New Phosphite-Oxazoline ligands for efficient Pd-catalyzed substitution reactions

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General procedure for the preparation of ligands 1 and 2. Phosphorochloridite¹ (2.2 mmol) produced *in situ* was dissolved in toluene (5 mL) and pyridine (0.36 mL, 4.6 mmol) was added. Oxazoline-alcohol² (1 mmol) was azeotropically dried with toluene (3 x 1 mL) and then dissolved in toluene (10 mL), to which pyridine (0.18 mL, 2.3 mmol) had been added. The diol solution was transferred slowly at -78 °C to the solution of phosphorochloridite. The reaction mixture was allowed to warm up to room temperature 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 a the corresponding ligand as white powder.

1a: Yield: 0.41 g, 63 %. ³¹P (CDCl₃), δ: 136.4 (s). ¹H (CDCl₃), δ: 0.97 (s, 9H), 1.33 (s, 9H), 1.39 (s, 18H), 1.49 (s, 9H), 4.11 (m, 2H), 4.29 (dd, 1H, *J*= 10 Hz, *J*= 8.4 Hz), 5.77 (b, 1H), 6.9-7.8 (7H). ¹³C (CDCl₃), δ: 26.3, 30.7, 31.2, 31.7, 31.8, 34.2, 34.8, 34.9, 35.4, 35.6, 68.4, 76.4, 123.5, 123.7, 124.3, 124.4, 126.8, 126.9, 130.4, 131.6, 133.2, 133.5, 140.3, 140.5, 146.6, 146.9.

1b: Yield: 0.41 g, 60 %. ³¹P (CDCl₃), δ: 136.5 (s). ¹H (CDCl₃), δ: 1.33 (s, 9H), 1.39 (s, 9H), 1.44 (s, 18H), 4.10 (t, 1H, *J*= 8.8 Hz), 4.73 (dd, 1H, *J*= 10.4 Hz, *J*= 8.4 Hz), 5.40 (m, 1H), 6.03 (bd, 1H, *J*= 7.2 Hz), 7.0-8.0 (12H). ¹³C (CDCl₃), δ: 30.9, 31.1, 31.7, 31.8, 34.8, 34.9, 35.5, 70.0, 74.6, 123.8, 123.9, 124.4, 124.5, 126.9, 127.0, 128.5, 128.8, 129.3, 130.9, 132.1, 133.1, 133.3, 140.5, 142.6, 146.3, 146.7, 147.0, 150.9, 151.0, 163.4.

1c: Yield: 0.44 g, 68 %. ³¹P (CDCl₃), δ: 136.6 (s). ¹H (CDCl₃), δ: 0.97 (d, 3H, *J*= 7.2 Hz), 1.11 (d, 3H, *J*= 7.2 Hz), 1.36 (s, 9H), 1.40 (s, 9H), 1.43 (s, 9H), 1.50 (s, 9H), 1.87 (sp, 1H, *J*= 7.2 Hz), 4.05 (m, 1H), 4.13 (m, 1H), 4.40 (dd, 1H, *J*= 8.8 Hz, *J*= 7.2 Hz), 5.79 (b, 1H), 6.9-7.8 (7H). ¹³C (CDCl₃), δ: 18.9, 19.6, 30.9, 31.2, 31.7, 31.8, 33.4, 34.9, 35.0, 35.5, 35.6, 70.2, 73.3, 123.6, 123.9, 124.3, 124.5, 126.9, 127.0, 130.0, 131.7, 133.2, 133.3, 133.4, 140.4, 140.5, 146.6, 146.7, 146.9, 151.1, 151.3.

¹ Phosphorochloridites are easily prepared in one step from the corresponding bisphenol as described in Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, 4, 1625.

1d: Yield: 0.40 g, 64 %. ^{31}P (CDCl_3), δ : 138.7 (s). ^1H (CDCl_3), δ : 0.73 (t, 3H, J = 7.5 Hz), 0.99 (m, 2H), 1.47 (s, 36H), 3.31 (dd, 1H, J = 10.8 Hz, J = 6.0 Hz), 3.40 (dd, 1H, J = 10.8 Hz, J = 4.2 Hz), 4.17 (m, 1H), 7.2-8.4 (8H). ^{13}C (CDCl_3), δ : 10.1, 24.4, 31.2, 31.5, 34.7, 35.4, 46.4, 51.8, 119.2, 119.5, 123.9, 124.6, 124.7, 126.6, 132.7, 140.4, 147.3, 163.8.

1e: Yield: 0.23 g, 50 %. ^{31}P (CDCl_3), δ : 142.3 (s). ^1H (CDCl_3), δ : 1.06 (t, 3H, J = 7.2 Hz), 1.69 (m, 1H), 1.83 (m, 1H), 4.06 (m, 1H), 4.32 (m, 1H), 4.48 (dd, 1H, J = 9.2 Hz, J = 8.0 Hz), 7.1-7.9 (12H). ^{13}C (CDCl_3), δ : 10.5, 28.9, 68.4, 72.1, 122.4, 122.5, 123.2, 123.3, 124.6, 125.5, 128.4, 129.2, 129.3, 130.1, 131.2, 131.5, 132.4, 149.5, 149.6, 150.5, 150.6, 161.7.

1f: Yield: 0.25 g, 40 %. ^{31}P (CDCl_3), δ : 140.2 (s). ^1H (CDCl_3), δ : 0.67 (t, 3H, J = 7.6 Hz), 0.92 (m, 2H), 1.38 (s, 18H), 3.25 (dd, 1H, J = 10.8 Hz, J = 6.0 Hz), 3.31 (dd, 1H, J = 10.8 Hz, J = 4.4 Hz), 3.85 (s, 6H), 4.09 (m, 1H), 6.7-8.3 (8H). ^{13}C (CDCl_3), δ : 10.3, 24.5, 31.2, 35.6, 35.7, 46.5, 51.9, 55.8, 113.0, 113.3, 114.7, 114.8, 119.4, 119.6, 123.7, 124.2, 132.9, 133.0, 133.9, 140.8, 143.2, 150.5, 150.6, 156.4, 164.3.

1g: Yield: 0.26 g, 44 %. ^{31}P (CDCl_3), δ : 136.0 (s). ^1H (CDCl_3), δ : 0.94 (d, 3H, J = 7.2 Hz), 1.06 (d, 3H, J = 7.2 Hz), 1.40 (s, 9H), 1.44 (s, 9H), 1.84 (sp, 1H, J = 7.2 Hz), 3.81 (s, 3H), 3.84 (s, 3H), 4.05 (m, 2H), 4.38 (dd, 1H, J = 8.4 Hz, J = 7.2 Hz), 6.20 (d, 1H, J = 8.4 Hz), 6.7-7.9 (7H). ^{13}C (CDCl_3), δ : 18.8, 19.5, 30.7, 30.8, 31.0, 31.1, 33.3, 35.2, 35.6, 55.8, 55.9, 70.2, 73.0, 112.9, 113.1, 114.5, 114.6, 123.7, 123.8, 123.9, 130.7, 131.9, 134.0, 134.2, 142.8, 142.9, 150.7, 155.8, 155.9, 161.6.

2: Yield: 0.39 g, 58 %. ^{31}P (CDCl_3), δ : 136.6 (s). ^1H (CDCl_3), δ : 1.33 (s, 9H), 1.39 (s, 9H), 1.44 (s, 9H), 1.45 (s, 9H), 4.10 (t, 1H, J = 8.8 Hz), 4.74 (dd, 1H, J = 10.4 Hz, J = 8.8 Hz), 5.40 (m, 1H), 6.04 (bd, 1H, J = 6.8 Hz), 7.0-8.0 (12H). ^{13}C (CDCl_3), δ : 30.9, 31.1, 31.7, 31.8, 34.8, 34.9, 35.5, 70.0, 74.6, 123.8, 124.4, 124.5, 126.9, 127.0, 128.4, 128.8, 129.2, 130.9, 132.1, 133.4, 140.4, 142.5, 146.7, 147.0, 163.4.

² Oxazoline-alcohols are easily prepared in one step from the corresponding amino alcohol as described in Gómez-Simón, M.; Jansat, S.; Muller, G.; Panyella, D.; Font-Bardía, M.; Solans, X. *J. Chem. Soc., Dalton Trans.* **1997**, 3755.

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-oxazoline (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 5 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 . Solvent was removed and conversion was measured by ^1H -NMR. To determine the ee 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-oxazoline 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 ee 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** using ligands **1** and **2**.^a

Entry	Ligand	% Conv (h) ^b	% ee ^c
1	1a	100 (6)	99% (<i>R</i>)
2	1b	100 (4)	98% (<i>R</i>)
3	1c	100 (5)	99% (<i>R</i>)
4	1d	98 (6)	98% (<i>R</i>)
5	1e	48 (6)	54% (<i>R</i>)
6	1g	100 (6)	95% (<i>R</i>)
7	2	100 (4)	98% (<i>S</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*-3-acetoxycyclohexene **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-oxazoline ligand (0.0055 mmol) in dimethylformamide (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S2** (70 mg, 0.5 mmol) in dimethylformamide (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 Et₂O (5 mL) and a saturated NH₄Cl (aq) (25 mL) was added. The mixture was extracted with Et₂O (3 x 10 mL) and the extract dried over MgSO₄. 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 2. Pd-catalyzed allylic alkylation of 3-acetoxycyclohexene **S2** using ligands **1** and **2**.^a

Entry	Ligand	% Conv (min) ^b	% ee ^c
1	1a	70 (30)	93% (<i>R</i>)
2	1b	100 (30)	91% (<i>R</i>)
3	1c	100 (30)	94% (<i>R</i>)
4	1d	100 (30)	91% (<i>R</i>)
5	1e	100 (30)	2% (<i>R</i>)
6	1f	100 (30)	93% (<i>R</i>)
7	1g	100 (30)	92% (<i>R</i>)
8	2	100 (30)	90% (<i>S</i>)
9 ^d	1c	13 (60)	99% (<i>R</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. DMF as solvent. ^b Measured by GC. Reaction time in minutes shown in brackets. ^c Measured by GC (F/S- β -Cyclodex). ^d Reaction carried out at 0 °C.

Typical procedure of allylic alkylation of *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S4.** A degassed solution of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (0.9 mg, 0.0025 mmol) and the phosphite-oxazoline (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S4** (64 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 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 3. Pd-catalyzed allylic alkylation of 1,3-dimethyl-3-acetoxyprop-1-ene **S4** using ligands **1** and **2**.^a

Entry	Ligand	% Conv (min) ^b	% ee ^c
1	1a	100 (30)	81 % (<i>R</i>)
2	1b	100 (30)	73 % (<i>R</i>)
3	1c	100 (30)	79 % (<i>R</i>)
4	2	100 (30)	74 % (<i>S</i>)
5 ^d	1a	18 (60)	93% (<i>R</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. Dichloromethane as solvent. ^b Measured by GC. Reaction time in minutes shown in brackets. ^c Determined by GC. ^d Reaction carried out at 0 °C.

Typical procedure of allylic alkylation of *rac*-3-acetoxycyclopentene **S5 and *rac*-3-acetoxycycloheptene **S6**.** A degassed solution of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (0.9 mg, 0.0025 mmol) and the phosphite-oxazoline ligand (0.0055 mmol) in dimethylformamide (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in dimethylformamide (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 was determined by GC. To determine the ee by ^1H NMR (using $\text{Eu}(\text{hfc})_3$ as resolving reagent), a sample was purified on silica using Et_2O /hexane (1/4) mixture as the eluent.

Table 4. Pd-catalyzed allylic alkylation of **S5** and **S6** using ligands **1** and **2**.^a

$\text{CH}_2(\text{COOMe})_2$ / BSA
 $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ / **1** or **2**

$n=0$ **S5**
 $n=2$ **S6**

Entry	Substrate	Ligand	% Conv (min) ^b	% ee ^c
1	S5	1a	100 (30)	87% (-)
2	S5	1b	100 (30)	90% (-)
3	S5	1c	100 (30)	89% (-)
4	S5	2	100 (30)	90% (+)
5 ^d	S5	2	12 (60)	97% (+)
6	S6	1a	100 (30)	88% (-)
7	S6	1b	100 (30)	89% (-)
8	S6	1c	100 (30)	93% (-)
9	S6	2	100 (30)	90% (+)
10 ^d	S6	2	9 (60)	98% (+)

^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. DMF as solvent. ^b Measured by GC. Reaction time in minutes shown in brackets. ^c Measured by ^1H NMR using $\text{Eu}(\text{hfc})_3$. ^d Reaction carried out at 0 °C.

Typical procedure of allylic alkylation of 1-phenylallyl acetate **S3 and 1-(1-naphthyl)allyl acetate **S7**.** A degassed solution of $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (3.6 mg, 0.01 mmol) and the phosphite-oxazoline ligand (0.022 mmol) in benzene (0.5 mL) was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C. Subsequently, a solution of substrate (0.5 mmol) in benzene (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 at 0 °C. After 2 hours the reaction mixture was diluted with Et₂O (5 mL) and a saturated NH₄Cl (aq) (25 mL) was added. The mixture was extracted with Et₂O (3 x 10 mL) and the extract dried over MgSO₄. Solvent was removed and conversion and regioselectivity were measured by ¹H-NMR. To determine the ee by HPLC (substrate **S3**: Chiracel OJ, 3% 2-propanol/hexane, flow 0.7 mL/min; substrate **S7**: Chiracel OJ, 13% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.