# Synthesis of 3, 4-*O*-Isopropylidene-(3*S*,4*S*)-dihydroxy-(2*R*,5*R*)-bis(diphenylphosphino)hexane and Its Application in Rh-Catalyzed Highly Enantioselective Hydrogenation of Enamides

Wenge Li and Xumu Zhang*

*Department of Chemistry, 152 Davey Laboratory, The Pennsylvania State University, University Park, Pennsylvania 16802*

*xumu@chem.psu.edu*

*Received March 28, 2000*

Development of chiral phosphine ligands has played a significant role in transition metal-catalyzed asymmetric synthesis and has attracted much attention of synthetic chemists.[1] Chiral $C_2$-symmetric diphosphines are of special interest due to their effectiveness in many asymmetric reactions.[2] Ligands such as DIOP,[3] DIPAMP,[4] Chiraphos,[5] Skewphos,[6] BPPM,[7] DEGPhos,[8] BINAP,[9] DuPhos,[10] BPE,[10] BICP,[11] and PennPhos[12] are some representative examples of 1,2-, 1,3-, and 1,4-diphosphines which form a five-, six-, and seven-membered ring with transition metals. Due to the limitation of existing chiral ligands in their activity and enantioselectivity for different reactions and substrates, design of new chiral phosphines is still an important and challenging goal. Herein, we report development of a new chiral 1,4-bisphosphine ligand for highly efficient Rh-catalyzed asymmetric hydrogenation as well as the principle of conformational analysis for designing effective chiral ligands.

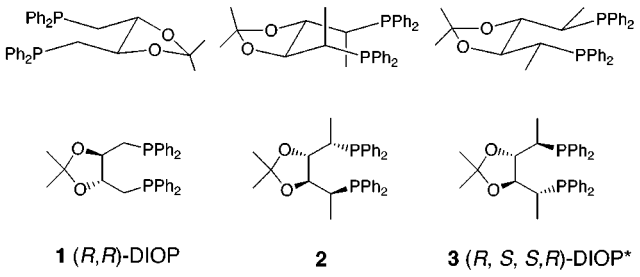



**Figure 1.**

The relationship between conformations of a chiral catalyst and reaction enantioselectivity has been extensively studied. In general, high asymmetric induction is attributed to a well-defined chiral conformation of the metal−ligand chelating compound.[13] For Rh-catalyzed asymmetric hydrogenation, orientation of phenyl groups of chiral diphenylphosphino ligands dictates the enantioselectivity.[14] Ligands such as BINAP, DIOP, BPPM, DEGPhos, Chiraphos, Skewphos, and BICP form metal complexes in which one chelate ring conformation is considered to be most stable. However, metal complexes with these ligands have different degrees of conformational flexibility. Generally, a seven-membered ring metal complex is more conformationally flexible than six- and five-membered ring metal species. The conformational flexibility in a chiral catalyst sometimes leads to erosion of enantioselectivity. For example, a metal−DIOP complex is conformationally flexible and the stereogenic centers may be too far from the substrate (transfer of backbone chirality to the phenyl groups on the phosphine goes through a methylene group).

To overcome this drawback, Kagan synthesized ligand **2** in which stereogenic centers are closer to the phosphines.[15] Unfortunately, enantioselectivity for Rh-catalyzed asymmetric hydrogenation of dehydroamino acids and enamides with ligand **2** is lower compared to the corresponding Rh-DIOP species.[15] We rationalized that the two methyl groups in **2** may locate in *axial positions* in the chelate ring resulting in an unfavorable conformation for enantioselective asymmetric reactions. To develop an effective asymmetric catalyst, we decided to invert the configuration of two stereogenic centers in **2** to make chiral ligand **3** (*R*, *S*, *S*,*R*)-DIOP*[16] so that methyl groups along with all other substituents orient in *equatorial positions*.[17] While this hypothesis needs to be approved,

(1) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis with Transition Metal Compounds*; VCH Verlagsgesellschaft: Weinheim, 1993; Vol. 2, Ligands-References, p 359.

(2) (a) Ojima, I. Ed. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993. (b) Sheldon, R. A. *Chirotechnology*, Marcel Dekker: New York, 1993. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (d) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis I−III*; Springer: New York, 1999.

(3) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

(4) (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Commun.* **1972**, 10. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

(5) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.

(6) MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273.

(7) (a) Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265. (b) Ojima, I.; Yoda, N. *Tetrahedron Lett.* **1980**, *21*, 1051.

(8) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326.

(9) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40* 1245. (c) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Takemomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(10) (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (c) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (d) Burk, M. J.; Lee, J. R.; Martine, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847. (e) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *119*, 5142.

(11) (a) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799. (b) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 3133. (c) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9591. (d) Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 7708.

(12) (a) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1100. (b) Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 516. (c) Zhang, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 1774.

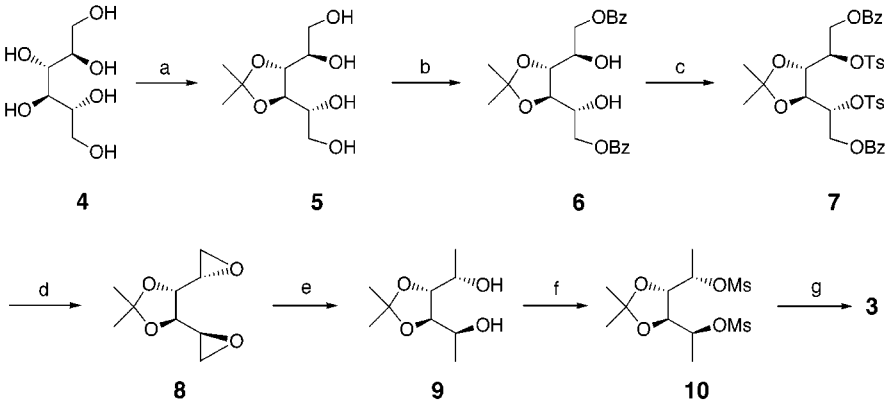
(13) (a) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491. (b) Slack, D. A.; Greveling, I.; Baird, M. C. *Inorg. Chem.* **1979**, *18*, 3125. (c) Bosnich, B.; Roberts, N. K. *Adv. Chem. Ser.* **1982**, *196*, 337. (d) Bacos, J.; Toth, I.; Heli, B.; Szalontai, G.; Parkanyi, L.; Fulop, V. *J. Organomet. Chem.* **1989**, *370*, 263. (e) Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoener, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315.

(14) (a) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. (b) Oliver, J. D.; Riley, D. P. *Organometallics* **1983**, *2*, 1032. (c) Brown, J. M.; Evans, P. L. *Tetrahedron*, **1988**, *44*, 4905. (d) Giovannetti, J. S.; Kelly, C. M.; Landis, C. R. *J. Am. Chem. Soc.* **1993**, *115*, 4040. (e) Brunner, H.; Winter, A.; Breu, J. *J. Organomet. Chem.* **1998**, *553*, 285.

(15) Kagan, H. B.; Fiaud, J. C.; Hoornaert, C.; Meyer, D.; Poulin, J. C. *Bull. Soc. Chim. Belg.* **1979**, *88*, 923.

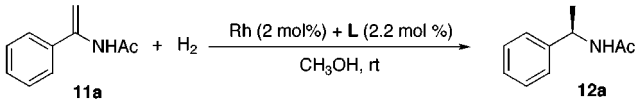
10.1021/jo0004613 CCC: $19.00 
Published on Web 08/17/2000

**Scheme 1**[a]




[a] Key: (a) (i) acetone, $H_2SO_4$, 81%, (ii) AcOH, $H_2O$, 40 °C, 2.5 h, 78%; (b) BzCl, pyridine, $CH_2Cl_2$, −78 °C; (c) TsCl, pyridine, DMAP, 0 °C, 4 h; (d) $K_2CO_3$, $CH_3OH$, rt, 65% from **5**; (e) $LiEt_3BH$, THF, 0 °C, 83%; (f) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 96%; (g) $Ph_2PH$, *n*-BuLi, THF, 0 °C to rt, 67%.

**Table 1. Asymmetric Hydrogenation of Enamide 11a Catalyzed by a Rhodium Bisphosphine Complex**[a]




11a 12a

| entry | catalyst | solvent | $H_2$ (bar) | ee[b] (%) | config[c] |
|---|---|---|---|---|---|
| 1[d] | $[RhCl(C_2H_4)_2]_2$/(+)-DIOP | EtOH | 1.1 | 42.5[e] | *R* |
| 2[d] | $[RhCl(C_2H_4)_2]_2$/(+)-DIOP | EtOH/benzene (2/1) | 1.1 | 45[e] | *R* |
| 3[d] | $[RhCl(C_2H_4)_2]_2$/(+)-DIOP | benzene | 1.1 | 44[e] | *S* |
| 4[d] | [Rh(COD)(+)-DIOP]$ClO_4$ | EtOH | 1.1 | 38.5[e] | *R* |
| 5[d] | [Rh(COD)(+)-DIOP]$ClO_4$ | benzene | 1.1 | 68[e] | *R* |
| 6[g] | $[Rh(COD)Cl]_2$/**3** | MeOH | 1.1 | 94.0 | *R* |
| 7 | $[Rh(COD)Cl]_2$/**3** | MeOH | 10 | 97.8 | *R* |
| 8 | $[Rh(COD)Cl]_2$/**3** | MeOH | 50 | 91.6 | *R* |
| 9 | $[Rh(COD)Cl]_2$/**3** | $CH_2Cl_2$ | 10 | 31.5 | *R* |
| 10 | $[Rh(COD)Cl]_2$/**3** | toluene | 10 | 5.4 | *R* |
| 11[f] | $[Rh(COD)_2SbF_6$/**3** | MeOH | 1.1 | 98.8 | *R* |
| 12 | $[Rh(COD)_2SbF_6$/**3** | MeOH | 10 | 98.3 | *R* |
| 13 | $[Rh(COD)_2SbF_6$/**3** | MeOH | 50 | 97.2 | *R* |
| 14[g] | $[Rh(COD)_2SbF_6$/(+)-DIOP | MeOH | 1.1 | 51.6 | *R* |
| 15 | $[Rh(COD)_2SbF_6$/**2** | MeOH | 10 | 17.3 | *S* |

[a] The reaction was carried out at rt under $H_2$ for 60 h. The catalyst was made in situ by stirring a solution of a Rh precusor and the bisphosphine ligand in solvent 3 mL [[substrate (0.25 mmol, 0.083 M)/[RH]/**L** = 1:0.02:0.022]]. The reaction went with >99% conversion unless stated otherwise. [b] Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 column (0.25 mm × 15 m). [c] The absolute configuration was assigned by comparison of optical rotation with reported data. [d] These results are from ref 20. [e] The ee's were determined by optical rotation. [f] In entries 6 and 11, 20% and 35% conversion was achieved by GC analysis, respectively. [g] The reaction proceeded with >99% conversion in 24 h.

we are pleased to report that the Rh-**3** complex leads to extremely high enantioselectivity for hydrogenation of enamides.

The synthetic route for ligand **3** (*R*,*S*,*S*,*R*)-DIOP* is shown in Scheme 1. Cheap, commercially available D-mannitol **4** was used as the starting material. D-mannitol **4** is first converted to 3,4-*O*-isopropylidene-D-mannitol **5** followed by dibenzoylation (**5** → **6**) and ditosylation (**6** → **7**). Transesterification of **7** followed by an intramolecular $S_N2$ reaction gives **8** with inversion of configuration of the two stereogenic centers.[18] Reduction of the diepoxide **8** affords the desired chiral diol **9**.[19] Bismesylate **10** was formed smoothly and nucleophilic attack of **10** with diphenylphosphine in the presence of *n*-BuLi produces **3** as a colorless oil in 67% yield. An advantage of this synthetic route is the versatility of the diepoxide **8**. Nucleophilic opening of the diepoxide **8** with various metal reagents (e.g., RMgBr) can lead to many enantiomerically pure 1,4-diols.[19]

We have applied ligand **3** (*R*,*S*,*S*,*R*)-DIOP* for rhodium-catalyzed asymmetric hydrogenation of enamides. The active catalyst employed in our study was generated *in situ* from a neutral Rh complex $[Rh(COD)Cl]_2$ or a cationic Rh complex $[Rh(COD)_2]SbF_6$ with **3** (*R*,*S*,*S*,*R*)-DIOP* (1:1.1). Enamide **11a** was chosen as a typical substrate to screen reaction conditions (Table 1). Both neutral (entries 6−8) and cationic Rh complexes (entries

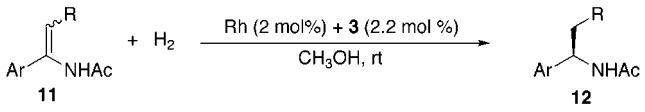
(16) We name the ligand as DIOP* to dedicate Professor Kagan's landmark contribution of metal−DIOP-catalyzed asymmetric reactions (ref 3). The result was presented in ChiraSource'99 in Philadephia, Nov 16, 1999, and this paper was submitted for publication in a different journal after the meeting. During this process, RajanBabu et al.[24d] independently reported the synthesis of **3** and its application in Pd-catalyzed asymmetric allylic alkylation *albeit* with a low ee.

(17) Related conformational studies show that substituents located in axial positions cause erosion of enantioselectivity while equatorial substituents lead to a more effective chiral catalyst in some chiral phosphine systems: (a) Michalik, M.; Freier, T.; Schwarze, M.; Selke, R. *Magn. Reson. Chem.* **1995**, *33*, 835. (b) Selke, R.; Ohff, R.; Riepe, A. *Tetrahedron* **1996**, *52*, 15079.

(18) Marrer, Y. L.; Dureault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J.-C. *Heterocycles* **1987**, *25*, 541.

(19) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron*: *Asymmetry* **1994**, *5*, 927.

**Table 2. Asymmetric Hydrogenation of Enamides 11 Catalyzed by a Rhodium−3 Complex[a]**




| entry | Ar | R | Rh | ee[b] (%) |
|---|---|---|---|---|
| 1 | $C_6H_5$ | H | $[Rh(COD)Cl]_2$ | 97.8 |
| 2 | $C_6H_5$ | H | $[Rh(COD)_2]SbF_6$ | 98.3 |
| 3 | *p*-$CF_3C_6H_4$ | H | $[RH(COD)Cl]_2$ | 97.6 |
| 4 | *p*-$CF_3C_6H_4$ | H | $[Rh(COD)_2]SbF_6$ | 97.7 |
| 5 | *m*-$CH_3C_6H_4$ | H | $[Rh(COD)Cl]_2$ | 98.5 |
| 6 | *m*-$CH_3C_6H_4$ | H | $[Rh(COD)_2]SbF_6$ | 98.8 |
| 7 | *p*-$PhC_6H_4$ | H | $[Rh(COD)Cl]_2$ | >99[c] |
| 8 | *p*-$PhC_6H_4$ | H | $[Rh(COD)_2]SbF_6$ | >99[c] |
| 9 | 2-naphthyl | H | $[Rh(COD)Cl]_2$ | >99[c] |
| 10 | 2-naphthyl | H | $[Rh(COD)_2]SbF_6$ | 99.0[c] |
| 11 | $C_6H_5$ | $CH_3$ | $[Rh(COD)_2]SbF_6$ | 97.3 |
| 12 | $C_6H_5$ | isopropyl | $[Rh(COD)_2]SbF_6$ | 99.0 |
| 13 | $C_6H_5$ | Bn | [Rh(COD)2]SbF6 | 98.6[c] |
| 14 | *p*-$CF_3C_6H_4$ | $CH_3$ | $[Rh(COD)_2]SbF_6$ | 98.3 |
| 15[d] | *p*-$MeOC_6H_4$ | $CH_3$ | $[Rh(COD)_2]SbF_6$ | 98.0[c] |
| 16 | 2-naphthyl | $CH_3$ | $[Rh(COD)_2]SbF_6$ | >99[c] |

[a] The reaction was carried out at rt under 10 bar of $H_2$ for 48−60 h. The catalyst was made in situ by stirring a solution of a Rh precusor and the bisphosphine ligand **3** in 3 mL of methanol [[substrate (0.25 mmol, 0.083 M)/[RH] / 3 = 1:0.02:0.022]]. The reaction went with >99% conversion unless stated otherwise. [b] Enantiomeric excesses were determined by chiral GC using a Supelco Chiral Select 1000 column (0.25 mm × 15 m). The *R* absolute configuration was assigned by comparing optical rotation with reported data. [c] Enantiomeric excesses were determined by chiral HPLC using a (*S*,*S*)-whelk-O1 column. [d] With 20% conversion based on GC analysis.

11−13) with **3** are highly enantioselective for hydrogenation of **11a** in MeOH. Increasing $H_2$ pressure allowed higher conversion albeit with slight erosion of enantioselectivity (entries 6−8 and entries 11−13). The most dramatic observation was the solvent effect. Changing from methanol to $CH_2Cl_2$ and toluene, reduced the ee significantly from 97.8% to 31.5% and 5.4%, respectively (entries 7, 9, and 10). A similar solvent effect was observed in Kagan's studies. For example, asymmetric hydrogenation of **11a** catalyzed by a Rh-DIOP complex gave 42.5% ee (*R*) in EtOH (entry 1) and 44% ee (*S*) in benzene (entry 3).[20a] It has been suggested that such effects are the results of conformational changes of the metal complex in different solvents.[21] Based on this assumption, we speculated one conformation of a Rh−**3** complex must be stable and highly effective for chiral recognition in methanol. All substituents are located in *equatorial positions* may be the reason that **3** is an excellent chiral ligand. The optimal conditions for hydrogenation **11a** with Rh−**3** are shown in entry 12. Under these reaction conditions, hydrogenation of **11a** catalyzed by a Rh−(+)-DIOP and an Rh−**2** species gave **12a** in 51.6% ee (*R*) (entry 14) and 17.3% ee (*S*) (entry 15), respectively. The subtle change of ligand structure indeed results in a huge difference in the hydrogenation reaction.

The scope of the asymmetric hydrogenation reaction with different substrates is shown in Table 2. High enantioselectivities (97−99% ee) were achieved for hydrogenation of α-aryl enamides using the optimal reaction conditions (entry 12, Table 1). An important feature of the Rh−**3** (*R*,*S*,*S*,*R*)-DIOP* catalyst is its high enantioselectivity for hydrogenation of an α-aryl enamide containing a *β*-alkyl group (entries 11−16). An isomeric mixture of (*Z*)- and (*E*)-enamides was reduced with high enantioselectivities. The enantioselectivities achieved in the Rh-**3**-catalyzed hydrogenation of enamides are comparable or better than those obtained with Rh−DuPhos,[10e] Rh−BICP,[11c] Rh−Binaphane,[22] and Rh−aminophenylphosphine systems.[23] However, we found that enantioselectivities (<90% ee) are much lower for hydrogenation of *N*-acyl dehydroamino acids with the Rh−**3** catalyst. The detailed reason for these results is still not clear.

In summary, a new bisphosphine ligand **3** (*R*,*S*,*S*,*R*)-DIOP* was developed as an effective ligand for Rh-catalyzed hydrogenation of enamides providing an efficient way to prepare chiral amines. A dramatic solvent effect has been observed. The concept of ligand conformational analysis has been illustrated and will be useful for future ligand design. (*R*, *S*, *S*, *R*)-DIOP* and its derivatives can be prepared easily from the readily available *D*-mannitol[24] and this type of ligands may be useful for many highly enantioselective catalytic reactions.

## Experimental Sections

**General Methods**. All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. Toluene, tetrahydrofuran (THF) and hexanes were distilled from sodium benzophenone ketyl under nitrogen. Methylene chloride ($CH_2Cl_2$) was distilled from $CaH_2$. Methanol ($CH_3OH$) was distilled from Mg under nitrogen. Gas chromatography was carried out on Helwett-Packard 6890 gas chromatograph using a Chiral Select 1000 column (Dimensions: 15 m × 0.25 mm), carrier gas: He (1 mL/min$^{-1}$). HPLC analysis was carried out on a Waters 600 chromatograph with an (*S*,*S*)-Whelk-01 column from Regis Technologies, Inc. [particle size: 5.0 *μ*m. column dimensions: 25 cm (length) × 0.46 cm (i.d.)].

**Synthesis of 3,4-*O*-Isopropylidene-(3*S*, 4*S*)-dihydroxy-(2*S*,5*S*)-hexanediol Bis(methanesulfonate) 10**. To a solution of 3,4-*O*-isopropylidene-(3*S*,4*S*)-dihydroxy-(2*S*,5*S*)-hexanediol (2.2 g, 11.6 mmol) and triethylamine (4.9 mL, 34.8 mmol) in $CH_2Cl_2$ (30 mL) was added dropwise a solution of methanesulfonyl chloride (2.0 mL, 25.8 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C. After 30 min at 0 °C, the reaction mixture was stirred for an additional 30 min at room temperature then quenched by saturated aqueous $NH_4Cl$ solution. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic solution was dried over $Na_2SO_4$. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel eluting with $CH_2Cl_2/Et_2O$ (9/1) to give a colorless oil 3.85 g in 96% yield: $[\alpha]^{24}_D = -1.3°$ (*c* = 1.04, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 360 MHz) *δ* 4.82−4.76 (m, 2H), 3.99−3.96 (m, 2H), 3.03 (s, 6H), 1.45 (d, *J* = 6.6, 6 Hz), 1.37 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 90 MHz) *δ* 110.14, 78.19, 76.26, 38.53, 26.75, 17.63; HRMS calcd for $C_{11}H_{23}O_8S_2$ ($MH^+$) 347.0834 and $C_{11}H_{22}O_8S_2Na$ ($MNa^+$) 369.0654, found 347.0834 and 369.0654.

**Synthesis of 3,4-*O*-Isopropylidene-(3*S*,4*S*)-dihydroxy-(2*R*,5*R*)-bis(diphenylphosphino)hexane 3 [(*R*,*S*,*S*,*R*)-DIOP*].** To a solution of diphenylphosphine (1.15 mL, 6.6 mmol) in THF (50 mL) was added *n*-BuLi in hexane (4.0 mL, 6.4 mmol)

(20) (a) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem*. **1975**, *90*, 353. (b) Sinou, D.; Kagan, H. B. *J. Organomet. Chem*. **1976**, *114*, 325 (up to 92% ee was observed with a Rh−DIOP catalyst for hydrogenation of a substrate listed in entry 11, Table 2).

(21) Bakos, J.; Toth, I.; Heli, B.; Szalontai, G.; Parkanyi, L.; Fulop, V. *J. Organomet. Chem*. **1989**, *370*, 263.

(22) Xiao, D.; Zhang, Z.; Zhang, X. *Organic Lett*. **1999**, *1*, 1679.

(23) F.-Y. Zhang, C.-C. Pai, A. S. C. Chan, *J. Am. Chem. Soc.* **1998**, *120*, 5808.

(24) For some recent chiral phosphine ligands made from D-mannitol, see: (a) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Sturmer, R.; Borner, A. *J. Org. Chem*. **1998**, *63*, 8031. (b) Carmichael, D.; Doueet, H.; Brown, J. M. *Chem. Commun*. **1999**, 261. (c) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett*. **1999**, *40*, 6701. (d) Yan, Y.-Y.; RajanBabu, T. V. *Org. Letter* **2000**, *2*, 199. (e) Yan, Y.-Y.; RajanBabu, T. V. *J. Org. Chem*. **2000**, *65*, 900. (f) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem*. **2000**, *65*, 3489.

at −78 °C over 5 min via syringe. The resulting orange solution was warmed to room temperature and stirred for 1 h. After cooling the mixture to −78 °C, 3,4-*O*-isopropylidene-(3*S*,4*S*)-dihydroxy-(2*S*,5*S*)-hexanediol bis(methanesulfonate) **10** (1.04 g, 3.0 mmol) in THF (20 mL) was added over 20 min. The resulting orange solution was warmed to room temperature and stirred overnight. The white suspension was hydrolyzed with saturated aqueous $NH_4Cl$ solution. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic solution was dried over anhydrous $Na_2SO_4$. After removal of the solvents under reduced pressure, the residue was purified by flash chromatography on silica gel eluting with hexanes/ethyl acetate (95/5) to give a colorless oil 1.06 g in 67% yield: $[\alpha]^{24}_D = +41.8°$ (*c* = 0.88, toluene); $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$ 7.56−7.52 (m, 8H), 7.38−7.33 (m, 12H), 3.78−3.76 (m, 2H), 2.50−2.46 (m, 2H), 1.14 (s, 6H), 0.91 (d, *J* = 7.0 Hz, 3H), 0,87 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR ($CD_2Cl_2$, 90 MHz) $\delta$ 137.46 (d, *J* = 15.9 Hz), 137.03 (d, *J* = 15.5 Hz), 134.14 (d, *J* = 3.7 Hz), 133.91 (d, *J* = 4.0 Hz), 129.30 (d, *J* = 8.6 Hz), 128.75 (d, *J* = 7.1 Hz), 108.27, 77.2 (dd, $J_1$= 12.0 Hz $J_2$ = 6.8 Hz), 31.33 (d, *J* = 14.3 Hz), 27.05, 10.74 (d, *J* = 17.6 Hz); $^{31}$P NMR ($CDCl_3$) $\delta$ = −6.3 ppm; HRMS calcd for $C_{33}H_{37}O_2P_2$ ($MH^+$) 527.2269, found 527.2271.

**General Procedure for Asymmetric Hydrogenation.** To a solution of a rhodium precursor (0.005 mmol) in methanol (3 mL) in a glovebox was added a bisphosphine (0.055 mL of 0.1 M solution in toluene, 0.0055 mmol). After the mixture was stirred for 10 min, an enamide (0.25 mmol) was added. The hydrogenation was performed at room temperature under 1.1−50 bar of hydrogen for 24−60 h. The hydrogen was released and the reaction mixture was passed through a short silica gel column to remove the catalyst. The enantiomeric excess was measured by GC or HPLC directly without any further purification. The absolute configuration of the products was determined by comparing the observed rotation with the reported value.[22]

**Acknowledgment.** This work was supported by a NIH grant. We acknowledge a generous loan of precious metals from Johnson Matthey Inc. and a gift of chiral GC columns from Supelco.

JO0004613