Development of Novel Hemilabile Segphos P–P=O Ligands

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Development of novel chiral hemilabile Segphos P–P=O ligands is described. The ligands are examined for enantioselective Pd-catalyzed allylic alkylation of cyclic allylic acetates.

Key words chiral hemilabile P–P=O ligand; Segphos; enantioselective Pd-catalyzed allylic alkylation; cyclic allylic acetate

Recently, we have developed hemilabile ligands with both soft and hard coordinated centers within one molecule.[1—7] As part of our research program in relation to hemilabile ligands, we began to develop new hemilabile Segphos P–P=O ligands. The synthesis of the hemilabile Segphos P–P=O ligands **4** was easily performed as shown in Chart 1.[8,9] Treatment of the Segphos derivatives **1** with $BH_3 \cdot THF$ in THF at 0 °C, and subsequent oxidation of **2** with 1% H_2O_2 in EtOAc at 0 °C afforded **3** with small amounts of impurities. Finally, removal of BH_3 in **3** with Et_2NH at rt provided the desired **4a**—**c** in 47—61% overall yields.

Investigations of the Pd-catalyzed asymmetric allylic substitution of acyclic substrates have spanned a variety of new and known ligands.[10] But, since the corresponding substitutions on cycloalkenyl acetates have been a formidable challenge,[10] we chose the above reaction as a test system. With the hemilabile Segphos P–P=O ligands **4a**—**c** in hand, the Pd-catalyzed enantioselective allylic alkylation of 2-cyclohexenyl acetate (**5**) with dibenzyl malonate as a pronucleophile was examined under standard conditions of the combination of BSA and KOAc (Table 1). As can be seen in entries 1—6, compared with Segphos **1a**—**c**, hemilabile Segphos P–P=O ligands **4a**—**c** exhibited better reactivity and enantioselectivity. Encouraged by the promising results with hemilabile Segphos P–P=O ligands **4a**, the solvent effect was examined (entries 7—9). The use of toluene as a solvent gave the best enantioselectivity (64% ee, entry 9).

Next, the reaction of 2-cyclopentyl acetate (**7**) with dibenzyl malonate was examined under the above same conditions (Table 2). Among the hemilabile Segphos P–P=O ligands **4a**—**c** employed, the use of DTBM-Segphos P–P=O **4c** was found to be effective, affording the corresponding product **8** in 86% yield and 65% ee. The enantioselectivity in entry 9, Table 1 and entry 3, Table 2 obtained by hemilabile Segphos P–P=O ligands, are of the good level reported in the literature.[11—17]

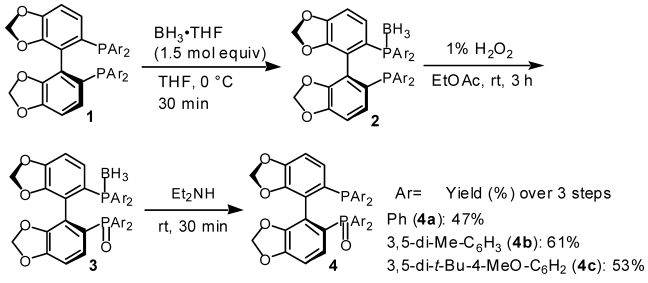


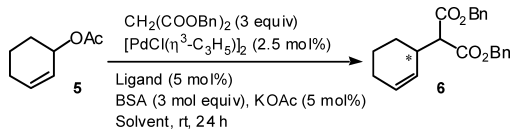
Chart 1. Synthesis of Hemilabile Segphos P–P=O Derivatives

In summary, we have shown that hemilabile Segphos P–P=O ligands are promising in enantioselective Pd-catalyzed allylic alkylation of cyclic allylic acetates. Further application for the hemilabile Segphos P–P=O ligands, and development of new hemilabile ligands are now in progress.

Experimental

IR spectra were measured on a SHIMADZU FTIR-8100 diffraction grating IR spectrophotometer. ^{1}H- (270 MHz) and ^{13}C-NMR (68 MHz) spectra were measured on a JEOL JNM-EX-270 NMR spectrometer. EI and FAB-MS spectra were measured on a JEOL JMS-SX-102A instrument. Commercially available reagents were used without any purification. Toluene was distilled from Na under a nitrogen atmosphere. Silica gel column chromatography was performed on Fuji silysia PSQ 60B.

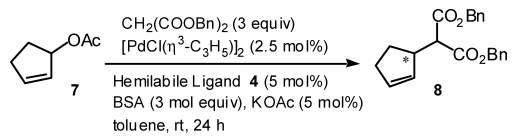
Table 1



Entry	Ligand	Solvent	Yield (%)	Ee[a] (%)
1	(*S*)-Segphos P–P=O **4a**	DMF	88	53
2	(*S*)-Segphos **1a**	DMF	46[b]	29
3	(*S*)-DM-Segphos P–P=O **4b**	DMF	95	24
4	(*S*)-DM-Segphos **1b**	DMF	<14[b,c]	11
5	(*S*)-DTBM-Segphos P–P=O **4c**	DMF	75[b]	51
6	(*S*)-DTBM-Segphos **1c**	DMF	Trace[b]	—
7	(*S*)-Segphos P–P=O **4a**	CH_3CN	81	49
8	(*S*)-Segphos P–P=O **4a**	THF	87	58
9	(*S*)-Segphos P–P=O **4a**	Toluene	89	64
10	(*S*)-DM-Segphos P–P=O **4b**	Toluene	90	30
11	(*S*)-DTBM-Segphos P–P=O **4c**	Toluene	89	59

a) Determined by HPLC analysis. *b*) Remainder of mass balance was the acetate **5**. *c*) A small amount of unknown impurities was included.

Table 2



Entry	Hemilabile ligand	Yield (%)	Ee[a] (%)
1	(*S*)-Segphos P–P=O **4a**	73[b]	58
2	(*S*)-DM-Segphos P–P=O **4b**	89	50
3	(*S*)-DTBM-Segphos P–P=O **4c**	86	65

a) Determined by HPLC analysis. *b*) Remainder of mass balance was the acetate **7**.

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Representative Procedure for Synthesis of Hemilabile (*S*)-Segphos P–P=O Ligand 4a To a stirred solution of (*S*)-Segphos (**1a**) (1.00 g, 1.64 mmol) in THF (30 ml) was added $BH_3 \cdot THF$ (1.0 M in THF, 2.50 ml, 2.50 mmol) at 0 °C. The reaction mixture was stirred for 0.5 h at the same temperature and quenched with water. The mixture was warmed up to rt and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude product **2a** was used for the next step without further separation.

To a stirred solution of the crude product **2a** in EtOAc (15 ml) was added 1% H_2O_2 aq. (15 ml) at 0 °C. After stirring for 3 h at rt, to the reaction mixture was added saturated $Na_2S_2O_3$ aq. (15 ml) at 0 °C. The whole mixture was stirred for 10 min at rt and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude product **3a** was used for the next step without further purification.

The crude product **3a** was dissolved in Et_2NH (5 ml) and the reaction mixture was stirred for 30 min at rt. The mixture was directly concentrated and purified by silica gel column chromatography (hexane : EtOAc, 1 : 1) to afford hemilabile (*S*)-Segphos P–P=O **4a** (482 mg, 47%) as white powders. IR (nujol): ν=1173 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=4.81 (d, *J*=1.5 Hz, 1H), 5.22 (d, *J*=1.5 Hz, 1H), 5.64 (d, *J*=1.5 Hz, 1H), 5.68 (d, *J*=1.5 Hz, 1H), 6.54 (dd, *J*=3.4, 8.1 Hz, 1H), 6.61 (d, *J*=8.1 Hz, 1H), 6.73 (dd, *J*=1.6, 8.1 Hz, 1H), 6.97 (dd, *J*=8.1, 14.0 Hz, 1H), 7.18—7.47 (m, 16H), 7.58 (dd, *J*=1.6, 7.8 Hz, 1H), 7.63 (dd, *J*=1.6, 7.8 Hz, 1H), 7.66 (dd, *J*=1.6, 7.8 Hz, 1H), 7.70 (dd, *J*=1.6, 7.8 Hz, 1H). ^{31}P-NMR ($CDCl_3$) δ: 14.39 (s), 27.33 (s). FAB-MS: *m*/*z*=627 (M^++1). EI-MS: *m*/*z*=441 (M^+-PPh_2), 425 (bp). HR-MS (EI, M^+-PPh_2) *m*/*z* Calcd for $C_{26}H_{18}O_5P$: 441.0892; Found: 441.0884.

(*S*)-DM-Segphos P–P=O (**4b**): Pale yellow powders. IR (nujol): ν=1169 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=2.11 (s, 12H), 2.30 (s, 12H), 5.42 (d, *J*=1.6 Hz, 2H), 5.76 (d, *J*=1.6 Hz, 2H), 6.64 (d, *J*=8.1 Hz, 1H), 6.65 (d, *J*=8.1 Hz, 1H), 6.89 (d, *J*=8.1 Hz, 1H), 6.94 (br s, 2H), 6.95 (d, *J*=8.1 Hz, 1H), 7.08 (br s, 2H), 7.12 (br s, 2H), 7.16 (br s, 2H), 7.34 (br s, 2H), 7.39 (br s, 2H). ^{31}P-NMR ($CDCl_3$): δ=14.71 (s), 29.54 (s). FAB-MS: *m*/*z*=739 (M^++1). EI-MS: *m*/*z*=497 (M^+-PPh_2), 482, 481 (bp). HR-MS (EI, M^+-PPh_2) *m*/*z* Calcd for $C_{30}H_{26}O_5P$: 497.1518; Found: 497.1523.

(*S*)-DTBM-Segphos P–P=O (**4c**): Pale yellow powders. IR (nujol): ν=1172 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=1.32 (s, 36H), 1.35 (s, 36H), 3.66 (s, 6H), 3.67 (s, 6H), 5.12 (d, *J*=1.6 Hz, 2H), 5.71 (d, *J*=1.6 Hz, 2H), 6.69 (d, *J*=8.1 Hz, 2H), 6.75 (d, *J*=8.1 Hz, 2H), 7.42 (s, 2H), 7.47 (s, 2H), 7.57 (s, 2H), 7.62 (s, 2H). ^{31}P-NMR ($CDCl_3$): δ=14.88 (s), 27.83 (s). FAB-MS: *m*/*z*=1196 (M^++1). EI-MS: *m*/*z*=725 (M^+-PPh_2, bp), 497, 485. HR-MS (EI, M^+-PPh_2) *m*/*z* Calcd for $C_{44}H_{54}O_7P$: 725.3607; Found: 725.3609.

Representative Procedure for the Asymmetric Substitution (Entry 9, Table 1) To a stirred solution of (cyclohex-2-enyl)acetate (**5**) (56.1 mg, 0.400 mol) in toluene (1.2 ml) were added (*S*)-Segphos P–P=O **4a** (12.5 mg, 0.0200 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (3.7 mg, 0.0100 mmol), KOAc (2.0 mg, 0.0200 mmol), dibenzyl malonate (0.30 ml, 1.20 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (0.30 ml, 1.20 mmol) at rt. The reaction mixture was stirred for 24 h at the same temperature. After usual work-up, purification by silica gel column (hexane/EtOAc, 20 : 1, the silica gel was pretreated with 3% Et_3N in hexane) gave 2-cyclohex-2-enylmalonic acid dibenzyl ester (**6**) (130 mg, 89%, 64% ee) as a colorless oil. The ee was determined by HPLC analysis (Daicel chiralpak AD-H) using hexane/2-propanol (9 : 1) as eluent, flow rate=1.0 ml/min. t_{R1}=8.1 min, t_{R2}=10.1 min. IR (neat): ν=1727 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=1.26—1.82 (m, 4H), 1.88—2.00 (m, 2H), 2.87—3.01 (m, 1H), 3.38 (d, *J*=9.2 Hz, 1H), 5.13 (s, 4H), 5.52 (dd, *J*=2.2, 10.3 Hz, 1H), 5.68—5.77 (m, 1H), 7.20—7.41 (m, 10H). ^{13}C-NMR ($CDCl_3$): δ=20.95, 24.94, 26.61, 35.41, 57.03, 66.91, 127.25, 127.99, 128.00, 128.10, 128.12, 128.35, 129.43, 135.26, 135.28, 167.90, 167.96. FAB-MS: *m*/*z*=365 (M^++1). EI-MS: *m*/*z*=273 (M^+-Bn), 229, 183, 91 (bp). HR-MS (EI, M^+-Bn) *m*/*z* Calcd for $C_{16}H_{17}O_4$: 273.1127; Found: 273.1123.

2-Cyclopent-2-enylmalonic Acid Dibenzyl Ester (**8**): Colorless oil. IR (neat): ν=1751, 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=1.53—1.68 (m, 1H), 2.02—2.16 (m, 1H), 2.20—2.40 (m, 2H), 3.36 (d, *J*=9.2 Hz, 1H), 3.35—3.46 (m, 1H), 5.14 (s, 4H), 5.60—5.65 (m, 1H), 5.76—5.82 (m, 1H), 7.23—7.39 (m, 10H). ^{13}C-NMR ($CDCl_3$): δ=27.77, 31.80, 45.43, 56.98, 66.94, 66.97, 128.03, 128.04, 128.07, 128.17, 128.40, 131.13, 132.98, 135.27, 168.20, 168.26. FAB-MS: *m*/*z*=351 (M^++1). EI-MS: *m*/*z*=259 (M^+-Bn), 215, 169, 91 (bp). HR-MS (EI, M^+-Bn) *m*/*z* Calcd for $C_{15}H_{15}O_4$: 259.0970; Found: 259.0970.

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