

Development of Novel Hemilabile Segphos P–P=O Ligands

Yoshimasa FUKUDA, Kazuhiro KONDO,* and Toyohiko AOYAMA*

Graduate School of Pharmaceutical Sciences, Nagoya City University; 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan. Received March 17, 2007; accepted April 7, 2007; published online April 10, 2007

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 $\text{BH}_3 \cdot \text{THF}$ 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)}

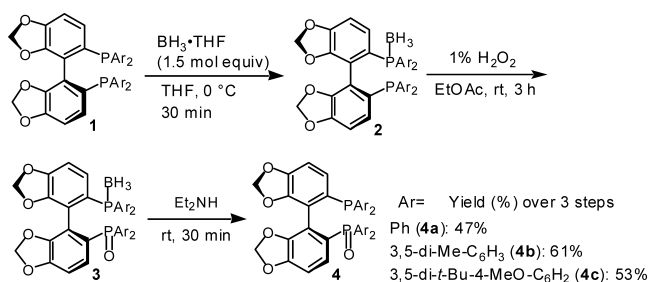


Chart 1. Synthesis of Hemilabile Segphos P–P=O Derivatives

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. ^1H - (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 silylia 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.

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 $\text{BH}_3 \cdot \text{THF}$ (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 $\text{Na}_2\text{S}_2\text{O}_3$ 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): $\nu=1173\text{ cm}^{-1}$. $^1\text{H-NMR}$ (CDCl_3): $\delta=4.81$ (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). $^{31}\text{P-NMR}$ (CDCl_3): $\delta=14.39$ (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 $\text{C}_{26}\text{H}_{18}\text{O}_5\text{P}$: 441.0892; Found: 441.0884.

(S)-DM-Segphos P=P=O (**4b**): Pale yellow powders. IR (nujol): $\nu=1169\text{ cm}^{-1}$. $^1\text{H-NMR}$ (CDCl_3): $\delta=2.11$ (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 (brs, 2H), 6.95 (d, $J=8.1$ Hz, 1H), 7.08 (brs, 2H), 7.12 (brs, 2H), 7.16 (brs, 2H), 7.34 (brs, 2H), 7.39 (brs, 2H). $^{31}\text{P-NMR}$ (CDCl_3): $\delta=14.71$ (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 $\text{C}_{30}\text{H}_{26}\text{O}_5\text{P}$: 497.1518; Found: 497.1523.

(S)-DTBM-Segphos P=P=O (**4c**): Pale yellow powders. IR (nujol): $\nu=1172\text{ cm}^{-1}$. $^1\text{H-NMR}$ (CDCl_3): $\delta=1.32$ (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). $^{31}\text{P-NMR}$ (CDCl_3): $\delta=14.88$ (s), 27.83 (s). FAB-MS: $m/z=1196$ (M^++1). EI-MS: $m/z=725$ (M^+-PPh_2), 497, 485. HR-MS (EI, M^+-PPh_2) m/z Calcd for $\text{C}_{44}\text{H}_{54}\text{O}_7\text{P}$: 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), $[(\eta^3\text{-C}_3\text{H}_5)_2\text{PdCl}]_2$ (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. $t_{\text{R}1}=8.1$ min, $t_{\text{R}2}=10.1$ min. IR (neat): $\nu=1727\text{ cm}^{-1}$. $^1\text{H-NMR}$ (CDCl_3): $\delta=1.26$ –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).

$^{13}\text{C-NMR}$ (CDCl_3): $\delta=20.95, 24.94, 26.61, 35.41, 57.03, 66.91, 127.25, 127.99, 128.00, 128.10, 128.12, 128.35, 129.43, 135.26, 135.28, 167.90, 167.96$. 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 $\text{C}_{16}\text{H}_{17}\text{O}_4$: 273.1127; Found: 273.1123.

2-Cyclopent-2-enylmalonic Acid Dibenzyl Ester (**8**): Colorless oil. IR (neat): $\nu=1751, 1732\text{ cm}^{-1}$. $^1\text{H-NMR}$ (CDCl_3): $\delta=1.53$ –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). $^{13}\text{C-NMR}$ (CDCl_3): $\delta=27.77, 31.80, 45.43, 56.98, 66.94, 66.97, 128.03, 128.04, 128.07, 128.17, 128.40, 131.13, 132.98, 135.27, 168.20, 168.26$. 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 $\text{C}_{15}\text{H}_{15}\text{O}_4$: 259.0970; Found: 259.0970.

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References and Notes

- 1) Kondo K., Kazuta K., Fujita H., Sakamoto Y., Murakami Y., *Tetrahedron*, **58**, 5209–5214 (2002).
- 2) Horibe H., Kazuta K., Kotoku M., Kondo K., Okuno H., Murakami Y., Aoyama T., *Synlett*, **2003**, 2047–2051 (2003).
- 3) Kondo K., Kazuta K., Saitoh A., Murakami Y., *Heterocycles*, **59**, 97–100 (2003).
- 4) Horibe H., Fukuda Y., Kondo K., Okuno H., Murakami Y., Aoyama T., *Tetrahedron*, **60**, 10701–10709 (2004).
- 5) Suzuki K., Ishii S., Kondo K., Aoyama T., *Synlett*, **2006**, 648–650 (2006).
- 6) Arao T., Suzuki K., Kondo K., Aoyama T., *Synthesis*, **2006**, 3809–3814 (2006).
- 7) Fukuda Y., Kondo K., Aoyama T., *Tetrahedron Lett.*, **48**, 3389–3391 (2007).
- 8) For a general synthetic method, see: Grushin V. V., *Chem. Rev.*, **104**, 1629–1662 (2004).
- 9) For the definition of hemilabile ligands, see: Braunstein P., Naud F., *Angew. Chem. Int. Ed.*, **40**, 680–699 (2001).
- 10) For a review, see: Trost B. M., Vranken D. L. V., *Chem. Rev.*, **96**, 395–422 (1996).
- 11) A selected successful example, see: Trost B. M., Bunt R. C., *J. Am. Chem. Soc.*, **116**, 4089–4090 (1994).
- 12) A selected successful example, see: Saitoh A., Misawa M., Morimoto T., *Tetrahedron: Asymmetry*, **10**, 1025–1028 (1999).
- 13) A selected successful example, see: Kudis S., Helmchen G., *Angew. Chem. Int. Ed.*, **37**, 3047–3050 (1998).
- 14) A selected successful example, see: Zhang W., Shimanuki T., Kida T., Nakatsuji Y., Ikeda I., *J. Org. Chem.*, **64**, 6247–6251 (1999).
- 15) A selected successful example, see: Evans D. A., Campos K. R., Tedrow J. S., Michael F. E., Gagné M. R., *J. Am. Chem. Soc.*, **122**, 7905–7920 (2000).
- 16) A selected successful example, see: Shibatomi K., Uozumi Y., *Tetrahedron: Asymmetry*, **13**, 1769–1772 (2002).
- 17) A selected successful example, see: Pámies O., Diéguez M., Claver C., *J. Am. Chem. Soc.*, **127**, 3646–3647 (2005).