First chiral phosphite-phosphoroamidite ligands for the highly enantioselective and versatile Pd-catalyzed asymmetric allylic substitution reactions

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General Considerations. All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Phosphite-phosphoroamidite ligands **3a,b** and **4a,b** were prepared as previously described.¹ 5-Amine-5-deoxy-1,2-*O*-isopropylidene-xylofuranose² and 5-amine-5-deoxy-1,2-*O*-isopropylidene-ribofuranose³ were prepared on large scale from D-xylose as previously reported. Phosphorochloridites are easily prepared in one step from the corresponding biaryls.⁴ Racemic substrates **S1-S5** were prepared as previously reported.^{5,6,7} ¹H, ¹³C{¹H}, and ³¹P{¹H} NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of SiMe₄ (¹H and ¹³C) as internal standard or H₃PO₄ (³¹P) as external standard.

General procedure for the preparation of ligands 3 and 4. Phosphorochloridite (2.2 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.36 mL, 4.6 mmol) was added. Amino-alcohol (1 mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.36 mL, 4.6 mmol) was added. The amino-alcohol solution was transferred slowly at 0 °C to the solution of phosphorochloridite. The reaction mixture was warmed up to 80 °C and stirred overnight, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (toluene/NEt₃= 100/1) to produce the corresponding ligand as white powder.

¹ M. Diéguez, A. Ruiz, C. Claver *Tetrahedron: Asymmetry* 2001, **12**, 2827.

² D. F. Ewing, G. Goethals, G. Mackenzie, P. Martin, G. Ronco, L. Vanbaelinghem, P. Villa, *J. Carbohydr. Chem.* 1999, **18**, 441.

³ D. F. Ewing, G. Goethals, G. Mackenzie, P. Martin, G. Ronco, L. Vanbaelinghem, P. Villa, *Carbohydr. Res.* 1999, **321**, 190.

⁴ a) G. J. H. Buisman, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron: Asymmetry* 1993, **4**, 1625. b) G. J. H. Buisman, L. A. van der Veen, A. Klootwijk, W. G. J. de Lange, P. C. J. Kamer, P. W. N. M. van Leeuwen, D. Vogt *Organometallics* 1997, **16**, 2929.

⁵ P. R. Auburn, P. B. Mackenzie, B. Bosnich *J. Am. Chem. Soc.* 1985, **107**, 2033.

⁶ C. Jia, P. Müller, H. Mimoun *J. Mol. Cat. A: Chem.* 1995, **101**, 127.

⁷ J. Lehman, G. C. Lloyd-Jones *Tetrahedron* 1995, **51**, 8863.

3c: Yield: 0.39 g, 35 %. ^{31}P NMR (C_6D_6), δ : 146.5 (s), 148.4 (s). ^1H NMR(C_6D_6), δ : 0.06 (s, 9H, SiCH₃), 0.39 (s, 9H, SiCH₃), 0.52 (s, 9H, SiCH₃), 0.54 (s, 9H, SiCH₃), 0.91 (s, 3H, CH₃), 1.21 (s, 3H, CH₃), 2.84 (m, 1H, H-5'), 3.01 (m, 1H, H-5), 3.33 (m, 1H, N-H), 4.53 (m, 1H, H-4), 4.70 (d, 1H, H-2, $^3J_{1-2} = 3.6$ Hz), 4.87 (dd, 1H, H-3, $^3J_{3-4} = 2.8$ Hz, $^2J_{\text{P-H}} = 11.2$ Hz), 5.84 (d, 1H, H-1, $^3J_{1-2} = 3.6$ Hz), 6.7-8.2 (m, 20H, CH=). ^{13}C NMR(C_6D_6), δ : 0.1 (SiCH₃), 0.6 (SiCH₃), 0.9 (SiCH₃), 1.0 (SiCH₃), 26.5 (CH₃), 27.1 (CH₃), 39.8 (d, C-5, $^2J_{\text{C-P}} = 5.3$ Hz), 78.5(d, C-3, $^2J_{\text{C-P}} = 9.1$ Hz), 81.0 (C-4), 85.1 (d, C-2, $^3J_{\text{C-P}} = 3.0$ Hz), 105.8 (C-1), 112.3 (CMe₂), 125.0 (CH=), 125.1 (CH=), 125.7 (CH=), 127.2 (CH=), 127.5 (CH=), 127.6 (CH=), 127.7 (CH=), 128.8 (CH=), 128.9 (CH=), 129.2 (CH=), 131.1 (C), 131.7 (C), 131.8 (C), 132.1 (C), 132.5 (C), 134.6 (C), 134.9 (C), 135.0 (C), 137.6 (CH=), 137.7 (CH=), 138.2 (CH=), 138.3 (CH=), 138.6 (CH=), 151.0 (C), 152.4 (C), 153.7 (C), 154.2 (C). Anal. calcd (%) for $\text{C}_{60}\text{H}_{69}\text{NO}_8\text{P}_2\text{Si}_4$: C 65.13, H 6.29, N 1.27; found: C 65.07, H 6.28, N 1.29.

3d: Yield: 0.42 g, 38 %. ^{31}P NMR(C_6D_6), δ : 145.3 (s), 149.5 (s). ^1H NMR(C_6D_6), δ : 0.20 (s, 9H, SiCH₃), 0.52 (s, 9H, SiCH₃), 0.54 (s, 9H, SiCH₃), 0.55 (s, 3H, CH₃), 0.57 (s, 9H, SiCH₃), 1.28 (s, 3H, CH₃), 3.24 (m, 3H, H-5, H-5', N-H), 3.51 (d, 1H, H-2, $^3J_{2-1} = 3.6$ Hz), 4.20 (m, 1H, H-4), 4.65 (dd, 1H, H-3, $^3J_{3-4} = 3.2$ Hz, $^2J_{3-\text{P}} = 7.6$ Hz), 5.65 (d, 1H, H-1, $^3J_{1-2} = 3.6$ Hz), 6.9-8.2 (m, 20H, CH=). ^{13}C NMR(C_6D_6), δ : 0.4 (SiCH₃), 0.6 (CH₃, SiMe₃), 0.7 (SiCH₃), 0.8 (SiCH₃), 25.7 (CH₃), 27.0 (CH₃), 40.5 (d, C-5, $^2J_{\text{C-P}} = 12.9$ Hz), 77.7 (d, C-3, $^2J_{\text{C-P}} = 4.5$ Hz), 81.9 (C-4), 84.9 (C-2), 105.5 (C-1), 111.6 (CMe₂), 125.1 (CH=), 125.2 (CH=), 125.6 (CH=), 126.0 (CH=), 127.1 (CH=), 127.3 (CH=), 127.5 (CH=), 128.8 (CH=), 129.1 (CH=), 129.6 (CH=), 131.4 (C), 131.6 (C), 131.8 (C), 131.9 (C), 132.9 (C), 133.0 (C), 134.9 (C), 135.0 (C), 137.3 (CH=), 137.7 (CH=), 137.9 (CH=), 152.0 (C), 152.6 (C), 153.2 (C), 154.5 (C). Anal. calcd (%) for $\text{C}_{60}\text{H}_{69}\text{NO}_8\text{P}_2\text{Si}_4$: C 65.13, H 6.29, N 1.27; found: C 65.11, H 6.29, N 1.24.

4c: Yield: 0.34 g, 31 %. ^{31}P NMR(C_6D_6), δ : 142.2 (s), 150.2 (s). ^1H NMR(C_6D_6), δ : 0.34 (s, 9H, SiCH₃), 0.51 (s, 9H, SiCH₃), 0.52 (s, 9H, SiCH₃), 0.54 (s, 9H, SiCH₃), 0.99 (s, 3H, CH₃), 1.43

(s, 3H, CH₃), 3.03 (m, 1H, H-5'), 3.21 (m, 1H, H-5), 3.26 (m, 2H, H-2, N-H), 4.07 (m, 1H, H-4), 4.21 (m, 1H, H-3), 4.95 (d, 1H, H-1, $^3J_{1-2} = 3.6$ Hz), 6.9-8.2 (m, 20H, CH=). ^{13}C NMR(C₆D₆), δ : 0.7 (SiCH₃), 0.8 (SiCH₃), 26.6 (CH₃), 27.2 (CH₃), 42.3 (d, C-5, $^2J_{\text{C-P}} = 5.3$ Hz), 73.8 (C-3), 78.7 (C-4), 79.2 (C-2), 103.9 (C-1), 113.1 (CMe₂), 125.1 (CH=), 125.2 (CH=), 125.5 (CH=), 127.1 (CH=), 127.3 (CH=), 127.4 (CH=), 127.5 (CH=), 127.6 (CH=), 128.7 (CH=), 129.1 (CH=), 129.2 (CH=), 129.6 (CH=), 131.4 (C), 131.8 (C), 132.6 (C), 132.9 (C), 133.0 (C), 133.8 (C), 134.5 (C), 134.9 (C), 136.9 (CH=), 137.6 (CH=), 137.7 (CH=), 137.9 (CH=), 152.3 (C), 153.2 (C), 154.5 (C), 154.8 (C). Anal. calcd (%) for C₆₀H₆₉NO₈P₂Si₄: C 65.13, H 6.29, N 1.27; found: C 65.24, H 6.21, N 1.28.

4d: Yield: 0.12 g, 11 %. ^{31}P NMR(C₆D₆), δ : 141.7 (br). ^1H NMR(C₆D₆), δ : 0.33 (s, 9H, SiCH₃), 0.46 (s, 9H, SiCH₃), 0.57 (s, 9H, SiCH₃), 0.59 (s, 9H, SiCH₃), 1.14 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 2.43 (m, 2H, H-5', NH), 3.22 (m, 1H, H-5), 3.65 (m, 1H, H-3), 4.43 (m, 1H, H-2), 4.81 (m, 1H, H-4), 5.29 (d, 1H, H-1, $^3J_{1-2} = 4.0$ Hz), 6.6-8.4 (m, 20H, CH=). ^{13}C NMR(C₆D₆), δ : 0.0 (SiCH₃), 0.3 (SiCH₃), 0.5 (SiCH₃), 1.0 (SiCH₃), 27.4 (CH₃), 27.7 (CH₃), 42.1 (m, C-5), 77.2 (C-3), 77.9 (C-4), 79.3 (C-2), 105.1 (C-1), 114.0 (CMe₂), 124.0 (CH=), 124.2 (CH=), 124.3 (CH=), 126.2 (CH=), 126.3 (CH=), 126.5 (CH=), 127.4 (CH=), 127.6 (CH=), 127.8 (CH=), 127.9 (CH=), 128.8 (CH=), 129.0 (CH=), 129.2 (CH=), 129.6 (CH=), 130.0 (C), 130.2 (C), 130.3 (C), 134.2 (C), 134.3 (C), 134.5 (C), 135.1 (C), 138.4 (CH=), 138.5 (CH=), 138.7 (CH=), 152.5 (C), 152.7 (C), 152.9 (C). Anal. calcd (%) for C₆₀H₆₉NO₈P₂Si₄: C 65.13, H 6.29, N 1.27; found: C 64.99, H 6.32, N 1.22.

Typical procedure of allylic alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1.** A degassed solution of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (0.9 mg, 0.0025 mmol) and the phosphite-phosphoroamidite (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **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 the desired reaction time, the mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over MgSO_4 . Solvent was removed and conversion was measured by $^1\text{H-NMR}$. To determine the enantiomeric excess by HPLC (Chiracel OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

Typical procedure of allylic amination of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1.** A degassed solution of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (1.8 mg, 0.005 mmol) and the phosphite-phosphoroamidite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (126 mg, 0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL , 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After the desired time the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over MgSO_4 . Solvent was removed and conversion was measured by ^1H -NMR. To determine the enantiomeric excess by HPLC (Chiracel OJ, 13% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over silica using 10% Et_2O /hexane mixture as the eluent.

Table 1. Pd-catalyzed allylic amination of 1,3-diphenyl-3-acetoxyprop-1-ene **S1**.^a

Entry	Ligand	% Conv (h) ^b	% ee ^c
1	3a	100 (6)	61% (<i>R</i>)
2	3b	100 (4)	56% (<i>R</i>)
3	3c	69 (6)	12% (<i>R</i>)
4	3d	98 (6)	97% (<i>R</i>)
5	4a	64 (6)	54% (<i>R</i>)
6	4b	100 (5)	51% (<i>R</i>)
7	4c	21 (6)	75% (<i>R</i>)
8	4d	27 (6)	11% (<i>R</i>)

^a 1 mol% $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of benzylamine, room temperature. Dichloromethane as solvent. ^b Measured by ^1H -NMR. Reaction time in hours shown in brackets. ^c Determined by HPLC (Chiralcel OJ).

Typical procedure of allylic alkylation of *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S2.** A degassed solution of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (0.9 mg, 0.0025 mmol) and the phosphite-phosphoroamidite (0.0055 mmol) in tetrahydrofuran (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S2** (64 mg, 0.5 mmol) in tetrahydrofuran (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 a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over MgSO_4 . Conversion and enantiomeric excess was determined by GC.

Table 2. Pd-catalyzed allylic alkylation of 1,3-dimethyl-3-acetoxyprop-1-ene **S2**.^a

Entry	Ligand	% Conv (min) ^b	% ee ^c
1	3a	100 (30)	16 % (<i>R</i>)
2	3b	100 (30)	8 % (<i>R</i>)
3	3c	100 (30)	58 % (<i>S</i>)
4	3d	100 (30)	39 % (<i>R</i>)
5	4a	100 (30)	10 % (<i>S</i>)
6	4b	100 (30)	9 % (<i>S</i>)
7	4c	43 (30)	21 % (<i>S</i>)
8	4d	42 (30)	74 % (<i>S</i>)

^a 0.5 mol% $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $\text{CH}_2(\text{COOMe})_2$ and BSA, a pinch of KOAc, room temperature. THF as solvent. ^b Measured by GC. Reaction time in minutes shown in brackets. ^c Determined by GC.

Typical procedure of allylic alkylation of *rac*-3-acetoxycyclohexene **S3 and *rac*-3-acetoxycycloheptene **S5**.** A degassed solution of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (0.9 mg, 0.0025 mmol) and the phosphite-phosphoroamidite ligand (0.0055 mmol) in tetrahydrofuran (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in tetrahydrofuran (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 hours the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over MgSO_4 . Conversion and enantiomeric excess was determined by GC using a FS-Cyclodex β -I/P 25 m column, internal diameter 0.2 mm, film thickness 0.33 mm, carrier gas: 100 kPa He, F.I.D. detector).

Table 3. Pd-catalyzed allylic alkylation of **S3** and **S5**.^a

$\text{CH}_2(\text{COOMe})_2$ / BSA
 $[\text{Pd}(\pi\text{-C}_3\text{H}_5)\text{Cl}]_2$ / **3** or **4**

$n = 1$ **S3**
 $n = 2$ **S5**

Entry	Substrate	Ligand	% Conv (min) ^b	% ee ^c
1	S3	3a	100 (120)	12% (<i>R</i>)
2	S3	3b	100 (120)	4% (<i>R</i>)
3	S3	3c	20 (120)	19% (<i>R</i>)
4	S3	3d	26 (120)	67% (<i>S</i>)
5	S3	4a	100 (120)	85% (<i>S</i>)
6	S3	4b	100 (120)	65% (<i>S</i>)
7	S3	4c	11 (120)	52% (<i>R</i>)
8	S3	4d	10 (120)	78% (<i>S</i>)
9	S5	4a	52 (360)	91% (<i>S</i>)

^a 0.5 mol% $[\text{Pd}(\pi\text{-C}_3\text{H}_5)\text{Cl}]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $\text{CH}_2(\text{COOMe})_2$ and BSA, a pinch of KOAc, room temperature. THF as solvent. ^b Measured by GC. Reaction time in minutes shown in brackets. ^c Measured by GC (F/S- β -Cyclodex).

Typical procedure of allylic alkylation of S4 and S6. A degassed solution of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (3.6 mg, 0.01 mmol) and the phosphite-phosphoroamidite ligand (0.022 mmol) in CH_2Cl_2 (0.5 mL) was stirred for 30 min at room temperature. Subsequently, a solution of substrate (113.1 mg, 0.5 mmol) in CH_2Cl_2 (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. After 2 hours the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over MgSO_4 . Solvent was removed and conversion and regioselectivity were measured by $^1\text{H-NMR}$. To determine the ee by HPLC (Chiracel OJ, 13% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

Table 4. Pd-catalyzed allylic alkylation of **S4** and **S6**.^a

R = 1-Naphthyl

Entry	Substrate	Ligand	% Conv. (t/min) ^b	b/l ^b	% ee ^c
1	S6	3a	100 (120)	20/80	21 (<i>S</i>)
2	S6	3b	100 (120)	30/70	17 (<i>S</i>)
3	S6	3c	100 (120)	70/30	7 (<i>R</i>)
4	S6	3d	100 (120)	65/35	66 (<i>S</i>)
5	S6	4a	100 (120)	70/30	71 (<i>S</i>)
6	S6	4b	100 (120)	70/30	9 (<i>S</i>)
7	S6	4c	73 (120)	70/30	90 (<i>S</i>)
7	S4	4c	72 (120)	70/30	90 (<i>S</i>)
8	S6	4d	100 (120)	60/40	61 (<i>S</i>)

^a All reactions were run at room temperature. 1 mol% $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$. CH_2Cl_2 as solvent.

^b Conversion percentage and linear-to-branched ratio determined by $^1\text{H-NMR}$. ^c Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.