J|A|C|S
ARTICLES
Published on Web 05/12/2006

A Hybrid Phosphorus Ligand for Highly Enantioselective Asymmetric Hydroformylation

Yongjun Yan and Xumu Zhang*

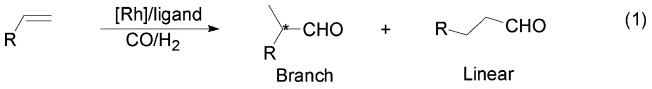
Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received October 17, 2005; E-mail: xumu@chem.psu.edu.

Abstract: A new hybrid phosphorus ligand has been prepared starting from chiral NOBIN (2-amino-2′-hydroxy-1,1′-binaphthyl). Excellent enantioselectivities (up to 99% ee) have been achieved in the Rh-catalyzed asymmetric hydroformylations of styrene derivatives and vinyl acetate.

Introduction

Hydroformylation is the reaction of alkenes with carbon monoxide and hydrogen to form aldehydes, which provides a versatile method for the functionalization of C−C double bonds [eq 1].



(1)

Today, hydroformylation is the largest industrially homogeneous catalytic process. Over 6 million tons of oxo products are being produced worldwide per year. Because chiral aldehydes can be easily converted into a variety of enantiomerically pure compounds, asymmetric hydroformylation[1] is potentially useful for the preparation of pharmaceutical products. Despite its importance, asymmetric hydroformylation is underdeveloped. Achieving high ee's (≥98% ee) remains a challenging goal due to the following reasons: First, hydroformylation reactions are often carried out at elevated temperature to achieve an acceptable reaction rate. However, high enantioselectivities are generally observed at low temperature with relatively low reaction rate and low conversion. This limits the utilities of this important transformation. Second, the aldehyde products, especially for those hydroformylated from styrene derivatives, can undergo racemization under certain hydroformylation reaction conditions.[1b] This racemization results in lower ee's at high conversion in some catalytic systems. To the best of our knowledge, only a few ligands[2] are capable of affording over 90% ee's in asymmetric hydroformylation. Recent reports have shown that mixed phosphorus ligands bearing two different phosphorus groups are effective in asymmetric hydroformylation.[2a,b,3] Binaphos,[2a,b,4] a hybrid phosphine−phosphite ligand developed by Takaya and co-workers, has been proved to be one of the benchmark ligands for the asymmetric hydroformylation of vinylarenes. For example, up to 94% ee has been achieved for the hydroformylation of styrene with Rh−Binaphos catalyst. However, racemization remains a major problem for Binaphos,[2b,4a] and the enantioselectivity can be further improved. The development of ligands for highly enantioselective hydroformylation without the racemization of chiral products is highly desirable. Herein, we would like to report the synthesis of a new hybrid phosphine−phosphoramidite ligand **1**[5] and its applications in asymmetric hydroformylation. With (*R*,*S*)-**1** as the ligand, unprecedented high enantioselectivities (up to 99% ee) have been achieved for hydroformylation, and significant performance

(1) For recent reviews, see: (a) Claver, C.; van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Claver, C., van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000. (b) Agbossou, F.; Carpentier, J.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485−2506. (c) Gladiali, S.; Bayön, J. C.; Claver, C. *Tetrahedron: Asymmetry* **1995**, *6*, 1453−1474. (d) Breit, B.; Seiche, W. *Synthesis* **2001**, 1−36. (e) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113−2122.

(2) (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc*. **1993**, *115*, 7033−7034. (b) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413−4423. (c) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 5040−5042. (d) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem., Int. Ed*. **2000**, *39*, 4106−4108. (e) Babin, J. E.; Whiteker, G. T. Patent WO 9303839, 1992. (f) Dieguez, M.; Pamies, O.; Ruiz, A.; Castillon, S.; Claver, C. *Chem.-Eur. J*. **2001**, *7*, 3086−3094. (g) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 5834−5838. (h) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. *Tetrahedron Lett.* **2005**, *46*, 7831−7834.

(3) (a) Ewalds, R.; Eggeling, E. B.; Hewat, A. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Chem.-Eur. J*. **2000**, *6*, 1496−1504. (b) Lot, O.; Suisse1, I.; Mortreux, A.; Agbossou, F. *J. Mol. Catal. A: Chem.* **2000**, *164*, 125−130. (c) Deerenberg, S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **2000**, *19*, 2065−2072. (d) Franciò, G.; Faraone, F.; Leitner, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1428−1430. (e) Kless, A.; Holz, J.; Heller, D.; Kadyrov, R.; Selke, R.; Fischer, C.; Bömer, A. *Tetrahedron: Asymmetry* **1996**, *7*, 33−36.

(4) (a) Solinas, M.; Gladiali, S.; Marchetti, M. *J. Mol. Catal. A: Chem.* **2005**, *226*, 141−147. (b) Nozaki, K.; Matsuo, T.; Shibahara, F.; Hiyama, T. *Adv. Synth. Catal*. **2001**, *343*, 61−63. (c) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285−4292. (d) Nozaki, K.; Hidemasa, T.; Tamejiro, H. *Top. Catal.* **1998**, *4*, 175−185. (e) Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Organometallics* **1997**, *16*, 2981−2986. (f) Nozaki, K.; Nanno, T.; Takaya, H. *J. Organomet. Chem*. **1997**, *527*, 103−108. (g) Nozaki, K.; Li, W.-G.; Horiuchi, T.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 4611−4614. (h) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron* **1997**, *53*, 7795−7804. (i) Nozaki, K.; Li, W.-G.; Horiuchi, T.; Takaya, H.; Saito, T.; Yoshida, A.; Matsumura, K.; Kato, Y.; Imai, T.; Miura, T.; Kumobayashi, H. *J. Org. Chem*. **1996**, *61*, 7658−7659. (j) Horiuchi, T.; Ohta, T.; Nozaki, K.; Takaya, H. *Chem. Commun*. **1996**, 155−156. (k) Nanno, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2583−2591. (l) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun*. **1994**, 395−396.

(5) We named this new hybrid phosphine−phosphoamidite ligand as YanPhos.

10.1021/ja057065s CCC: $33.50

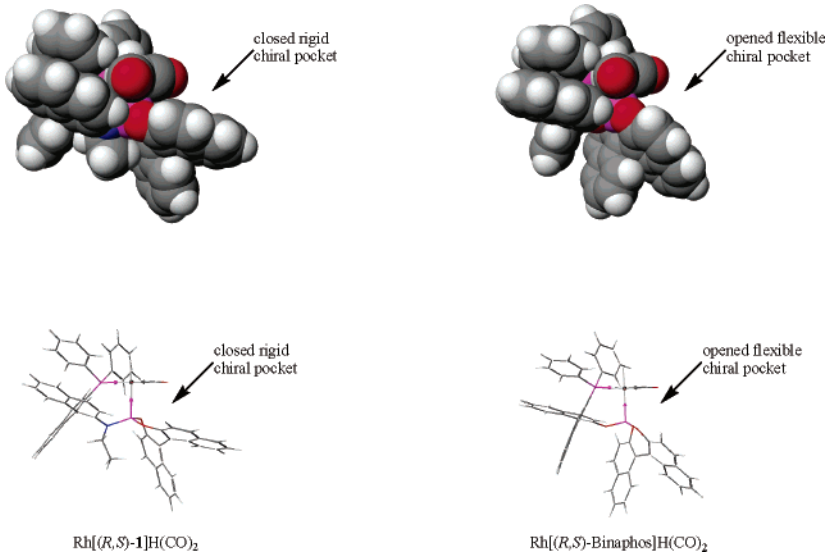
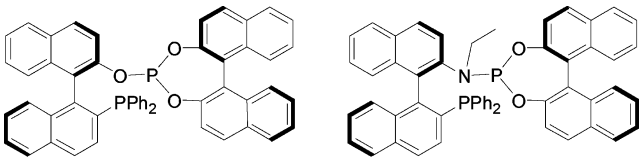


Figure 1. Space-filling and stick models for Rh[(*R*,*S*)-**1**]H(CO)$_2$ and Rh[(*R*,*S*)-Binaphos]H(CO)$_2$ based on CAChe MM2 calculation.

enhancements have been obtained as compared to the benchmark ligand, Binaphos.



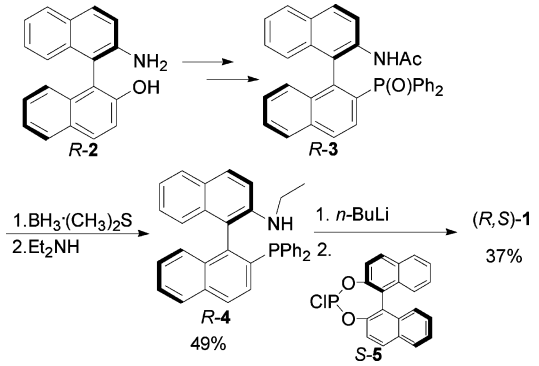
(*R*,*S*)-Binaphos (*R*,*S*)-**1**

Results and Discussion

Takaya and co-workers have demonstrated that configuration matched (*R*,*S* and *S*,*R*) Binaphos led to better enantioselectivity than mismatched (*R*,*R* and *S*,*S*) Binaphos.[2b] As the phosphine−phosphoramidite analogue of Binaphos, we anticipated that (*R*,*S*)-**1** and its enantiomer are the configuration matched isomers. We thus synthesized (*R*,*S*)-**1** for the current study. Despite the similarity, there is a significant difference between Binaphos and ligand **1**, both electronically (phosphoramidites are more electron-donating than phosphites because the electronegativity of nitrogen (3.04) is less than that of oxygen (3.44)) and sterically. Hence, replacing the phosphite group in Binaphos with the *N*-substituted phosphoramidite group in ligand **1** represents substantial change. Figure 1 shows the space-filling and stick models (based on CAChe MM2 calculation) for Rh[(*R*,*S*)-**1**]H(CO)$_2$ and Rh[(*R*,*S*)-Binaphos]H(CO)$_2$ complexes, which are presumed to be the active intermediates in hydroformylation reactions.[2a,b] As shown in Figure 1, in the presence of the crowded *N*-substituent, Rh[(*R*,*S*)-**1**]H(CO)$_2$ complex can provide a deeper and more closed chiral pocket than the corresponding Rh[(*R*,*S*)-Binaphos]H(CO)$_2$ complex. Molecular dynamics simulation based on the CAChe program also indicates that the Rh complex of ligand **1** is more conformationally rigid than the analogous Binaphos complex due to the presence of *N*-substituent of the phosphoramidite part in ligand **1**. We envision that a more closed rigid chiral pocket provided by Rh[(*R*,*S*)-**1**]H(CO)$_2$ complex could lead to high asymmetric induction.

Ligand **1** was prepared from chiral 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) **2**. Following the literature procedure,[6] the phosphine oxide amide **3** was easily obtained in high yield. Reduction of both phosphine oxide and amide groups with excess BH_3, followed by treatment with diethylamine, gave **4** in 49% yield. After deprotonation with *n*-BuLi and quenching with phosphorochloridite **5**, the desired ligand (*R*,*S*)-**1** was obtained in 37% yield as an air-stable solid (Scheme 1).

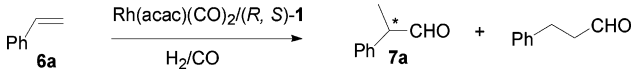
Scheme 1. Synthesis of (*R*,*S*)-**1**



Using the chiral ligand (*R*,*S*)-**1**, rhodium-catalyzed asymmetric hydroformylation has been explored. Styrene was selected as the standard substrate for the optimization of reaction conditions. The catalyst was prepared in situ by mixing Rh(acac)(CO)$_2$ with 4 equiv of ligand **1**. Hydroformylation reactions were performed using 1:1 CO/H_2 gas with 0.1 mol % of the catalyst. The chemoselectivities of the hydroformylation reactions were excellent, and no hydrogenation product was detected via ^{1}H NMR. The regioselectivities were moderate with a branch/linear ratio generally over 85:15, which were comparable to the results obtained with Binaphos.[2a,b] The enantioselectivities strongly depended on reaction conditions. Significant solvent effect was observed (Table 1, entries 1−4). High enantioselectivities were obtained when the reactions were run in nonpolar solvents such as methylene chloride and benzene, while low ee values were observed in THF and EtOAc. The competition for coordination sites between polar solvents and substrates may account for this solvent effect.[1b] Increasing reaction temperature led to faster

(6) Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7738−7748.

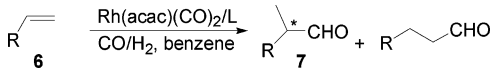
Table 1. Optimization of Asymmetric Hydroformylation of Styrene with Rh-(*R*,*S*)-**1** Catalyst[a]



entry	solvent	*T* (°C)	H_2/CO (atm)	time (h)	conv. (%)[b]	b/l[c]	ee (%)[d]
1	C_6H_6	60	10/10	24	>99	88/12	98(*R*)
2	CH_2Cl_2	60	10/10	24	93	91/9	97(*R*)
3	THF	60	10/10	24	95	88/12	78(*R*)
4	EtOAC	60	10/10	24	98	89/11	84(*R*)
5	C_6H_6	40	10/10	24	25	91/9	99(*R*)
6	C_6H_6	80	10/10	24	>99	85/15	81(*R*)
7	C_6H_6	60	20/20	24	91	89/11	98(*R*)
8	C_6H_6	60	30/30	24	83	88/12	98(*R*)
9	C_6H_6	60	10/10	12	87	89/11	99(*R*)
10	C_6H_6	60	10/10	36	>99	88/12	97(*R*)

[a] All reactions were carried out with L:Rh = 4:1, substrate:Rh = 1000. [b] Conversions were determined on the basis of ^{1}H NMR. [c] (b/l) branched−linear ratio. Determined on the basis of ^{1}H NMR. [d] Determined by converting the aldehyde to the corresponding alcohol with $NaBH_4$ followed by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*R*) was assigned by comparing the sign of the optical rotation of the resulting alcohol with (*R*)-2-phenylpropan-1-ol.

Table 2. Asymmetric Hydroformylations with Rh−L Catalysts[a]



entry	R	ligand	S/C[b]	*T* (°C)	H_2/CO (atm)	time (h)	conv. (%)[c]	b/l[d]	ee (%)[e]
1	Ph **6a**	(*R*,*S*)-**1**	1000	60	10/10	24	>99	88/12	98(*R*)
2	Ph **6a**	(*S*,*R*)-Binaphos	1000	60	10/10	24	>99	83/17	84(*S*)
3[f]	Ph **6a**	(*S*,*R*)-Binaphos	2000	60	50/50	43	>99	88/12	94(*S*)
4	*p*-Me−Ph **6b**	(*R*,*S*)-**1**	1000	60	10/10	24	98	87/13	99(*R*)
5[f]	*p*-Me−Ph **6b**	(*S*,*R*)-Binaphos	1000	60	50/50	20	97	86/14	95(*S*)
6	*p*-F−Ph **6c**	(*R*,*S*)-**1**	1000	60	10/10	24	>99	88/12	98(*R*)
7[g]	*p*-F−Ph **6c**	(*R*,*S*)-Binaphos	2000	40	50/50	39	43	89/11	92(*R*)
8	*o*-F−Ph **6d**	(*R*,*S*)-**1**	1000	60	10/10	24	99	91/9	98(*R*)
9[g]	*o*-F−Ph **6d**	(*R*,*S*)-Binaphos	2000	40	50/50	30	52	91/9	95(*R*)
10	*p*-Cl−Ph **6e**	(*R*,*S*)-**1**	1000	60	10/10	24	>99	87/13	98(*R*)
11[f]	*p*-Cl−Ph **6e**	(*S*,*R*)-Binaphos	1000	60	50/50	34	>99	87/13	93(*S*)
12	*p*-Meo−Ph **6f**	(*R*,*S*)-**1**	1000	60	10/10	24	97	86/14	98(*R*)
13[f]	*p*-Meo−Ph **6f**	(*S*,*R*)-Binaphos	1000	60	50/50	34	>99	87/13	88(*S*)
14	*p*-^{i}Bu−Ph **6g**	(*R*,*S*)-**1**	1000	60	10/10	24	98	89/11	98(*R*)
15[f]	*p*-^{i}Bu−Ph **6g**	(*S*,*R*)-Binaphos	300	60	50/50	66	>99	88/12	92(*S*)
16	OAc **6h**	(*R*,*S*)-**1**	1000	60	10/10	24	75	93/7	96(*S*)
17[f]	OAc **6h**	(*R*,*S*)-Binaphos	400	60	50/50	36	>99	86/14	92(*S*)
18	Ph **6a**	(*R*,*S*)-**1**	10 000	60	10/10	24	89	88/12	98(*R*)

[a] All reactions were carried out with L:Rh = 4:1 in benzene. [b] Substrate−catalyst ratio. [c] Conversions were determined on the basis of ^{1}H NMR. [d] (b/l) branched−linear ratio. Determined on the basis of ^{1}H NMR. [e] See Supporting Information for details. [f] Data taken from ref 2a for comparison. [g] Data taken from ref 2b for comparison.

reaction rate and lower ee (Table 1, entries 1, 5, and 6). Enantiomeric excess of 99% was achieved when the reaction was run at 40 °C with 25% conversion. Up to 98% ee was achieved in asymmetric hydroformylation with 100% conversion at 60 °C, while the enantioselectivity dropped to 81% ee at 80 °C. No significant influence of the CO/H_2 pressure on regio- and enantioselectivity was observed. The total pressure dramatically affected the reaction rate (Table 1, entries 1, 7, and 8). Under low CO/H_2 pressure, the reaction was fast and complete conversion was achieved in 24 h under 20 atm of CO/H_2. The pressure effect on the reaction rate can be explained by the lower dissociation rate of CO from the Rh center at high pressure. It is worth noting that the racemization of the hydroformylation product was significantly lower with ligand **1** than with Binaphos.[2b] For example, elongation of the reaction time after the reaction was complete only slightly lowered the enantiomeric excess of the chiral product with ligand **1** (Table 1, entries 1, 9, and 10). With Binaphos as the ligand, a dramatic decrease of enantiomeric excess after full conversion has been observed.[2b] It has also been reported that significant racemization may occur even before full conversion was reached in the hydroformylation of styrene with Binaphos.[4a] After reaction conditions were screened, hydroformylation of styrene with the Rh-(*R*,*S*)-**1** catalyst was performed under 20 atm of 1:1 CO/H_2 at 60 °C in benzene. Optimized conversion, regioselectivity, and enantioselectivity were achieved under this condition.

A series of styrene derivatives were hydroformylated using the Rh-(*R*,*S*)-**1** catalyst under the optimized reaction condition (Table 2). Under the same reaction condition, 98% ee (Table 2, entry 1) in the hydroformylation of styrene was achieved with ligand **1**, while only 84% ee (Table 2, entry 2) was obtained with Binaphos. The result with Binaphos under current reaction condition is much lower than the literature reported result (Table 2, entry 3, 94% ee).[2a,b] Because optimized reaction conditions for Binaphos and ligand **1** are very different due to different steric and electronic properties of two ligands, direct comparison of ligand **1** with Binaphos under the same reaction condition is not appropriate. To demonstrate the utilities of this new ligand,

we have selected the best reported results with Binaphos for a side-by-side comparison. With ligand **1**, up to 99% ee was obtained for the hydroformylation of *para*-methyl styrene (Table 2, entry 4). Halogen-substituted styrene derivatives were also hydroformylated with excellent enantioselectivities with ligand **1** (Table 2, entries 6, 8, and 10). It is worth noting that high enantioselectivities at high conversions were achieved for fluorinated styrene derivatives (Table 2, entries 6 and 8). For comparison, the reactions with Binaphos needed to be terminated at moderate conversions to obtain high enantioselectivities due to the racemization of the chiral products (Table 2, entries 7 and 9).[2b] With ligand **1**, *para*-methoxy styrene was hydroformylated with high enantioselectivity (98% ee) (Table 2, entry 12), which is significantly higher than the result (88% ee) reported with Binaphos.[2a,b] Up to 98% ee for the hydroformylation of *para*-isobutyl styrene was achieved with ligand **1** (Table 2, entry 14). Oxidation of the aldehyde product affords the corresponding acid, ibuprofen, one of the most widely used nonsteroidal antiinflammatory agents. (*S*)-Ibuprofen is the biological active form of two enantiomers. With Binaphos, only 92% ee was obtained (Table 2, entry 15), and the turnover frequency was very low (300 turnover after 66 h).[2a,b] Hydroformylation of vinyl acetate was also tested with ligand **1**. The hydroformylation product 2-acetoxypropanal is a precursor for the Strecker synthesis of the amino acid threonine.[7] The hydroformylation was performed under the identical reaction condition for styrene. After 24 h, 75% of the starting material was converted to aldehyde with 96% ee and with a 13:1 branch/linear ratio (Table 2, entry 16). The enantioselectivity with ligand **1** was higher as compared to Binaphos ligand (Table 2, entry 17, 92% ee) [2a,b] and matched the previous best result using chiral diazaphospholane ligand (96% ee).[2c] To demonstrate the catalytic efficiency of Rh-(*R*,*S*)-**1** catalyst, hydroformylation of styrene was carried out with substrate/catalyst molar ratio of 10 000:1 (Table 2, entry 18). With this low catalyst loading, Rh-(*R*,*S*)-**1** catalyst still showed high reactivity (89% conversion after 24 h) and maintained high enantioselectivity (98% ee) for the hydroformylation reaction.

Conclusion

In conclusion, a new hybrid phosphine−phosphoramidite ligand **1** has been developed. Unprecedented high enantioselectivities have been achieved for Rh-catalyzed asymmetric hydroformylations. The high reactivity and excellent enantioselectivity of this new ligand make the catalyst system potentially useful for industrial applications. Further structural variation of *N*-substituted phosphoramidite ligands will be developed in the future for asymmetric hydroformylation and other metal-catalyzed transformations.

Experimental Section

General Methods. All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N_2. Column chromatography was performed using 200−400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ^{1}H, ^{13}C NMR, and ^{31}P spectra were recorded on Bruker AM-300 and AMX-360 spectrometers. Optical rotation was obtained on a Perkin-Elmer 241 polarimeter. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50. GC analysis was carried out on Hewlett-Packard 6890 gas chromatography using chiral capillary columns. Compound **3** was synthesized according to known literature procedure.[6]

Synthesis of Compound 4. To a solution of **3** (3.70 g, 7.24 mmol) in THF (200 mL) was added dropwise a 10 M borane−dimethyl sulfide complex in THF (7.24 mL, 72.4 mmol) at 0 °C. The mixture was refluxed for 18 h. After being cooled to room temperature, the mixture was diluted with EtOAc (200 mL) and poured into ice water. The mixture was stirred for 30 min, and the organic layer was separated and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. To the residue was added 270 mL of diethylamine, and the reaction mixture was stirred at room temperature for 30 min. After removal of diethylamine, the residue was chromatographed on silica gel (eluted with hexane/EtOAc, 16:1) to give **4** (1.71 g) in 49% yield. ^{1}H NMR (360 MHz, $CDCl_2$) δ: 7.91 (t, J = 8.92 Hz, 3H), 7.77 (d, J = 8.01 Hz, 1H), 7.54−7.7.44 (m, 2H), 7.33−7.16 (m, 11H), 7.12 (t, J = 7.40 Hz, 1H), 7.07−7.01 (m, 3H), 6.65 (d, J = 8.47 Hz, 1H), 3.21 (m, 1H), 3.07−3.00 (m, 1H), 2.81−2.72 (m, 1H), 0.76 (t, J = 7.11 Hz, 3H). ^{13}C NMR (91 MHz, CD_2Cl_2) δ: 144.81, 144.78, 142.62, 142.24, 138.65, 138.50, 138.10, 137.65, 134.79, 134.18, 133.96, 133.63, 133.42, 133.35, 131.34, 129.91, 128.97, 128.91, 128.90, 128.81, 128.66, 128.59, 128.56, 128.47, 128.31, 127.60, 127.34, 127.19, 126.77, 126.74, 126.57, 124.31, 121.79, 116.24, 116.14, 113.92, 38.68, 15.17. ^{31}P NMR (146 MHz, CH_2Cl_2) δ: −14.235 (s). HRMS (ES+) (*m*/*z*): calcd for $C_{34}H_{29}NP$, 482.2038; found, 482.2029.

Synthesis of Ligand 1. To a solution of **4** (0.24 g, 0.5 mmol) in THF (5 mL) at 0 °C was added dropwise *n*-BuLi (0.65 mmol, 0.26 mL of 2.5 M hexane solution). The reaction mixture was allowed to warm to room temperature and stirred for 30 min to give a deep red solution. The reaction mixture was then recooled to 0 °C, and **5** (262 mg, 0.75 mmol) in THF (5 mL) was added dropwise. After addition, the cooling bath was removed and the mixture was stirred at room temperature overnight. The volatiles were evaporated under reduced pressure. To the residue was added CH_2Cl_2 (10 mL), and the mixture was filtered to remove the salt. The filtration was concentrated and subjected to chromatography on silica gel (eluted with hexane/EtOAc 9:1) to afford pure ligand **1** (145 mg) in 37% yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 8.10−8.01 (m, 3H), 7.93 (t, J = 7.28 Hz, 2H), 7.81-(d, J = 8.20 Hz, 2H), 7.67−7.55 (m, 4H), 7.41−7.05 (m, 16H), 6.99 (t, J = 6.75 Hz, 2H), 6.87 (t, J = 7.08 Hz, 2H), 6.57 (t, J = 7.68 Hz, 1H), 6.41−6.32 (m, 2H), 2.74 (m, 1H), 2.35 (m, 1H), 0.66 (t, J = 7.01 Hz, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 150.30, 150.21, 149.92, 142.36, 141.94, 138.59, 138.39, 138.27, 138.20, 135.44, 135.14, 134.10, 133.57, 133.36, 131.68, 130.51, 129.88, 129.11, 128.66, 128.58, 128.55, 128.49, 128.46, 128.42, 128.30, 128.12, 127.56, 127.19, 127.12, 127.03, 126.66, 126.29, 126.18, 125.71, 125.54, 125.06, 124.75, 122.49, 122.23, 122.19, 41.03, 14.98. ^{31}P NMR (146 MHz, CD_2Cl_2) δ: 141.63 (d, J = 53.3 Hz), −13.57 (d, J = 53.3 Hz). HRMS (ES+) (*m*/*z*): calcd for $C_{54}H_{40}NO_2P_2$, 796.2534; found, 796.2552.

General Procedure for Asymmetric Hydroformylation. In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar were added ligand **1** (0.004 mmol),[8] $Rh(acac)(CO)_2$ (0.001 mmol in 0.10 mL of benzene), and substrate (1.0 mmol), and additional benzene was charged to bring the total volume of the reaction mixture to 1.0 mL. After the mixture was stirred for 10 min, the vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (10 atm) and dihydrogen (10 atm) were charged in sequence. The reaction mixture was stirred (60 rpm)[9] at 60 °C (oil bath) for 24

(7) Chibata, I. In *Synthetic Production and Utilization of Amino Acids*; Kaneoko, T., Izumi, Y., Chibata, I., Itoh, T., Eds.; Wiley: New York, 1974.

(8) Hydroformylation at lower ligand/metal ratio resulted in decreased enantioselectivity. For example, when the ligand/metal = 2, enantiomeric excess dropped to 54% (branch/linear ratio = 85/15).

(9) This is sufficient for good stirring due to the small volume of the reaction mixture. Stirring at 160 rpm gave the same results. However, further increasing the stirring rate (260 rpm) caused the reaction mixture to spill out of the reaction vessel.

h. The reaction was cooled, and the pressure was carefully released in a well-ventilated hood. The conversion and regioselectivity were determined by ^{1}H NMR spectroscopy from the crude reaction mixture. For styrene derivatives, the enantiomeric excesses of the hydroformylation products were determined by reduction with $NaBH_4$ or oxidation with Jones reagent to the corresponding alcohols or carboxylic acids, and then analyzed by GC. For the hydroformylation product of vinyl acetate, the enantiomeric excess was determined directly by GC analysis of the crude reaction mixture.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (5R01GM058832-07).

Supporting Information Available: Determination of the enantiomeric excess of hydroformylation products and ligand NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JA057065S