Ligand Substituent Effects on Asymmetric Induction. Effect of Structural Variations of the DIOP Ligand on the Rh-Catalyzed Asymmetric Hydrogenation of Enamides

Yuan-Yong Yan and T. V. RajanBabu*
Department of Chemistry, The Ohio State University, 100 W. 18th Avenue, Columbus, OH 43210

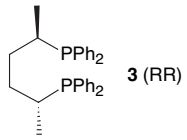
Supporting Information

General. All anaerobic reactions were carried out an inert atmosphere of nitrogen in a Vacuum Atmospheres drybox, or using Schlenk techniques. Methylene chloride was distilled from calcium hydride under nitrogen and stored over molecular sieves. Tetrahydrofuran (THF), diethyl ether, hexane and toluene were distilled under nitrogen from sodium / benzophenone ketyl. All chemicals were purchased from Aldrich Chemical Company or ACROS Company unless otherwise noted. Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel-60 F_{254} plates. Column chromatography was conducted by using silica gel 40 (Scientific Adsorbents Inorprated, Microns Flash). ^{1}H NMR, ^{13}C NMR spectra were recorded on a Brucker AM-400 spectrometers in $CDCl_3$. ^{31}P NMR spectrum was recorded on a Brucker AM-250 spectrometer in $CDCl_3$. Gas chromatographic analyses were performed on a Hewlett-Packard 5890 equipped with an HP-ultra-1 crosslinked methyl silicone capillary column (25 m length × 0.2 mm i.d.) and an FID detector connected to an HP 3396 integrator. As carrier gas helium was used. All the enamide substrates were prepared following reported procedures from the corresponding ketones [1]

The hydrogenation reactions were carried out as follows. In a drybox, a Fisher-Porter tube was charged with the enamide substrate (0.1 mmol), the appropriate solvent (2 mL) and preformed $Rh^{+}L^{*}(COD)\ X^{-}$ (1 mol%). After sealing, the tube was removed from the drybox and placed behind proper shielding. After five vacuum-refilling cycles with hydrogen, the tube was brought to the appropriate pressure (20 or 40 psi) of H_2 and the mixture was vigourously stirred for 10 h. After removing the catalyst on a plug of silica gel, the ee's of the product were determined by chiral GC (Chirasil-L-Val on WCOT fused silica 25m X 0.25 mm).

Synthesis of Ligands

*(2R,5R)-2,5-bis-(diphenylphosphino)-hexane (**3**).*



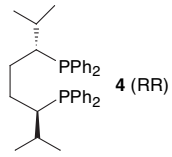
3 (RR)

*(2S,5S)-2,5-di-O-methanesulfonyloxyhexane (**10**-dimesylate).* To a mixture of 1.11 g (10.8 mmol) of (2*S*,5*S*)-2,5-hexanediol (**10**) and 20 mg of DMAP in 10 mL of pyridine and 5 mL of CH_2Cl_2 was added 3.3 mL (42.6 mmol) of methanesulfonyl chloride at 0 °C (ice bath). After stirring for 4 h at the same temperature, the reaction mixture was poured into 50 mL of ice-cold 2N HCl solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were successively with 30 mL of H_2O, saturated $NaHCO_3$ solution washed and dried with anhydrous $MgSO_4$. Removal of the solvent on evaporator gave the crude product which was purified by column chromatography on silica gel (elution with ethyl acetate / hexane 3/7) to get 2.73 g (92%) of the dimesylate as an oil. ^{1}H NMR ($CDCl_3$): δ 1.38 (d, J = 6.3 Hz, 6 H), 1.75 (m, 4 H), 2.97 (s, 6 H), 4.80 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 20.96, 31.77, 38.49, 78.78.

*(2R,5R)-2,5-bis-(diphenylphosphino)-hexane (**3**).* In a Schlenk tube, 1.9 mL of n-BuLi (1.6 M solution in hexane) was added dropwise to a solution of diphenyphosphine (0.466 g, 2.5 mmol) in 10 mL of THF via syringe at 0 °C (ice bath). The mixture was stirred for 1 h at room temperature. To the resulting deep red solution was added slowly (2*S*,5*S*)-2,5-dimethanesulfonyloxyhexane (**10**-dimesylate**,** 0.274 g, 1.0 mmol) in 4 mL of THF, and the mixture was stirred for an additional 4 h at ambient temperature. A few drops of methanol were added to quench any excess n-BuLi. The solvent was pumped off, and the residue was partitioned between 15 mL of Et_2O and 8 mL of saturated NH_4Cl solution (degassed). The organic phase was separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered through a short column of silica gel. The solvent was distilled off under reduced pressure. The crude product was purified by recrystallization from Et_2O and hexane (5 / 95) gave 0.24 g (52.8 %) of (2*R*,5*R*)-2,5-*bis*-(diphenylphosphino)hexane (**3**) as white powder. Elemental analysis Calcd for $C_{30}H_{32}P_2$: C, 79.26, H, 7.10. Found: C, 79.16, H, 7.26. ^{1}H NMR ($CDCl_3$): δ 0.91 (d, J = 6.9 Hz, 3 H) 0.95 (d, J = 6.8 Hz, 3 H), 1.44 (m, 2 H), 1.56 (m, 2 H), 2.23 (m, 2 H), 7.23 (m, 12 H), 7.46 (m, 8 H). 13C NMR (CDCl3): δ 15.92, 16.08, 29.89, 29.98, 31.30 (t, J = 14.9 Hz), 128.18,

128.25, 128.31, 128.34, 128.59, 128.65, 133.33, 133.52, 133.59, 133.78, 137.28 (d, J = 12.5 Hz), 137.42 (d, J = 11.8 Hz). ^{31}P NMR ($CDCl_3$): δ -0.28 (s).

*(3R, 6R)-2,7-dimethyl-3,6-bis-(diphenylphosphino)-octane (**4**).*

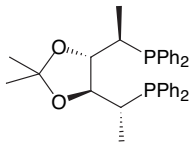


4 (RR)

(3*S*,6*S*)-2,7-dimethyl-3,6-di-O-methanesulfonyloxyoctane (**11**-dimesylate). To a mixture of 1.03 g (6.0 mmol) of (3*S*,6*S*)-2,7-dimethyloctane-3,6-diol (**11**) and 20 mg of DMAP in 10 mL of pyridine and 5 mL of CH_2Cl_2 was added 1.8 mL (23.2 mmol) of methanesulfonyl chloride at 0 °C (ice bath). After stirring for 4 h at the same temperature, the reaction mixture was poured into 50 mL of ice-cold 2 N HCl solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were successively with 30 mL of H_2O, saturated $NaHCO_3$ solution washed and dried with anhydrous $MgSO_4$. Removal of the solvent on evaporator gave the crude product which purified by column chromatography on silica gel (elution with ethyl acetate / hexane 3/7) to get 1.73 g (87%) of the dimesylate as an white powder. ^{1}H NMR ($CDCl_3$): δ 0.97 (d, J = 6.5 Hz, 6 H), 0.98 (d, J = 6.5 Hz, 6 H), 1.79 (m, 4 H) 2.00 (m, 2 H), 3.01 (s, 6 H), 4.59 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 17.60, 17.97, 26.55, 31.56, 38.67, 87.30.

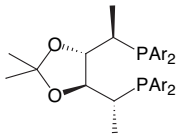
*(3R, 6R)-2,7-dimethyl-3,6-bis-(diphenylphosphino)-octane (**4**).* In a Schlenk tube, 1.9 mL of n-BuLi (1.6 M solution in hexane) was added dropwise to a solution of diphenyphosphine (0.466 g, 2.5 mmol) in 10 mL of THF via syringe at 0 °C (ice bath). The mixture was stirred for 1 h at room temperature. To the resulting deep red solution was added slowly (3S, 6S)-2,7-dimethyl-3,6-dimethanesulfonyloxyoctane (**11**-dimesylate, 0.330 g, 1.0 mmol) in 5 mL of THF, and the mixture was stirred for an additional 4 h at ambient temperature. A few drops of methanol were added to quench any excess n-BuLi. The solvent was pumped off, and the residue was partitioned between 15 mL of Et_2O and 8 mL of saturated NH_4Cl solution (degassed). The organic phase was separated, and the aqueous phase was extracted with Et_2O (2×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered through a thin lay silica gel. The solvent was distilled off under reduced pressure. The crude was purified by recrystallization from Et_2O and hexane (5 / 95) gave 0.290 g (57%) of (3R, 6R)-2,7-dimethyl-3,6-bis-(diphenylphosphino)-octane **4** as white powder. Elemental analysis Calcd for $C_{34}H_{40}P_2$: C, 79.96, H, 7.90. Found: C, 79.49, H, 7.90. ^{1}H NMR ($CDCl_3$): δ 0.81 (d, J = 6.9 Hz, 6 H), 0.87 (d, J = 6.9 Hz, 6 H), 1.22 (m, 2 H), 1.45 (m, 2 H), 1.77 (m, 2 H), 2.08 (m, 2 H), 7.29 (m, 12 H), 7.44 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 18.97, 19.08, 21.97, 22.07,

28.19 (dd, J = 7.9, 15.3 Hz), 28.56, 28.71, 128.13, 128.21, 128.30, 128.43, 128.64, 133.29, 133.49, 134.07, 134.27, 137.67 (d, J = 15.0 Hz), 138.34 (d, J = 14.6 Hz). ^{31}P NMR ($CDCl_3$): δ -7.29 (s).



5 (RSSR)

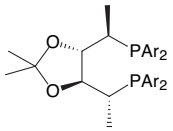
[[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]di(R)-ethylidene]bis[diphenylphosphine] ***(5)***. To a solution of diphenylphosphnine (0.409 g, 2.2 mmol) in 10 mL of THF at 0 °C, n-BuLi (1.9 mL, 3.0 mmol, 1.6 M in hexane) was added dropwise and the mixture was stirred for 1 h at room temperature. To the resulting deep red solution was added a solution of (2*S*,3*S*,4*S*,5*S*)-2,5-di-*O*-methanesulfonyl3,4-O-isopropylidenehexanetetraol (0.346 g, 1 mmol) in 5 mL of THF. The mixture was stirred for 6 h at room temperature. A few drops of methanol were added to quench any excess n-BuLi. The solvent was pumped off, collecting the volatile materials at liquid nitrogen temperature. The crude product was purified by flash chromatography eluting with ether-hexane (5:95, v/v, in the dry box) to obtain 0.332 g (63%) of the diphosphine **5** as a white solid. Elemental analysis: calcd for $C_{33}H_{36}O_2P_2$.: C, 75.27, H, 6.89. Found: C, 75.36, H, 6.90. ^{1}H NMR ($CDCl_3$): δ 0.88 ppm (d, J = 6.9 Hz, 3 H), 0.92 ppm (d, J = 6.9 Hz, 3H), 1.36 ppm (s, 6 H), 2.48 ppm (m, 2 H), 3.78 ppm (m, 2 H), 7.35 ppm (m, 12 H), 7.54 ppm (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 10.51 ppm (d, J = 17.2 Hz), 26.86 ppm, 31.07 ppm (d, J = 13.9 Hz), 76.80 ppm, (t, J = 6.1 Hz), 108.00 ppm, 128.26 ppm, 128.33 ppm, 128.85 ppm, 128.87 ppm, 133.49 ppm, 133.58 ppm, 133.69 ppm, 133.78 ppm, 136.20 ppm (d, J = 15.0 Hz), 136.73 ppm (d, J = 15.2 Hz). ^{31}P NMR ($CDCl_3$): δ -5.42 ppm (s).



6 (RSSR) [Ar = 3,5-$(Me)_2$-C_6H_3)

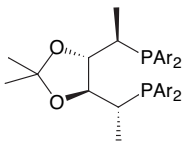
[[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]di(R)-ethylidene]bis-[di(3,5-dimethyl-phenyl)phosphine] ***(6)***. In a 50 mL of Schlenk tube was charged 83 mg (11.9 mmol) of lithium strips, 5 mL of anhydrous THF and 0.221 g (0.8 mmol) of *bis*-(3,5-dimethylphenyl)chlorophosphine. The mixture was stirred at room temperature for 1 h. The excess of lithium strips was fetched out by a spatula. The resultant deep red solution was added to a solution of 1,6-dideoxy-3,4-*O*-isopropylidene-L-iditol dimethanesulfonate (0.110 g, 0.32 mmol) in 3 mL of the same solvent over a period of 10 min. at 0 °C. The mixture was stirred for 8 h at room temperature. The solvent was pumped off, and the residue was purified by flash chromatography on silica gel (elution with ether-

hexane, 5:95, v/v, in the drybox) to get 0.090 g (44%) of the bisphosphine **6** as a white powder. Elemental analysis calcd. for $C_{41}H_{52}O_2P_2$: C, 77.07, H, 8.21. Found: C, 76.96, H, 8.28. ^{1}H NMR ($CDCl_3$): δ 0.85 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.9 Hz, 3 H), 1.33 (s, 6 H), 2.28 (s, 12 H), 2.32 (s, 12 H), 2.47 (m, 2 H), 3.76 (dd, J = 2.1, 3.6 Hz, 2 H), 6.94 (s, 2 H), 6.98 (s, 2 H), 7.15 (s, 4 H), 7.17 (s, 4 H). ^{13}C NMR ($CDCl_3$): δ 10.31 (d, J = 17.7 Hz), 21.29 (d, J = 8.2 Hz), 26.96, 30.67 (d, J = 13.9 Hz), 76.75 (dd, J = 6.6, 11.6 Hz), 108.09, 130.56, 130.68, 131.14, 131.29, 131.34, 131.50, 136.30 (d, J = 14.7 Hz), 136.56 (d, J = 14.7 Hz), 137.58, 137.60, 137.66, 137.67. ^{31}P NMR ($CDCl_3$): δ -5.51 (s).



7 (RSSR) [Ar = 3,5-$(CF_3)_2$-C_6H_3)

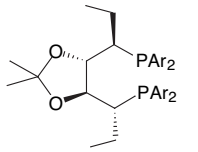
[[(4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]di(R)-ethylidene]bis-{di[(3,5-di(trifluoromethyl)phenyl]phosphine} (7). To a suspension solution of KH (44 mg, 1.1 mmol) in THF (5 mL) was added dropwise bis[3,5-di(trifluoromethyl)phnyl]phosphine, $[3,5\text{-}(CF_3)_2C_6H_3]_2PH$[2a] (412 mg, 0.9 mmol) in THF (3 mL) at -78 °C. Then the solution was warmed up to room temperature and stirring was continued for 1 h. To the purple phosphide solution was added a solution of 1,6-dideoxy-3,4-*O*-isopropylidene-L-iditol dimethanesulfonate (120 mg, 0.34 mol) in THF (2 mL) and the mixture was stirred for 6 h at room temperature. A few drops of methanol were added to quench the reaction. The solvent was removed in vacuum, and the residue was purified by flash chromatography on silica gel (elution with ether-hexane, 5:95, v/v, in the dry box) to get 0.237 g (64%) of the bisphosphine **7** as an oil. ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 1.23 (s, 6 H), 2.59 (m, 2 H), 3.96 (m, 2 H), 7.86~7.94 (m, 12 H). ^{13}C NMR ($CDCl_3$): δ 10.47 (d, J = 12.8 Hz), 26.50, 31.44 (d, J = 16.9 Hz), 77.23 (t, J = 10.9 Hz), 109.18, 121.38, 121.62, 123.58, 124.09, 124.33, 131.92, 131.99, 132.08, 132.25, 132.41, 133.17, 133.49, 133.71, 138.10 (d, J = 22.4 Hz), 138.45 (d, J = 21.6 Hz). ^{31}P NMR ($CDCl_3$): δ 1.50 (s).



8 (RSSR) [Ar = 4-OMe-C_6H_3)

[[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]di(*R*)-ethylidene]bis[di(4-methoxyphenyl) phosphine] **(8)**. To a suspension solution of KH (80 mg, 2.0 mmol) in THF (10 mL) was added dropwise bis[4-methoxyphenyl]phosphine, $[4\text{-}(OMe)C_6H_4]_2PH$[2b] (380 mg, 1.54 mmol) in THF (5 mL) at -78 °C.

Then the solution was warmed up to room temperature and stirring was continued for 1 h. To the red phosphide solution was added a solution of 1,6-dideoxy-3,4-*O*-isopropylidene-L-iditol dimethanesulfonate (230 mg, 0.63 mol) in THF (5 mL) and the mixture was stirred overnight at room temperature. A few drops of methanol were added to quench the reaction. The solvent was removed in vacuum, and the residue was purified by flash chromatography on silica gel (elution with ether-hexane, 30:70, v/v, in the dry box) to get 0.181 g (44%) of the bisphosphine **8** as a white powder. Elemental analysis for $C_{37}H_{44}O_6P_2$. Calcd: C, 68.70, H, 6.86. Found: C, 68.56, H, 6.80. ^{1}H NMR ($CDCl_3$): δ 0.82 (d, J = 6.9 Hz, 3 H), 0.86 (d, J = 6.9 Hz, 3 H), 1.32 (s, 6 H), 2.35 (m, 2 H), 3.73 (m, 2 H), 3.78 (s, 6 H), 3.81 (s, 6 H), 6.86 (d, J = 8.5 Hz, 4 H), 6.90 (d, J = 11.6 Hz, 4 H), 7.45 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 10.46 (d, J = 17.6 Hz), 26.92, 31.46 (d, J = 12.8 Hz), 55.13, 76.72 (dd, J = 6.4, 12.0 Hz), 107.90, 113.93, 113.97, 114.00, 114.05, 127.41 (d, J = 12.2 Hz), 127.91 (d, J = 12.7 Hz), 134.81, 134.97, 135.01, 135.19, 160.22, 160.30. ^{31}P NMR ($CDCl_3$): δ -9.08 (s).



9 (RSSR)

*(3S,4S,5S,6S)-3,6-dimethanesulfonyloxy-di-O-isopropylidene-4,5-octanediol (**14**)*. To a mixture of 2.1 g (9.62 mmol) of (3*S*,4*R*,5*R*,6*S*)-4,5-isopropylidenedioxyoctane-3,6-diol[3] and 30 mg of DMAP in 10 mL of pyridine and 5 mL of CH_2Cl_2 was added slowly 1.95 mL (25.2 mmol) of methanesulfonyl chloride at 0 °C (ice bath). After stirring for 6 h at the same temperature, the reaction mixture was poured into 100 mL of ice-cold 2N HCl solution and extracted with CH_2Cl_2 (3×30 mL). The combined extracts were successively washed with 30 mL of H_2O, saturated $NaHCO_3$ solution and dried with anhydrous $MgSO_4$. Removal of the solvent on the evaporator gave the crude product which purified by column chromatography on silica gel (elution with ethyl acetate / hexane 30/70) to get 3.055 g (85 %) of the dimesylate as an oil. ^{1}H NMR ($CDCl_3$): δ 1.06 (t, J = 7.5 Hz, 6 H), 1.42 (s, 6 H), 1.86 (m, 4 H), 3.08 (s, 6 H), 4.15 (m, 2 H), 4.68 (t, J = 7.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 9.96, 25.02, 26.85, 38.79, 76.75, 81.10, 109.73.

*[(4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyl]di(R)-1-propylidene]bis-diphenylphosphine (**9**)*. To a solution of diphenylphosphine (0.409 g, 2.2 mmol) in 10 mL of THF at 0 °C was added 1.9 mL of n-BuLi (3.0 mmol, 1.6 M in hexane) and the mixture was stirred for 1 h at room temperature. To the resulting deep red solution was added a solution of **14** (0.375 g, 1 mmol) in 5 mL of THF. The mixture was stirred for 6 h at room temperature. A few drops of methanol were added to quench any excess n-BuLi. The solvent was pumped off. The crude product was purified by flash

chromatography eluting with ether-hexane (5:95, v/v, in the dry box) to obtain 0.296 g (53%) of the diphosphine **9** as white crystalline solid. Elemental analysis calcd for $C_{35}H_{40}O_2P_2$: C, 75.79, H, 7.27. Found: C, 75.79, H, 7.27. ^{1}H NMR ($CDCl_3$): δ 0.54 (t, J = 7.5 Hz, 6 H), 1.29 (m, 2 H), 1.33 (s, 6 H), 1.52 (m, 2 H), 2.18 (m, 2 H), 3.71 (m, 2 H), 7.27 (m, 6 H), 7.38 (m, 6 H), 7.49 (m, 4 H), 7.59 (m 4 H). ^{13}C NMR ($CDCl_3$): δ 14.37 (d, J = 9.8 Hz), 19.77 (d, J = 19.4 Hz), 26.91, 37.50 (d, J = 15.8 Hz), 77.18 (d, J = 6.2 Hz), 107.52, 128.14, 128.21, 128.32, 128.40, 128.92, 128.97, 133.73, 133.93, 134.13, 136.23 (d, J = 14.5 Hz), 136.84 (d, J = 16.6 Hz). ^{31}P NMR ($CDCl_3$): δ -6.95 (s).

References and Notes for Supporting Information

1. Burk M. J.; Casy G.; Johnson N. B. *J. Org. Chem.* **1998**, *63*, 6084.

2. (a) *Bis*-[3,5-di(trifloromethyl)phenyl]phosphine: Casey C.P.; Paulsen E.L.; Beuttenmueller .W.; Proft B.R.; Petrovich L.M.; Matter B.A.; Powell D.R. *J. Am. Chem. Soc.* **1997**, *119*, 11817. (b) (4-MeO-C_6H_4)$_2$PH was prepared by a route similar to the previous experiment for the synthesis of [3,5-(CF_3)$_2$-C_6H_3]$_2$PH to give the product as an oil (80 %). ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 6 H), 5.20 (d, J = 218.8 Hz, 1 H), 6.86 (m, 2 H), 6.88 (m, 2 H), 7.41 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 55.13, 114.20 (d, J = 7.0 Hz), 125.75 (d, J = 7.4 Hz), 135.41 (d, J = 18.2 Hz), 160.01. ^{31}P NMR ($CDCl_3$): δ -43.47 (s).

3. Horita K., Inoue T., Tanaka K., Yonemitsu O. *Tetrahedron* **1996**, *52(2)*, 531. (3S,4R,5R,6S)-4,5-isopropylidenedioxyoctane-3,6-diol: ^{1}H NMR ($CDCl_3$): δ 1,00 (t, J = 7.4 Hz, 6 H), 1.42 (s, 6 H), 1.54 (m, 4 H), 2.01 (b, 2 H), 3.41 (t, J = 6.6 Hz, 2 H), 3.91 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 10.17, 27.29, 27.83, 71.52, 79.65, 109.21.