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Palladium-Diphosphite Catalysts for the Asymmetric Allylic Substitution Reactions

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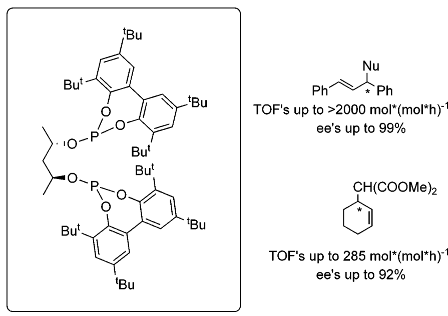

We have designed a series of diphosphite ligands to study the effect of the backbone, the size of the chelate ring, and the substituents of the biphenyl moieties and to determine the scope of this type of ligand in the Pd-catalyzed asymmetric substitution reactions of different types of substrates. Good-to-excellent activities and enantioselectivities have been obtained for disubstituted linear substrate **11** (TOF's up to >2000 mol × (mol × h)$^{-1}$, ee values up to 99%) and cyclic substrate **14** (TOF up to 285 mol × (mol × h)$^{-1}$, ee values up to 92%). However, these ligands are inadequate for the Pd-catalyzed allylic alkylation of monosubstituted linear substrates because they provide low enantioselectivities.

Introduction

One of the main aims of modern synthetic organic chemistry is the catalytic enantioselective formation of C−C and C−heteroatom bonds. In this context, palladium-catalyzed asymmetric allylic substitution is a powerful and highly versatile procedure.[1] A large number of chiral ligands, mainly P- and N-containing ligands, which possess either C_2- or C_1-symmetry, have provided high enantiomeric excesses. Among the P-ligands, diphosphines have played a dominant role in the success of allylic substitution.[1d] Recently, a group of less electron-rich phosphorus compounds—diphosphite ligands—have also demonstrated their potential utility in this process, providing excellent enantioselectivities and activities.[2] However, only one series of diphosphite ligands possessing a furanoside backbone has been used.[2] More research into the scope of the diphosphite ligands in this process is therefore needed.

Phosphite ligands are extremely attractive for catalysis because they are easy to prepare from readily available alcohols. The variety of alcohols available make simple ligand tuning possible, enabling the synthesis of many series of chiral ligands that can be screened in the search for high activity and selectivity.[3] Taking advantage of this high modularity, in this paper we describe the use of a series of diphosphite ligands (Figure 1) for studying the effect of the backbone, the size of the chelate ring, and the substituents of the biphenyl moieties in the Pd-catalyzed asymmetric substitution reactions of several model substrates.

(1) For recent reviews, see: (a) Tsuji, J. Palladium Reagents and Catalysis. In *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, Germany, 1999; Vol. 2, Chapter 24. (e) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(2) (a) Diéguez, M.; Jansat, S.; Gomez, M.; Ruiz, A.; Muller, G.; Claver, C. *Chem. Commun.* **2001**, 1132. (b) Pàmies, O.; van Strijdonck, G. P. F.; Diéguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001**, *66*, 8867.

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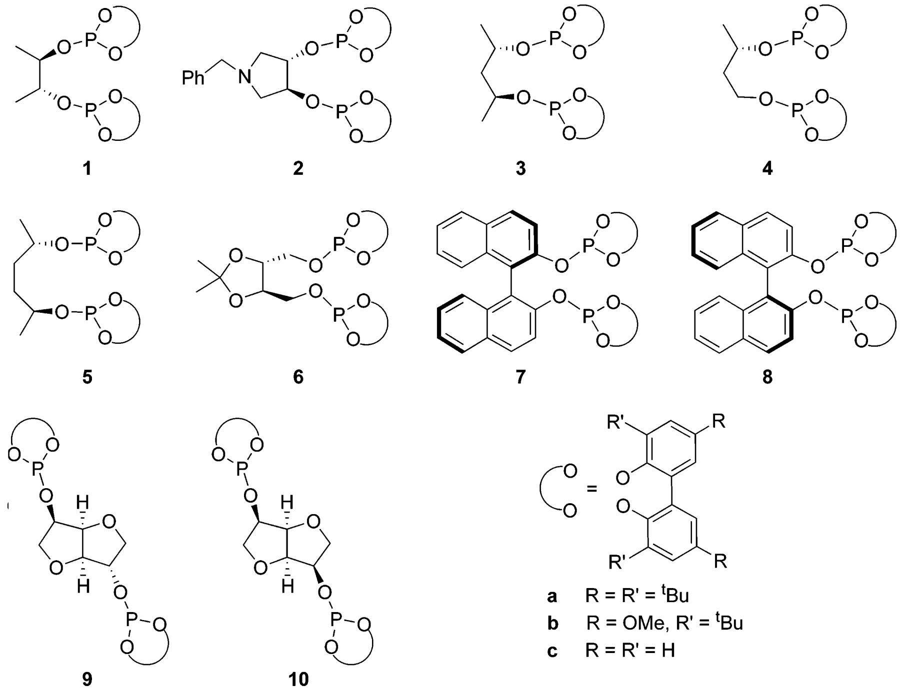


FIGURE 1. Diphosphite ligands **1**−**10a**−**c**.

SCHEME 1. Synthesis of the New Diphosphite Ligands 2, 4, 6−8, 10a

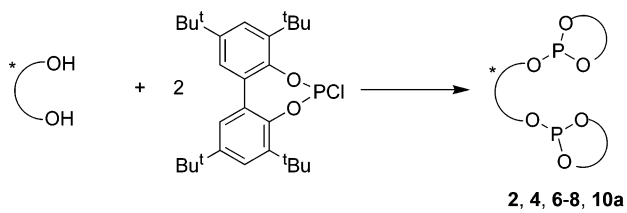


TABLE 1. Pd-Catalyzed Allylic Alkylation of 11, Using Ligand 1a[a]

entry	solvent	ratio **1a**/Pd	% conv[b] (min)	% ee[c]
1	CH_2Cl_2	1.1	100 (30)	80 (*R*)
2	DMF	1.1	100 (30)	75 (*R*)
3	toluene	1.1	29 (30)	76 (*R*)
4	THF	1.1	45 (30)	72 (*R*)
5	CH_2Cl_2	0.9	100 (30)	80 (*R*)
6	CH_2Cl_2	2	100 (30)	80 (*R*)

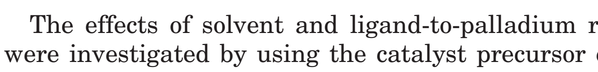
[a] 0.5 mol % of $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N,O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Measured by ^1H NMR. Reaction time in minutes shown in parentheses. [c] Determined by HPLC (Chiralcel OD).

Results and Discussions

Ligand Synthesis. The new diphosphite ligands **2**, **4**, **6**−**8**, and **10a** were synthesized very efficiently in one step from the corresponding diols (Scheme 1). The reaction of the corresponding diol with 2 equiv of the desired in situ-formed phosphorochloridite[4] in the presence of base afforded the desired ligands.

All the new ligands were stable during purification on neutral silica gel under an atmosphere of argon and isolated in moderate-to-good yields (45−78%) as white solids.

Asymmetric Allylic Substitution Reactions. We first investigated the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**11**), which is widely used as a model substrate, with dimethyl malonate using the chiral diphosphite ligands **1**−**10** (eq 1). The catalysts were generated in situ from 0.5 mol % of π-allylpalladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, the corresponding ligand, and a catalytic amount of KOAc.



(1)

The effects of solvent and ligand-to-palladium ratio were investigated by using the catalyst precursor containing ligand **1a** (Table 1). Our results indicate that (i) dichloromethane as solvent provides the best combination of activity and enantioselectivity (entries 1−4) and (ii) no excess of ligand is necessary for good enantioselec-

(3) For recent successful application in catalysis, see: (a) Buisman, G. J. H.; van deer Veen, L. A.; Klootwijk, A.; de Lange, W. G. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Organometallics* **1997**, *16*, 2929. (b) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413. (c) Franciò, G.; Leitner, W. *Chem. Commun.* **1999**, 1663. (d) Diéguez, M.; Pàmies, O.; Ruiz, A.; Castillón, S.; Claver, C. *Chem. Commun.* **2000**, 1607. (e) Diéguez, M.; Pàmies, O.; Ruiz, A.; Castillón, S.; Claver, C. *Chem. Eur. J.* **2001**, *7*, 3086. (f) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (g) Selvakumar, K.; Valentini, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 4591. (h) Dreisbach, C.; Meseguer, B.; Prinz, T.; Scholz, U.; Militzer, H. C.; Agel, F.; Driessen-Hoelscher, B. European Patent Appl. 1298136 A2, 2003. (i) Reetz, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179. (j) Reetz, M. T.; Goosen, L. J.; Meiswinkel, A.; Paetzol, J.; Jensen, J. F. *Org. Lett.* **2003**, *5*, 3099. (k) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *Org. Lett.* **2003**, *5*, 4137. (l) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Levêque, J. M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011. (m) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869. (n) Yan, M.; Yang, L. W.; Wong, K. Y.; Chan, A. S. C. *Chem. Commun.* **1999**, 11. (o) Yan, M.; Zhou, Z. Y.; Chan, A. S. C. *Chem. Commun.* **2000**, 115.

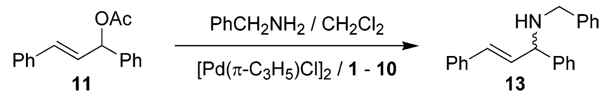
(4) Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1625.

TABLE 2. Pd-Catalyzed Allylic Alkylation of 11 with Ligands 1−10[a]

entry	ligand	% conv (min)[b]	% ee[c]
1	**1a**	100 (30)	80 (*R*)
2	**2a**	82 (30)	18 (*S*)
3	**3a**	100 (5)	94 (*R*)
4	**4a**	93 (5)	73 (*R*)
5	**5a**	100 (30)	10 (*S*)
6	**6a**	100 (30)	3 (*S*)
7	**7a**	84 (30)	9 (*S*)
8	**8a**	30 (30)	41 (*R*)
9	**9a**	60 (30)	49 (*S*)
10	**10a**	87 (30)	30 (*S*)
11	**3b**	100 (5)	89 (*R*)
12	**3c**	43 (30)	12 (*R*)
13[d]	**3a**	100 (30)	99 (*R*)
14[e]	**3a**	100 (30)	93 (*R*)

[a] 0.5 mol % of $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol % of ligand, room temperature. [b] Conversion percentage of acetate **12** determined by ^1H NMR. Reaction time in minutes shown in parentheses. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OD column. Absolute configuration drawn in parentheses. [d] Reaction carried out at 0 °C. [e] Substrate/Pd ratio of 1000.

TABLE 3. Pd-Catalyzed Allylic Amination of 11 with Ligands 1−10[a]



entry	ligand	% conv (h)[b]	% ee[c]
1	**1a**	100 (20)	82 (*S*)
2	**2a**	100 (20)	25 (*R*)
3	**3a**	100 (15)	96 (*S*)
4	**4a**	100 (15)	80 (*S*)
5	**5a**	100 (20)	6 (*R*)
6	**6a**	100 (20)	4 (*R*)
7	**7a**	16 (20)	13 (*R*)
8	**8a**	19 (20)	80 (*S*)
9	**9a**	32 (20)	36 (*S*)
10	**10a**	42 (20)	12 (*S*)
11	**3b**	100 (15)	93 (*S*)
12	**3c**	46 (20)	21 (*S*)

[a] 0.5 mol % of $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol % of ligand, room temperature. [b] Conversion percentage of **13** determined by ^1H NMR. Reaction time in hours shown in parentheses. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

tivities (entries 1, 5, and 6). Good activity (TOF > 200 mol × (mol × h)$^{-1}$) and enantioselectivity (80% (*R*) ee) were therefore both obtained in the alkylation of **11** by using ligand **1a** when dichloromethane was used as solvent.

For comparative purposes, the rest of the ligands were tested under the conditions that provided the optimum tradeoff between enantioselectivities and reaction rates, i.e., a ligand-to-palladium ratio of 1.1 and dichloromethane as solvent. The results, shown in Table 2, indicate that catalytic performance (activities and enantioselectivities) is highly affected by the size of the chelate ring, the backbone, and the substituents of the biphenyl moieties.

Ligand **2a**, which differs from ligand **1a** in the introduction of a more rigid pyrrolidine backbone, showed not only lower activity but also much lower asymmetric induction (entry 2).

Ligand **3a**, which has a longer backbone than ligand **1a**, provided higher activity (TOF > 1200 mol × (mol × h)$^{-1}$) and enantioselectivity (94% (*R*)). Ligand **4a** indicated that the presence of the two stereocenters in the backbone is necessary for high enantioselectivity (entry 3 vs 4).

Ligands **5**−**10a**, which form a nine-membered chelate ring with the metal center, were less active and enantioselective than ligands **3a** and **4a**, which form an eight-membered chelate ring (entries 5−10 vs 3 and 4). Ligand **5a**, which resembles ligand **3a** but has a longer backbone, therefore showed very low enantioselectivity (entry 5). Moreover, the results with ligands **5**−**10** showed that there is a backbone effect in the enantioselectivity. In general, ligands containing a more rigid backbone produced better ee values (entries 8−10 vs 5 and 6). This behavior contrasts with that of ligands **1** and **2**, which form a seven-membered chelate ring. A plausible explanation for this is that the larger the chelate ring, the more rigid the backbone needed to control its fluxionability.

The effect of the different substituents in the ortho and para positions at the biphenyl phosphite moieties was studied with ligand backbone **3** (entries 3, 11, and 12). Our results indicate that both activities and enantioselectivities are higher when bulky *tert*-butyl substituents at both ortho and para positions of the biphenyl phosphite moieties are present (entries 3 and 11 vs 12).[5]

Enantioselectivity can be further improved (ee values up to 99%) with ligand **3a** by lowering the reaction temperature to 0 °C (entry 13). We also performed the reaction at a low catalyst concentration (**11**/Pd = 1000) using ligand **3a** (entry 14). Excellent enantioselectivity (93% (*S*) ee) and excellent activity (TOF> 2000 mol × (mol × h)$^{-1}$) were obtained.

We then tested ligands **1**−**10** in the Pd-catalyzed allylic amination of **11** with benzylamine. The results, which are summarized in Table 3, indicate that the catalytic performance (activities and enantioselectivities) follows the same trend as for the allylic alkylation of **11**, which is not unexpected because the reactions have a similar mechanism.[1c] However, the enantiomeric excesses were higher (ee values up to 96% at room temperature). Although, as expected, the activities were lower than in the alkylation reaction, they were much higher than those obtained with other homodonor ligands.[1c] The catalyst precursor containing the diphosphite ligand **3a** therefore provided excellent activities and enantioselectivities (entry 3). The absolute stereochemistry of the amination was the same as that for the alkylation reaction, though the CIP descriptor was inverted because of the change in the priority of the groups.

Enantioselectivity in cyclic substrates is usually more difficult to control, mainly because of the presence of less sterically demanding syn substituents, which are thought to play a crucial role in the enantioselection observed with acyclic substrates in the corresponding Pd-allyl intermediate.[1d] Although high enantioselective catalysts have been developed for cyclic substrates, these systems generally provide low enantiocontrol in linear substrates.[1,6] The development of enantioselective catalysts for both cyclic and linear substrates is still therefore a

(5) These results contrast with those previously published using furanoside diphosphite ligands, ref 2.

TABLE 4. Pd-Catalyzed Allylic Alkylation of 14, Using Ligand 1a[a]

entry	solvent	ratio **1a**/Pd	% conv[b](h)	% ee[c]
1	CH_2Cl_2	1.1	100 (0.5)	39 (*R*)
2	DMF	1.1	100 (0.4)	33 (*R*)
3	Toluene	1.1	34 (1)	37 (*R*)
4	THF	1.1	53 (0.5)	38 (*R*)
5	CH_2Cl_2	0.9	100 (0.5)	39 (*R*)
6	CH_2Cl_2	2	100 (0.5)	39 (*R*)

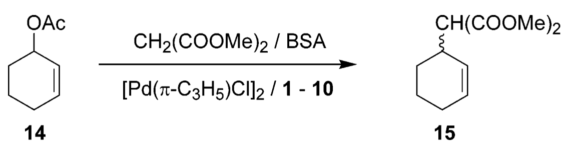
[a] 0.5 mol % of [Pd(π-C_3H_5)Cl]$_2$, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), a pinch of KOAc, room temperature. [b] Conversion percentage of acetate **15** determined by GC. Reaction time in hours shown in parentheses. [c] Enantiomeric excesses determined by GC (FS-β-Cyclodex). Absolute configuration drawn in parentheses.

TABLE 5. Pd-Catalyzed Allylic Alkylation of 14 with Ligands 1−10[a]

entry	ligand	% conv (h)[b]	% ee[c]
1	**1a**	100 (0.5)	39 (*R*)
2	**2a**	100 (0.5)	33 (*S*)
3	**3a**	100 (0.35)	74 (*S*)
4	**4a**	100 (0.35)	45 (*S*)
5	**5a**	100 (0.5)	4 (*R*)
6	**6a**	100 (0.5)	3 (*R*)
7	**7a**	19 (0.5)	19 (*S*)
8	**8a**	16 (0.5)	34 (*R*)
9	**9a**	65 (0.5)	32 (*S*)
10	**10a**	46 (0.5)	18 (*S*)
11	**3b**	100 (0.35)	59 (*S*)
12	**3c**	23 (0.5)	4 (*S*)
12[d]	**3a**	8 (20)	92 (*S*)

[a] 0.5 mol % of [Pd(π-C_3H_5)Cl]$_2$, 1.1 mol % of ligand, room temperature. [b] Conversion percentage of acetate **15** determined by GC. Reaction time in hours shown in parentheses. [c] Enantiomeric excesses determined by GC (FS-β-Cyclodex). Absolute configuration drawn in parentheses. [d] Reaction carried out at −20 °C.

challenge, so we decided to test the chiral ligands **1**−**10** in the Pd-catalyzed allylic alkylation of 3-acetoxycyclohexene **14** (eq 2), which is usually used as a model cyclic substrate.



(2)

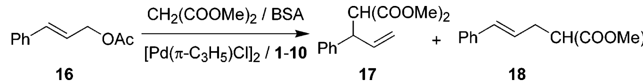
The preliminary investigations were performed on the solvent effect, and the ligand-to-palladium ratio with ligand **1a** provided the same trends as those observed in the previously tested disubstituted linear substrate **11** (Table 4). The optimum tradeoff between enantioselectivities and reaction rates was therefore obtained when dichloromethane was used as solvent and the ligand-to-palladium ratio was 1.1.

The results of using ligands **1**−**10** under the optimized conditions are shown in Table 5. In general, these results followed the same trend as for the allylic alkylation of **11**. However, enantiomeric excesses and activities were lower. Again, the catalyst's precursor containing the diphosphite ligand **3a**, which forms an eight-membered chelate ring and has *tert*-butyl substituents at both ortho and para positions of the biphenyl phosphite moieties, provided the best activities (TOF up to 285 mol × (mol × h)$^{-1}$, entry 3) and enantioselectivities (ee values up to 92%, entry 12).

To sum up, our results (Tables 2, 3, and 5) show that diphosphite ligand **3a** offers excellent enantioselectivities for the Pd-catalyzed asymmetric allylic substitution of both cyclic and acyclic substrates. It is therefore an exceptional ligand as it competes favorably with the few ligands that provide high ee values for both types of substrates.[6]

Encouraged by the excellent results obtained so far for both disubstituted linear and cyclic substrates, we next applied ligands **1**−**10** in the Pd-catalyzed allylic alkylation with dimethyl malonate of a more demanding substrate: the cinnamyl acetate **16**. For this substrate, the development of highly regio- and enantioselective Pd-catalysts still represents a challenge. Most Pd catalysts developed to date favor the formation of the achiral linear product **18** rather than the desired branched isomer **17**.[7] The results are summarized in Table 6. Unfortunately, the regioselectivity in the desired product **17** and enantioselectivity were low. The low enantioselectivity can be attributed to the fact that these ligands lead to a fast nucleophilic attack so that there is no time for the formation of the terminal σ-complex and rotation of the terminal C−C bond that is known to be necessary to obtain high ee values for this kind of substrate.[1b]

TABLE 6. Selected Results for the Pd-Catalyzed Allylic Alkylation of 16[a]



entry	ligand	% conv[b]	**17/18**[c]	% ee[d]
1	**1a**	75	16/84	<5
2	**3a**	100	12/88	7 (*R*)
3	**5a**	93	24/76	<5
4	**8a**	42	13/87	< 5

[a] All reactions were run at room temperature. Ratio **16**/Pd = 50. [b] Conversion percentage by ^{1}H NMR determined after 30 min. [c] Branched-to-linear ratio determined by GC. [d] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

Conclusion

We have designed a series of diphosphite ligands for studying the effect of the backbone, the size of the chelate ring, and the substituents of the biphenyl moieties and determining the scope of this type of ligands in the Pd-catalyzed asymmetric substitution reactions of different types of substrates. Good-to-excellent activities and enantioselectivities have been obtained for disubstituted linear substrate **11** (TOF's up to >2000 mol × (mol × h)$^{-1}$, ee values up to 99%) and cyclic substrate **14** (TOF

(6) So far only the ligands developed in the groups of Osborn and Evans have provided good ee values for both linear and cyclic substrates. (a) 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. (b) Evans, D. A.; Campos, J. R.; Tedrow, J. R.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.

(7) 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.

up to 285 mol × (mol × h)$^{-1}$, ee values up to 92%). However, these ligands are inadequate in terms of enantioselectivity in the Pd-catalyzed allylic alkylation of monosubstituted linear substrate **16**.

Results obtained in the Pd-catalyzed allylic substitution reaction of **11** and **14** indicated that enantiomeric excess is highly affected by the size of the chelate ring and the substituents of the biphenyl phosphite moieties. With regard to the size of the chelate ring, enantioselectivities were higher for ligands **3** and **4**, which forms an eight-membered chelate ring, than for ligands that form a seven-membered chelate ring (ligands **1** and **2**) or nine-membered chelate ring (ligands **5**−**10**). With regard to the substituents of the biphenyl phosphite moieties, the highest activities and enantioselectivities were obtained with ligands containing bulky *tert*-butyl substituents at both ortho and para positions of the biphenyl moieties (**a**).

Experimental Section

General Considerations. All reactions were carried out with standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Diphosphite ligands **1a**,[8] **3a**−**c**,[8] **5a**,[8] and **9a**[3i] and phosphorochloridite[4] were prepared as previously described. Racemic 1,3-diphenyl-3-acetoxyprop-1-ene (**11**)[9] and 3-acetoxycyclohexene (**14**)[10] were prepared as previously reported. ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded on 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. All assignments in NMR spectra were determined by ^{1}H−^{1}H (COSY) and ^{13}C−^{1}H (HSQC) spectra.

1-Benzyl-3,4-bis[(3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]pyrrolidine (2a). Phosphorochloridite (2.2 mmol) produced in situ was dissolved in toluene (5 mL), and pyridine (0.36 mL, 4.6 mmol) was added. 1-Benzyl-3,4-pyrrolidinediol (193.2 mg, 1 mmol) was azeotropically dried with toluene (3 × 1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.18 mL, 2.3 mmol) was added. The diol solution was transferred slowly over 30 min at room temperature to the solution of phosphorochloridite. 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 (toluene/hexane = 1/1) to produce a white powder. Yield: 0.48 g, 45%. $[\alpha]^{20}_{D}$ −54 (0.25, $CHCl_3$). ^{31}P NMR: δ 143.3 (s). ^{1}H NMR: δ 1.37 (s, 18H, CH_3, ^{t}Bu), 1.39 (s, 18H, CH_3, ^{t}Bu), 1.44 (s, 18H, CH_3, ^{t}Bu), 1.48 (s, 18H, CH_3, ^{t}Bu), 2.43 (dd, 2H, CH_2, $^{3}J_{H-H}$ = 3.6 Hz, $^{2}J_{H-H}$ = 11.2 Hz), 2.72 (dd, 2H, CH_2, $^{3}J_{H-H}$ = 6.0 Hz, $^{2}J_{H-H}$ = 11.2 Hz), 3.32 (d, 1H, CH_2−N, $^{2}J_{H-H}$ = 12.8 Hz), 3.48 (d, 1H, CH_2−N, $^{2}J_{H-H}$ = 12.8 Hz), 4.82 (m, 2H, CH), 7.2−7.5 (m, 13H, CH=). ^{13}C NMR: δ 31.4 (CH_3, ^{t}Bu), 31.5 (CH_3, ^{t}Bu), 31.6 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 59.4 (CH_2), 60.2 (CH_2−N), 80.5 (m, CH), 124.4 (CH=), 125.5 (CH=), 126.7 (d, CH=, J_{C-P} = 5.3 Hz), 127.3 (CH=), 128.5 (d, CH=, J_{C-P} = 4.4 Hz), 129.1 (CH=), 129.3 (CH=), 132.8 (C), 133.1 (C), 138.1 (C), 138.2 (C), 140.2 (C), 140.3 (C), 145.8 (C), 146.2 (C), 146.5 (C), 146.7 (C). Anal. Calcd (%) for $C_{67}H_{93}NO_6P_2$: C 75.18, H 8.76, N 1.31. Found: C 75.23, H 8.71, N 1.39.

(*S*)-1,3-Bis[(3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]butane (4a). Treatment of phosphorochloridite (2.2 mmol) produced in situ and (*S*)-1,3-butanediol (85 μL, 1 mmol), as described for compound **2a**, afforded diphosphite **4a**, which was purified by flash chromatography (toluene/hexane = 1/3) to produce a white powder. Yield: 0.45 g, 47%. $[\alpha]^{20}_{D}$ −8.1 (1, $CHCl_3$). ^{31}P NMR: δ 136.7 (s), 146.4 (s). ^{1}H NMR: δ 1.21 (d, 3H, $^{3}J_{H-H}$ = 7.2 Hz), 1.37 (s, 9H, CH_3, ^{t}Bu), 1.38 (s, 9H, CH_3, ^{t}Bu), 1.39 (s, 9H, CH_3, ^{t}Bu), 1.40 (s, 9H, CH_3, ^{t}Bu), 1.48 (s, 9H, CH_3, ^{t}Bu), 1.51 (s, 9H, CH_3, ^{t}Bu), 1.52 (s, 9H, CH_3, ^{t}Bu), 1.53 (s, 9H, CH_3, ^{t}Bu), 1.82 (m, 1H, CH_2), 1.96 (m, 1H, CH_2), 3.89 (m, 2H, CH_2−O), 4.60 (m, 1H, CH), 7.2−7.5 (m, 8H, CH=). ^{13}C NMR: δ 22.3 (d, CH_3, J_{C-P} = 3.8 Hz), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 31.9 (CH_3, ^{t}Bu), 34.7 (C, ^{t}Bu), 34.8 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 39.3 (m, CH_2), 61.5 (CH_2−O), 70.2 (d, CH, J_{C-P} = 14.5 Hz), 122.6 (CH=), 124.3 (CH=), 124.4 (CH=), 125.1 (CH=), 125.5 (CH=), 126.8 (CH=), 128.5 (CH=), 129.3 (CH=), 132.9 (C), 133.2 (C), 140.0 (C), 140.1 (C), 140.2 (C), 140.3 (C), 146.4 (C), 146.5 (C), 146.6 (C). Anal. Calcd (%) for $C_{60}H_{88}O_6P_2$: C 74.50, H 9.17. Found: C 74.43, H 9.22.

4,5-Bis[(3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)-phosphite]-2,2-dimethyl-1,3-dioxolane (6a). Treatment of phosphorochloridite (2.2 mmol) produced in situ and (−)-2,3-*O*-isopropylidene-D-threitol (162.2 mg, 1 mmol), as described for compound **2a**, afforded diphosphite **6a**, which was purified by flash chromatography (toluene/hexane = 1/3) to produce a white powder. Yield: 0.66 g, 65%. $[\alpha]^{20}_{D}$ +57 (1, $CHCl_3$). ^{31}P NMR: δ 134.5 (s). ^{1}H NMR: δ 1.29 (s, 6H, CH_3), 1.35 (s, 36H, CH_3, ^{t}Bu), 1.45 (s, 18H, CH_3, ^{t}Bu), 1.47 (s, 18H, CH_3, ^{t}Bu), 3.78 (m, 4H, CH_2), 3.86 (m, 2H, CH), 7.1−7.5 (m, 8H, CH=). ^{13}C NMR: δ 27.3 (CH_3), 31.1 (CH_3, ^{t}Bu), 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.8 (CH_3, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 64.3 (CH_2), 77.2 (CH), 110.2 (C), 124.4 (CH=), 125.5 (CH=), 126.7 (CH=), 126.8 (CH=), 128.5 (CH=), 129.3 (CH=), 132.6 (C), 132.7 (C), 132.8 (C), 132.9 (C), 139.9 (C), 140.2 (C), 146.2 (C), 146.3 (C), 146.6 (C), 146.7 (C). Anal. Calcd (%) for $C_{63}H_{92}O_8P_2$: C 72.80, H 8.92. Found: C 72.65, H 8.91.

(*R*)-2,2′-Bis[(3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]-1,1′-binaphthyl (7a). Treatment of phosphorochloridite (2.2 mmol) produced in situ and (*R*)-binaphthol (286.3 mg, 1 mmol), as described for compound **2a**, afforded diphosphite **7a**, which was purified by flash chromatography (toluene/hexane = 1/3) to produce a white powder. Yield: 0.51 g, 45%. $[\alpha]^{20}_{D}$ −11.6 (1, $CHCl_3$). ^{31}P NMR: δ 131.8 (s). ^{1}H NMR: δ 1.09 (s, 9H, CH_3, ^{t}Bu), 1.12 (s, 9H, CH_3, ^{t}Bu), 1.33 (s, 18H, CH_3, ^{t}Bu), 1.34 (s, 9H, CH_3, ^{t}Bu), 1.36 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 18H, CH_3, ^{t}Bu), 7.1−8.0 (m, 20H, CH=). ^{13}C NMR: δ 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 35.0 (C, ^{t}Bu), 35.1 (C, ^{t}Bu), 35.2 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 121.8 (CH=), 122.1 (CH=), 122.2 (CH=), 123.3 (CH=), 123.6 (CH=), 124.8 (CH=), 125.1 (CH=), 125.9 (CH=), 126.5 (CH=), 126.7 (CH=), 128.3 (CH=), 128.5 (CH=), 128.9 (CH=), 129.1 (CH=), 130.2 (C), 131.7 (C), 132.2 (C), 133.2 (C), 137.1 (C), 137.6 (C), 137.7 (C), 139.4 (C), 139.8 (C), 145.3(C), 145.5 (C), 146.4 (C), 146.8 (C), 146.9 (C), 147.8 (C). Anal. Calcd (%) for $C_{76}H_{92}O_6P_2$: C 78.45, H 7.97. Found: C 78.31, H 8.02.

(*S*)-2,2′-Bis[(3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]-1,1′-binaphthyl (8a). Treatment of phosphorochloridite (2.2 mmol) produced in situ and (*S*)-binaphthol (286.3 mg, 1 mmol), as described for compound **2a**, afforded diphosphite **8a**, which was purified by flash chromatography (toluene/hexane = 1/3) to produce a white powder. Yield: 0.57 g, 49%. $[\alpha]^{20}_{D}$ +11.6 (1, $CHCl_3$). ^{31}P NMR: δ 131.8 (s). ^{1}H NMR: δ 1.12 (s, 18H, CH_3, ^{t}Bu), 1.16 (s, 18H, CH_3, ^{t}Bu), 1.38 (s, 18H, CH_3, ^{t}Bu), 1.40 (s, 18H, CH_3, ^{t}Bu), 7.1−8.0 (m, 20H, CH=). ^{13}C NMR: δ 30.9 (CH_3, ^{t}Bu), 31.0 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.8 (C, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.3 (C, ^{t}Bu), 122.7 (CH=), 123.0 (CH=), 123.3 (CH=), 124.4 (CH=), 124.5 (CH=), 124.9 (CH=), 125.5 (CH=), 126.6 (CH=), 126.7 (CH=), 126.8 (CH=), 128.1 (CH=), 128.4 (CH=), 129.0 (CH=), 129.3 (CH=), 130.9 (C), 132.6 (C), 133.2 (C), 134.2 (C), 138.1 (C), 138.6 (C), 138.7 (C), 140.4 (C), 140.8 (C), 145.4 (C), 145.5 (C), 146.4 (C), 146.8

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(C), 146.9 (C), 147.9 (C). Anal. Calcd (%) for $C_{76}H_{92}O_6P_2$: C 78.45, H 7.97. Found: C 78.52, H 8.07.

2,5-Bis[(3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)-phosphite]-1,4:3,6-dianhydro-D-sorbide (10a). Treatment of phosphorochloridite (2.2 mmol) produced in situ and isosorbide (146 mg, 1 mmol), as described for compound **2a**, afforded diphosphite **10a**, which was purified by flash chromatography (toluene/hexane = 1/1) to produce a white powder. Yield: 0.79 g, 78%.$[\alpha]^{20}_{D}$ +19.9 (1, $CHCl_3$). ^{31}P NMR: δ 136.2 (s), 140.1 (s). ^{1}H NMR: δ 1.34 (s, 9H, CH_3, ^{t}Bu), 1.35 (s, 27H, CH_3, ^{t}Bu), 1.44 (s, 9H, CH_3, ^{t}Bu), 1.45 (s, 9H, CH_3, ^{t}Bu), 1.46 (s, 9H, CH_3, ^{t}Bu), 1.49 (s, 9H, CH_3, ^{t}Bu), 3.37 (m, 1H, CH_2), 3.63 (m, 1H, CH_2), 3.80 (dd, 1H, CH_2, $^{3}J_{H-H}$ = 4.0 Hz, $^{2}J_{H-H}$ = 10.8 Hz), 3.91 (bd, 1H, CH_2, $^{2}J_{H-H}$ = 10.8 Hz), 4.28 (m, 1H, CH), 4.35 (m, 2H, CH), 4.51 (m, 1H, CH), 7.1−7.5 (m, 8H, CH=). ^{13}C NMR: δ 31.2 (CH_3, ^{t}Bu), 31.3 (CH_3, ^{t}Bu), 31.4 (CH_3, ^{t}Bu), 31.7 (CH_3, ^{t}Bu), 34.9 (C, ^{t}Bu), 35.5 (C, ^{t}Bu), 35.6 (C, ^{t}Bu), 70.0 (CH_2), 74.9 (CH_2), 75,4 (CH), 79.7 (CH), 80.9 (CH), 86.8 (CH), 124.4 (CH=), 124.6 (CH=), 124.6 (CH=), 126.8 (CH=), 128.5 (CH=), 129.3 (CH=), 131.8 (C), 131.9 (C), 132.5 (C), 132.8 (C), 140.0 (C), 140.1 (C), 140.3 (C), 140.4 (C), 146.7 (C), 146.8 (C), 146.9 (C), 147.0 (C). Anal. Calcd (%) for $C_{64}H_{92}O_6P_2$: C 75.41, H 9.10. Found: C 75.54, H 9.06.

Allylic Alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (11). A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the diphosphite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-**11** (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 dried over $MgSO_4$. Solvent was removed and conversion was measured by ^{1}H 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 (14). A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the diphosphite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-**14** (70 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 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 dried over $MgSO_4$. Conversion and enantiomeric excess was determined by GC, using a FS-β-Cyclodex 25 m column F.I.D. detector (internal diameter 0.2 mm; film thickness 0.33 mm; carrier gas 100 kPa He).

Allylic Alkylation of Cinnamyl Acetate (16). A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the diphosphite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-**16** (88.1 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 dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^{1}H 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 with dichloromethane as the eluent.

Allylic Amination of *rac*-1,3-Diphenyl-3-acetoxyprop-1-ene (11). A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the diphosphite ligand (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-**11** (126 mg, 0.5 mmol) and benzylamine (131 μL, 1.5 mmol) in dichloromethane (1.5 mL) was added. The reaction mixture was stirred at room temperature. After 1 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 dried over $MgSO_4$. Solvent was removed and conversion was measured by ^{1}H NMR. To determine the ee by HPLC (Chiralcel-OJ, 13% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over silica with 10% Et_2O/hexane mixture as the eluent.

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