6.7−7.7 (m, 22 H, CH═). ^{13}C NMR (CD_2Cl_2), δ: 0−2.2 (CH_3−Si), 26.3 (CH_3), 39.1 (m, C-5), 53.1 (m, C-3), 78.6 (m, C-2), 79.5 (b, C-4), 95.4 (m, CH terminal), 97.1 (m, CH terminal), 104.3 (C-1), 112.2 (m, CH central), 114.1 (CMe_2), 125−155 (aromatic carbons).

Isomer 15A: ^{31}P NMR (CD_2Cl_2), δ: 145.8 (d, 1P, P next to C-3, J_P-P = 97 Hz), 149.7 (d, 1P, P next to C-5, J_P-P = 97 Hz). ^{1}H NMR (CD_2Cl_2), δ: 0.3−0.7 (m, 36H, CH_3−Si), 1.2−1.3 (m, 6H, CH_3), 2.9 (m, 1H, NH), 3.4−3.9 (m, 5H, H-3, H-4, H-5, H-5′, NH), 4.70 (m, 1H, H-2), 5.40 (m, 1H, CH terminal), 5.44 (m, 1H, CH terminal), 5.71 (d, 1H, H-1, $^3J_1$-2 = 4.0 Hz), 6.52 (m, 1H, CH central), 6.7−7.7 (m, 22 H, CH═). ^{13}C NMR (CD_2Cl_2), δ: 0−2.2 (CH_3−Si), 26.3 (CH_3), 39.1 (m, C-5), 53.1 (m, C-3), 78.6 (m, C-2), 79.5 (b, C-4), 95.9 (m, CH terminal), 96.9 (m, CH terminal), 104.3 (C-1), 112.2 (m, CH central), 114.1 (CMe_2), 125−155 (aromatic carbons).

Preparation of [Pd(*cyclo*-C_6H_9)(1)]BF_4. Ligand **1** (53.2 mg, 0.05 mmol) and the complex of [Pd(μ-Cl)(*cyclo*-C_6H_9)]$_2$ (11.0 mg, 0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temper-

ature under argon. $AgBF_4$ (9.8 mg, 0.5 mmol) was added after 30 min, and the mixture was stirred for 30 min. The mixture was then filtered over Celite under argon, and the resulting solution was analyzed by NMR.

Isomer 16A: ^{31}P NMR (CD_2Cl_2), δ: 144.5 (d, 1P, P next to C-3, J_P-P = 75.8 Hz), 145.7 (d, 1P, P next to C-5, J_P-P = 75.8 Hz). ^1H NMR (CD_2Cl_2), δ: 1.2−1.6 (m, 82H, CH_3, CH_3 *t*-Bu, CH_2), 1.83 (m, 2H, CH_2), 3.49 (m, 1H, H-5′), 3.70 (m, 2H, NH), 3.78 (m, 2H, H-4, H-5), 4.07 (m, 1H, H-3), 4.38 (m, 1H, CH terminal), 4.72 (m, 1H, H-2), 5.02 (m, 1H, CH central), 5.83 (d, 1H, H-1, $^3J_1$-2 = 4.0 Hz), 5.93 (m, 1H, CH terminal), 7.1−7.6 (m, 8 H, CH═). ^{13}C NMR (CD_2Cl_2), δ: 18.7 (CH_2), 26.0 (CH_2), 26.4 (CH_3), 26.7 (CH_3), 28.0 (CH_2), 31.6−32.6 (CH_3, *t*-Bu), 35.2 (C, *t*-Bu), 35.9 (C, *t*-Bu), 38.2 (m, C-5), 53.8 (m, C-3), 78.6 (C-2), 79.9 (C-4), 91.2 (m, CH terminal), 97.9 (m, CH terminal), 104.9 (C-1), 113.6 (m, CH central), 114.2 (CMe_2), 125−150 (aromatic carbons).

Isomer 16B: ^{31}P NMR (CD_2Cl_2), δ: 140.9 (bd, 1P, P next to C-3, J_P-P = 75.8 Hz), 148.6 (d, 1P, P next to C-5, J_P-P = 75.8 Hz). ^1H NMR (CD_2Cl_2), δ: 1.2−1.6 (m, 82H, CH_3, CH_3 *t*-Bu, CH_2), 3.49 (m, 2H, H-5, H-5′), 3.78 (m, 2H, H-4, H-3), 4.21 (m, 1H, N−H), 4.37 (m, 1H, N−H), 4.54 (m, 1H, CH terminal), 4.62 (m, 1H, H-2), 5.02 (m, 1H, CH central), 5.81 (d, 1H, H-1, $^3J_1$-2 = 4.0 Hz), 5.83 (m, 1H, CH terminal), 7.1−7.6 (m, 8 H, CH═). ^{13}C NMR (CD_2Cl_2), δ: 18.8 (CH_2), 26.4 (CH_3), 26.7 (CH_3), 28.2 (CH_2), 28.3 (CH_2), 31.6−32.6 (CH_3, *t*-Bu), 35.2 (C, *t*-Bu), 35.9 (C, *t*-Bu), 38.2 (m, C-5), 53.8 (m, C-3), 78.7 (C-2), 80.2 (C-4), 90.8 (m, CH terminal), 101.9 (m, CH terminal), 104.9 (C-1), 113.6 (m, CH central), 114.2 (CMe_2), 125−150 (aromatic carbons).

Preparation of [Pd(*cyclo*-C_6H_9)(4)]BF_4. Ligand **4** (36.5 mg, 0.05 mmol) and the complex of [Pd(μ-Cl)(*cyclo*-C_6H_9)]$_2$ (11.0 mg, 0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under argon. $AgBF_4$ (9.8 mg, 0.5 mmol) was added after 30 min, and the mixture was stirred for 30 min. The mixture was then filtered over Celite under argon, and the resulting solution was analyzed by NMR.

Isomer 17A: ^{31}P NMR (CD_2Cl_2), δ: 148.0 (d, 1P, P next to C-3, J_P-P = 78 Hz), 149.2 (d, 1P, P next to C-5, J_P-P = 78 Hz). ^1H NMR (CD_2Cl_2), δ: 0.9−1.2 (m, 2H, CH_2), 1.59 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.6−2.2 (m, 4H, CH_2), 2.40 (s, 3H, CH_3−Ar), 2.60 (m, 18H, CH_3−Ar), 2.78 (s, 3H, CH_3−Ar), 3.61 (m, 2H, H-5, H-5′), 3.83 (m, 1H, H-4), 4.18 (m, 2H, H-3, N−H), 4.36 (m, 1H, NH), 4.75 (m, 1H, H-2), 5.14 (m, 1H, CH terminal), 5.24 (m, 1H, CH central), 5.83 (d, 1H, H-1, $^3J_1$-2 = 3.6 Hz), 6.02 (m, 1H, CH terminal), 7.2−7.5 (m, 8 H, CH═). ^{13}C NMR (CD_2Cl_2), δ: 16.9−17.3 (CH_3−Ar), 18.6 (CH_2), 21.1 (CH_3−Ar), 26.6 (CH_3), 28.2 (CH_2), 28.8 (CH_2), 39.2 (d, C-5, J_C-P = 19.2 Hz), 52.6 (d, C-3, J_C-P = 19.7 Hz), 79.5 (m, C-2), 80.2 (b, C-4), 93.2 (dd, CH terminal, J_C-P = 31.4 Hz, J_C-P = 5.2 Hz), 96.7 (dd, CH terminal, J_C-P = 33.9 Hz, J_C-P = 5.4 Hz), 104.7 (C-1), 113.7 (m, CH central), 114.1 (CMe_2), 128.9−138.0 (aromatic carbons).

Isomer 17B: ^{31}P NMR (CD_2Cl_2), δ: 146.3 (d, 1P, P next to C-3, J_P-P = 79 Hz), 151.3 (d, 1P, P next to C-5, J_P-P = 79 Hz). ^1H NMR (CD_2Cl_2), δ: 0.9−1.2 (m, 2H, CH_2), 1,45 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.6−2.2 (m, 4H, CH_2), 2.42 (s, 3H, CH_3−Ar), 2.60 (m, 18H, CH_3−Ar), 2.76 (s, 3H, CH_3−Ar), 3.61 (m, 1H, H-5′), 3.76 (m, 1H, H-3), 3.83 (m, 1H, H-4), 3.97 (m, 1H, H-5), 4.18 (m, 2H, N−H), 4.75 (m, 1H, H-2), 5.24 (m, 1H, CH central), 5.33 (m, 1H, CH terminal), 5.83 (d, 1H, H-1, $^3J_1$-2 = 3.6 Hz), 5.88 (m, 1H, CH terminal), 7.2−7.5 (m, 8 H, CH═). ^{13}C NMR (CD_2Cl_2), δ: 16.9−17.3 (CH_3−Ar), 18.7 (CH_2), 21.2 (CH_3−Ar), 26.6 (CH_3), 28.2 (CH_2), 28.8 (CH_2), 37.1 (d, C-5, J_C-P = 16 Hz), 53.5 (m, C-3), 79.5 (m, C-2), 80.2 (b, C-4), 91.8 (dd, CH terminal, J_C-P = 31.6 Hz, J_C-P = 8 Hz), 97.3 (m, CH terminal), 104.8 (C-1), 113.7 (m, CH central), 114.1 (CMe_2), 128.9−138.0 (aromatic carbons).

Allylic Alkylation of *rac*-1,3-Diphenyl-3-acetoxyprop-1-ene (S1). A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (0.9 mg, 0.0025 mmol) and the diphosphoroamidite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-**S1** (126 mg, 0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol), and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 5 min the reaction mixture was diluted with Et_2O (5 mL), and saturated NH_4Cl(aq) (25 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL), and the extract was dried over $MgSO_4$. The solvent was removed, and the conversion was measured by ^1H NMR. To determine the ee by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

Allylic Alkylation of *rac*-3-Acetoxycyclohexene (S2) and *rac*-3-Acetoxycycloheptene (S3). A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (0.9 mg, 0.0025 mmol) and the diphosphoroamidite ligand (0.0055 mmol) in THF (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in THF (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol), and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 30 min the reaction mixture was diluted with Et_2O (5 mL), and saturated NH_4Cl(aq) (25 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL), and the extract was dried over $MgSO_4$. Conversion and enantiomeric excess were determined by GC using an FS-β-Cyclodex 25 m column (i.d. 0.2 mm, film thickness 0.33 mm, carrier gas, 100 kPa He, FID detector).

Allylic Alkylation of 1-(1-Naphthyl)allyl Acetate (S4). A degassed solution of [PdCl(η^3-C_3H_5)]$_2$ (1.8 mg, 0.005 mmol) and the diphosphoroamidite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-**S4** (113 mg, 0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol), and a pinch of KOAc were added. The reaction mixture was stirred at room temperature. After 2 h the reaction mixture was diluted with Et_2O (5 mL), and saturated NH_4Cl(aq) (25 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL), and the extract was dried over $MgSO_4$. The solvent was removed, and the conversion and regioselectivity were measured by ^1H NMR. To determine the ee by HPLC (Chiralcel-OJ, 3% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

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