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Synthesis of a Bulky and Electron-Rich Derivative of SEGPhos and Its Application in Ru-Catalyzed Enantioselective Hydrogenation of β-Ketoesters

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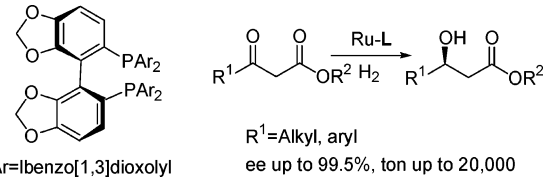

The synthesis and resolution of a bulky and electron-rich derivative of SEGPhos and its application in Ru-catalyzed asymmetric hydrogenation reaction of β-ketoesters are reported. Up to 99.5% ee was achieved. Under solvent-free reaction conditions, acetoacetates could be reduced with good enantioselectivity and high efficiency; a TON of 20 000 was obtained within 3.5 h. The results obtained were comparable to those when SEGPhos was applied.

Transition metal-catalyzed enantioselective hydrogenation has been established as one of the most efficient strategies for the synthesis of optically pure molecules, in which the reasonable design of chiral ligands is the key issue for obtaining high activity and selectivity.[1,2] Over the past 30 years, thousands of chiral ligands have been synthesized to effect a variety of catalytic asymmetric hydrogenation processes in both academic research and industrial production.[1,2] Many atropisomeric C_2-symmetric biaryl biphosphines such as BINAP,[3] BIPHEMP,[4] MeO-BIPHEP,[4] TunePhos,[5] P-Phos,[6] SEGPhos,[7] Diflurophos,[8] and other important biaryl phosphine ligands[9] (Figure 1) have been developed in the past 20 years. Although tremendous success has been achieved in catalytic asymmetric hydrogenation, developing easily preparable, finely tunable, easily handled, cheap yet efficient ligands is still a challenging issue.

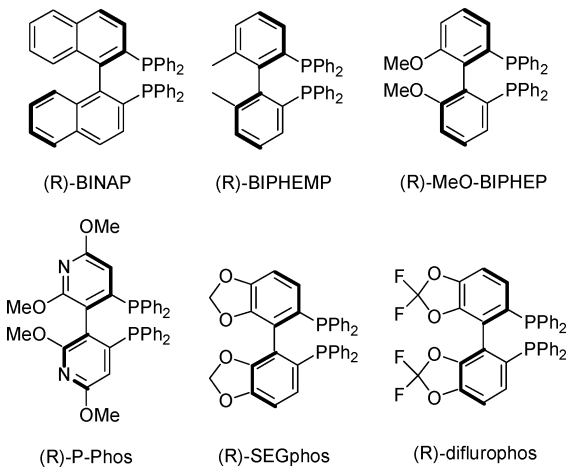

FIGURE 1. Some atropisomeric C_2-symmetric biaryl ligands.

Herein, we report the synthesis and resolution of a bulky and electron-rich derivative of SEGPhos (Scheme 1) and its application in Ru-catalyzed asymmetric hydrogenation reaction. The synthetic route was concise and straightforward: Grignard reagent of 5-bromo-benzo[1,3]-dioxole (**1**) was slowly added to a solution of PCl_3 in dry THF, followed by oxidation with H_2O_2 to provide (**2**). Treatment of (**2**) with 1.2 equiv of LDA at −15 °C for 4 h and oxidative coupling with anhydrous ferric chloride afforded **3** in moderate yield (42.1%). Optical resolution of **3** was performed by employing (−)-2,3-dibenzoyl tartaric acid ((−)-DBTA) as a resolving agent in *i*-PrOH. At last, a steric and electron-rich biaryl ligand (**4**) was

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(1) (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008, and references therein. (b) Knowles, W. S. *Adv. Synth. Catal.* **2003**, *345*, 3. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (d) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley: New York, 2000. (e) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.

(2) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(3) (a) Miyashita, A.; Yasuda, H.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc*. **1980**, *102*, 7932. (b) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (c) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187.

(4) (a) Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897. (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370. (c) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure. Appl. Chem.* **1996**, *68*, 131.

(5) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223.

(6) (a) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W.-K. *J. Am. Chem. Soc.* **2000**, *122*, 11513. (b) Wu, J.; Chen, H.; Kwok, W.; Guo, R.; Zhou, Z.; Yeung, C.; Chan, A. S. C. *J. Org. Chem.* **2002**, *67*, 7908. (c) Wu, J.; Chen, H.; Kwok, W.-H.; Lam, K.-H.; Zhou, Z.-Y.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1539.

(7) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(8) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed*. **2004**, *43*, 320.

(9) (a) Yamamoto, N.; Masano, M.; Toshiaki, M.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 1085. (b) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, *16*, 2039. (c) Enev, V.; Ewers, Ch. L. J.; Harre, M.; Nickisch, K.; Mohr, J. T. *J. Org. Chem.* **1997**, *62*, 7092. (d) Gelpke, A. E. S.; Kooijman, H.; Spek, A. L.; Hiemstra, H. *Chem. Eur. J.* **1999**, *5*, 2472. (e) Henschke, J. P.; Burk, M. J.; Malan, C. G.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300. (f) Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2501. (g) Pai, C.-C.; Li, Y.-M.; Zhou, Z.-Y.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 2789. (h) Qiu, L.; Qi, J.; Pai, C.-C.; Chan, S.; Zhou, Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 4599. (i) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Tetrahedron Lett.* **2003**, *44*, 823. (j) Genêt, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908. (k) Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 2185.

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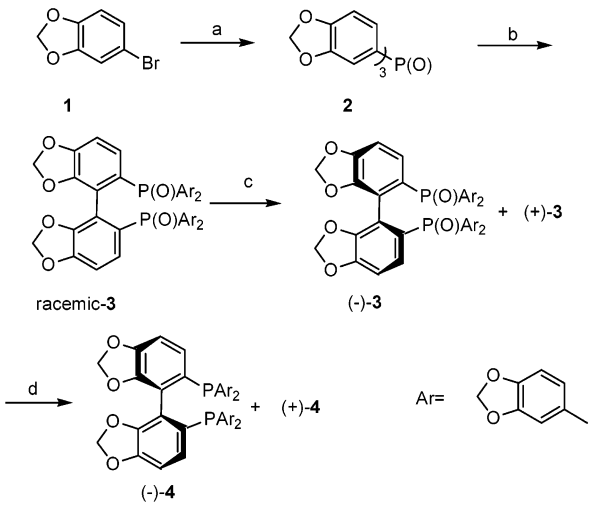
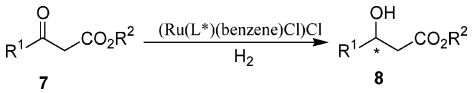
SCHEME 1. Synthesis of the Ligand[a]



[a] Conditions: (a) (i) Mg, THF; (ii) PCl_3; (iii) H_2O_2. (b) (i) LDA, −15 °C, 4 h; (ii) $FeCl_3$, 0 °C−rt, 4 h. (c) (i) (−)-DBTA, *i*-PrOH; (ii) NaOH. (d) $HSiCl_3$, $PhNMe_2$, reflux, 10 h.

TABLE 1. Asymmetric Hydrogenation of $R^1COCH_2CO_2R^2$ with (Ru(L*)(Benzene)Cl)Cl[a]



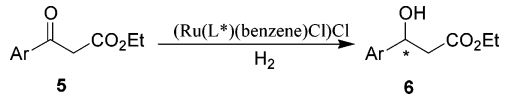
entry	R^1/R^2 (**7**)	temp (°C)	time (h)	ee (%)[b]
1	Me/Et (**7a**)	65	20	99.1
2	Me/Et (**7a**)	65	20	99.2[c]
3	Me/*i*-Pr (**7b**)	65	20	99.5
4	Me/^{t}Bu (**7c**)	65	20	99.2
5	^{t}Bu/Et (**7d**)	65	20	94.9[d,e]
6	^{t}Bu/Et (**7d**)	65	20	94.8[c]
7	^{t}Bu/Et (**7d**)	90	6	98.1
8	^{t}Bu/Et (**7d**)	90	6	98.6[c]
9	$ClCH_2$/Et (**7e**)	65	20	93.2[f]
10	$ClCH_2$/Et (**7e**)	65	20	93.6[c]
11	$ClCH_2$/Et (**7e**)	90	6	96.6
12	$ClCH_2$/Et (**7e**)	90	6	96.4[c]

[a] All reactions were carried out in EtOH with a substrate concentration of 0.5 M and 30 atm of H_2. Substrate/[Ru(benzene)Cl_2]$_2$/ligand = 200/0.5/1.1, conversion = 100%. [b] Ee values were determined by GC on a *β*-DEX 325 capillary column. [c] Ligand: Segphos. [d] Conversion = 76.2%. [e] Conversion = 75.3%. [f] Product was acylated to 3-acetoxy-4-chloro-butyric acid ethyl ester (**9e**) in pyridine and acetic anhydride. Ee (%) of **9e** was determined by GC on a *β*-DEX 325 capillary column.

obtained by reducing **3** with $HSiCl_3$. It is noteworthy that all of intermediates and our ligand are stable in air for at least one month. Furthermore, every reagent is cheap and the overall synthesis steps are easy to handle.

To test the synthetic utility of our ligand, we have explored the Ru-catalyzed asymmetric hydrogenation of *β*-ketoesters. Our ligand is excellent for the asymmetric reduction of alkyl acetoacetates; a high ee was obtained, regardless of the bulkiness of the alkyl group (Table 1, entries 1−4). When 4,4-dimethyl-3-oxo-pentanoic acid ethyl ester (**7d**) and 4-chloro-3-oxo-butyric acid ethyl ester (**7e**) were employed as a substrate for the asymmetric reduction, their ee values were highly dependent on the reaction temperature: the ees increased greatly if the reaction temperature was elevated (Table 1, entries 5, 7, 9, 11). Analogous results were obtained when SEGPhos was applied at the same conditions (Table 1, entries 2, 6, 8, 10, 12).

TABLE 2. Asymmetric Hydrogenation of $ArCOCH_2CO_2Et$[a]



entry	Ar	ee (%)
1	Ph (**5a**)[c]	96.9
2	Ph (**5a**)[b]	96.5
3	4-MeO-C_6H_4 (**5b**)[d]	93.2
4	4-MeO-C_6H_4 (**5b**)[b]	93.0
5	4-Me-C_6H_4 (**5c**)[d]	96.0
6	4-Br-C_6H_4 (**5d**)[e]	96.7
7	4-Cl-C_6H_4 (**5e**)[e]	96.6
8	4-F-C_6H_4 (**5f**)[c]	97.1
9	3-Me-C_6H_4 (**5g**)[c]	96.2
10	3-Cl-C_6H_4 (**5h**)[e]	95.3
11	2-Me-C_6H_4 (**5i**)[e]	96.7

[a] All reactions were carried out at 65 °C with a substrate concentration of 0.5 M and 30 atm of H_2 in EtOH for 20 h. Additive: HI. Substrate/[Ru(benzene)Cl_2]/ligand/additive = 200/0.5/1.1/1.5, conversion = 100%. [b] Ligand: Segphos. [c] Ee values were determined by HPLC on Chiralpak OD-H column. [d] Ee values were determined by HPLC on Chiralpak AS−H column. [e] Ee values were determined by HPLC on Chiralpak AD-H column.

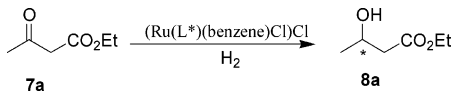
Our ligand is also fruitful in the asymmetric hydrogenation of 3-oxo-3-arylpropionic acid ethyl esters (**5**); good enantioselectivity was obtained. The enantiomeric excess of (**6**) was comparable to that obtained when SEGPhos was employed as a ligand (Table 2, entries 2, 4) and better than when BINAP (89.3% ee)[9i] or MeO-BIPHEP (74.8% ee)[7] was used. Hydrogenation of **5** was not sensitive to substituents (*o*-, *m*-, and *p*- and electron-denoting or electron-withdrawing) on the aromatic ring (Table 2).

Although thousands of chiral phosphorus ligands have been obtained for the asymmetric hydrogenation process, the development of truly efficient and practical catalytic process is still a challenging topic because of the expensive noble metal, chiral ligand and/or high catalyst loadings.[1,2] Solvent-free reaction is a cost-effective, safe, and environmentally benign process.[10] Herein, we report the solvent-free catalytic enantioselective hydrogenation of ethyl acetoacetates (**7a**) with extremely low catalyst loading. Under the solvent-free conditions, the reaction was accelerated with the sacrifice of enantioselectivity. Interstingly, addition of catalytic sulfuric acid elevates both the reaction rate and the enantioselectivity with high TON (Table 5, TON = 20 000). Unfortunately, the reason for the dramatic effect of sulfuric acid was unclear, and further study is in progress. Similar results were obtained when SEGPhos was applied under the same conditions (Table 3, entries 2, 4, 6, 8).

In conclusion, we have developed a steric and electron-rich biphosphine ligand that was analogous to SEGPhos and applied it in Ru-catalyzed enantioselective hydrogenation of aryl- and alkyl-substituted *β*-ketoesters, and high enantioselectivity was achieved. Solvent-free, highly enantioselective hydrogenation with extremely low cata-

(10) Tokunaga, M.; Larrow, J. F.; KaKiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

TABLE 3. Asymmetric Hydrogenation of 7a under Solvent-Free Conditions[a]



7a 8a

entry	additive	conversion (%)	ee (%)
1[c]		35.9	96.0
2[b,c]		35.7	96.6
3		56.8	91.6
4[b]		62.5	88.4
5[d]	H_2SO_4	100	96.8
6[b]	H_2SO_4	100	97.5

[a] All reactions were carried out with a ratio of 20 000:1 (substrate/catalyst) at 30 atm of H_2, 110 °C for 3.5 h. [b] Ligand: Segphos. [c] Solvent: EtOH, concentration = 1.0 M. [d] Additive/[Ru] = 1.5:1.

lyst loading was reported. Extension of the scope of the substrate and development of its application in asymmetric C−C bond-forming reactions are in progress.

Experimental Section

General and Materials. All manipulations involving air-sensitive reagents were carried out under an argon atmosphere. The hydrogenation reactions were performed in a 300 mL stainless steel autoclave. All solvents were dried using standard procedure.

Preparation of 2. Under an argon atmosphere, a mixture of magnesium turnings (2.64 g, 0.11 mol) and trace iodine was added dropwise to a solution of 5-bromo-benzo[1,3]dioxole (**1**, 20.1 g, 0.10 mol) in dry THF (100 mL). The reaction mixture was further stirred for 1 h at refluxing temperature. After the reaction mixture was cooled to room temperature, a solution of PCl_3 (2.9 mL, 33.3 mmol) in 50 mL of dry THF was added dropwise, and the reaction mixture was further stirred for 2 h at refluxing temperature. When the reaction mixture was cooled to room temperature again, 30 mL of H_2O was added dropwise to quench the reaction. THF was removed, and 100 mL of CH_2Cl_2 and 70 mL of H_2O were introduced; the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). To the combined organic layer was added an aqueous H_2O_2 solution (30%, 12.0 mL) in an ice bath. After the reaction was complete and quenched with $NaHSO_3$, the mixture was purified by silica gel column chromatography (eluent: EtOAc/hexane 2/1) to give the product (**2**): 11.9 g. Yield: 87.3%. Mp: 152−4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20−6.86 (m, 9 H), 6.02 (s, 6 H). ^{31}P NMR (300 MHz, $CDCl_3$): δ 30.7. IR (KBr, cm^{-1}): 3022, 1600, 1505, 1480, 1419, 1243, 1066. MS (ESI): *m/z* 411.1 $(M + 1)^+$. EA (%): Anal. Calcd for $C_{21}H_{15}O_7P$: C, 61.46; H, 3.66; P, 7.55. Found: C, 61.17; H, 3.59; P, 7.41. HRMS (ESI): Anal. Calcd for $C_{21}H_{15}O_7NaP$ 433.0449, found 433.0448.

Preparation of (±)-3. Under an argon atmosphere, LDA (84 mmol, 1 M solution in THF) was added dropwise to a mixture of **2** (28.7 g, 70 mmol) and THF (140 mL) at −15 °C. After stirring for an additional 4 h, a solution of $FeCl_3$ (13.7 g, 84 mmol) in 120 mL of THF was introduced to the reaction mixture. The temperature was increased to 0 °C and held constant for 2 h, and 30 mL of H_2O was added to this reaction mixture. The crude product was purified by silica gel column chromatography (eluent: EtOAc/hexane 3/1) to give the product (±)-**3**: 12.0 g. Yield: 42.1%. Mp: 237−239 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16−6.64 (m, 16 H), 5.99−5.60 (m, 12 H). ^{31}P NMR (300 MHz, $CDCl_3$): δ 30.79. MS (ESI): *m/z* 819.0 $(M + 1^+)$. IR (KBr, cm^{-1}): 3396, 2900, 1480, 1423, 1243, 1037. HRMS (ESI): Anal. Calcd for $C_{42}H_{29}O_{14}P_2$ 819.1059, found 819.1027.

Optical Resolution of (±)-3. A mixture of (±)-**3** (14.7 g, 18 mmol), (−)-DBTA (10.7 g, 30 mmol), and *i*-PrOH (100 mL) was stirred at reflux for 1 h. The precipitates were washed with *i*-PrOH to give the complex (−)-**3**−(−)-DBTA. The complex was treated with a mixture of CH_2Cl_2 (100 mL) and 2 N NaOH (50 mL). The organic layer was washed with water, evaporated, and dried under vacuum to give (−)-**3**: 6.47 g. Yield: 44%. ^{1}H NMR, ^{31}P NMR, IR, MS (ESI), and HRMS (ESI) were identical to (±)-**3**. $[\alpha]^{20}_D$: −90.3° (*c* 0.985, $CHCl_3$).

Preparation of (−)-4. A mixture of (−)-**3** (0.818 g, 1 mmol), *N*,*N*-dimethylaniline (1.4 mL, 10 mmol), and trichlorosilane (1.01 mL, 10 mmol) was stirred in toluene (11 mL) at 110 °C for 10 h. After the solution was cooled to 0 °C, a deoxygenated 15% sodium hydroxide solution (50 mL) was added carefully. The organic layer was washed with water, evaporated, and purified by silica gel column chromatography (eluent: EtOAc/hexane 1/8) to give (−)-**4**: 0.72 g. Yield: 91.6%. Mp: 126−8 °C. $[\alpha]^{20}_D$: −10.3° (*c* 0.85, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79−6.59 (m, 16 H), 5.92−5.45 (m, 12 H). ^{31}P NMR (300 MHz, $CDCl_3$): δ −10.3. IR (KBr, cm^{-1}): 2889, 1481, 1234, 1039. MS (ESI): *m/z* 787.1 $(M + 1^+)$. HRMS (ESI): Anal. Calcd for $C_{42}H_{29}NaO_{12}P_2$ 787.1139, found 787.1129.

Asymmetric Hydrogenation of β-Ketoesters. To a 10 mL Schlenk tube were added $[Ru(benzene)Cl_2]_2$ (10 mg, 0.02 mmol) and (−)-**4** (34.6 mg, 0.044 mmol). The tube was purged with Argon three times before addition of freshly distilled and degassed EtOH/CH_2Cl_2 (3 mL/3 mL). The resulting mixture was heated at 50 °C for 1 h. The catalyst was dried under reduced pressure and taken into a glovebox in a dry nitrogen atmosphere and dissolved in degassed ethanol (16 mL). The solution (2 mL) was added to each vial containing β-keto ester (1 mmol), and these vials were taken into a Parr bomb. The reaction was carried out at the desired hydrogen pressure and temperature for a designated period of time. The solvent was removed, and the residue was passed through a short silica gel column to give the product. The enantiomeric purity of the product was determined by GC or HPLC.

Asymmetric Hydrogenation of Ethyl Acetoacetates (7a) under Solvent-Free Conditions. The preparation of catalyst ($[Ru(benzene)Cl_2]_2$ (10 mg, 0.02 mmol) and (−)-**4** (34.6 mg, 0.044 mmol)) was the same as above. A mixture of the catalyst, sulfuric acid (5.9 mg, 0.06 mmol), and ethylacetoacetates (**7a**) (104 g, 0.8 mol) was transferred into a Parr bomb. The reaction was conducted at 30 atm and 110 °C for 3.5 h. The enantiomeric purity of the product was determined by GC.

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Supporting Information Available: GC, HPLC, and NMR data of compounds **1**−**4**, **6a**−**h**, and **8a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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