# Synthesis of Chiral Hydroxyl Phospholanes from d-mannitol and Their Use in Asymmetric Catalytic Reactions

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# Synthesis of Chiral Hydroxyl Phospholanes from D-mannitol and Their Use in Asymmetric Catalytic Reactions

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Chiral hydroxyl monophosphane **3** [(2*S*,3*S*,4*S*,5*S*)-3,4-dihydroxy-2,5-dimethyl-1-phenylphospholane] and bisphospholanes **5a** [1,2-bis[(2*S*,3*S*,4*S*,5*S*)-3,4-dihydroxy-2,5-dimethylphospholanyl]benzene] and **5b** [1,2-bis[(2*S*,3*S*,4*S*,5*S*)-2,5-diethyl-3,4-dihydroxyphospholanyl]benzene] were synthesized from readily available D-mannitol in high yields. Strategies for protection and deprotection of OH-groups in the presence of phosphines have been explored. Rate acceleration in the Baylis−Hillman reaction was observed when a hydroxyl phosphine was used as the catalyst. Rhodium complexes with chiral bisphospholanes are highly enantioselective catalysts for the asymmetric hydrogenation of various kinds of functionalized olefins such as dehydroamino acid derivatives, itaconic acid derivatives, and enamides. An interesting feature of the hydroxyl phospholane system is that hydrogenation of some substrates can be carried out in water with >99% ee and 100% conversion (e.g., itaconic acid).

## Introduction

Transition metal-catalyzed asymmetric reactions are one of the most efficient methods for preparing a wide range of enantiomerically pure compounds.[1] Design and synthesis of new efficient chiral ligands is crucial for the development of practical asymmetric catalytic reactions. Of particular interest in ligand design is the development of novel structural motifs or introduction of concepts such as "hemi-labile ligands" and ligands with secondary interactions with substrates.[2] Recently, we introduced several classes of structurally innovative bisphosphines based on chiral 1,4-diols containing four stereogenic centers (e.g., BICP and PennPhos), which have shown excellent enantioselectivities in Rh- and Ru-catalyzed hydrogenation of olefins and ketones.[3] Naturally, we have planned to make more chiral phosphines from a variety of 1,4-diols, especially those from readily available materials such as sugars and tartaric acid derivatives. Herein we report the synthesis of hydroxyl phospholanes **3** and **5** from D-mannitol as well as their application in the asymmetric Baylis−Hillman reaction and asymmetric hydrogenation of various functionalized olefins.[4]

Burk et al. have developed $C_2$-symmetric bisphospholanes DuPhos and BPE, and their rhodium(I) complexes have shown broad utility for catalytic asymmetric hydrogenation.[5] We proposed to introduce hydroxyl groups in the ligand framework as in monophospholane **3** and bisphospholane **5** for achieving the following significant goals: (1) to introduce a secondary interaction site between the hydroxyl group and substrate, (2) to make water-soluble ligands for carrying out reactions in aqueous media or to link the hydroxyl groups to a polymer chain that can be separated easily from the reaction mixture, and (3) to make ligands easily by using readily available chiral materials. It is common to use D-mannitol as a chiral auxiliary or ligand backbone.[6] We have learned from recent literature that the Borner, Brown, and RajanBabu groups have independently pursued the synthesis of chiral phospholanes derived from D-mannitol during the course of our study.[2c,6d−h] The so-called RoPhos, 1,2-bis[(2*S*,3*S*,4*S*,5*S*)-3,4-bis(benzyloxy)-2,5-dimethylphospholanyl]benzene, by Borner is an excellent ligand for Rh-catalyzed asymmetric hydrogenation reactions.[6d] Borner's results prompted us to disclose our findings with the hydroxyl phospholanes **3** and **5** since they are more amenable for ligand modification than RoPhos. In addition, we envision that different diaste-

(1) (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) Sheldon, R. A. *Chirotechnology*; Marcel Dekker: New York, 1993. (c) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; Wiley: New York, 1994.

(2) (a) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857 and references therein. (b) Holz, J.; Quirmbach, M.; Borner, A. *Synthesis* **1997**, 983 and references therein. (c) Carmichael, D.; Doueet, H.; Brown, J. M. *Chem. Commun.* **1999**, 261. (d) Nomura, N,; Jin, J.; Park, H.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459. (e) Rajanbabu, T. V.; Nomura, N.; Jin, J.; Radetich, B.; Park, H.; Nandi. M. *Chem. Eur. J.* **1999**, *5*, 1963.

(3) (a) Zhang, X. US Provisional Patent, 60/019,938, filed June 14, 1996, and PTC International Patent 96,2055-A, filed June 13, 1997. (b) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799. (c) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 3133. (d) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100. (e) Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *37*, 516. (f) Zhang, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 1774. (g) Cao, P.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 2127. (h) Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 7708.

(4) The preliminarily results of asymmetric hydrogenation of dehydroamino acid derivatives with Rh(I)−**5a** complex were reported. See: Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 6701.

(5) (a) Burk, M. J. J. *Am. Chem. Soc.* **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlaw, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (c) Burk, M. J.; Kalberg, C.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345. (d) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931. (e) Burk, M. J.; Allen, J. G.; Kiesman, W. *J. Am. Chem. Soc.* **1998**, *120*, 657. (f) Burk, M. J. Casy, G.; Johnson, N. *J. Org. Chem.* **1998**, *63*, 6084. (g) Burk, M. J.; Bienewald, F.; Challenger, S.; Derrick, A.; Ransden, J. *J. Org. Chem.* **1999**, *64*, 3290.

(6) (a) Bakos, J.; Heil, B.; Marko, L. *J. Organomet. Chem.* **1983**, *253*, 249. (b) Stoss, P.; Hemmer, R. *Adv. Carbohydr. Chem. Biochem.* **1992**, *49*, 93−173. (c) Reetz, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179. (d) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Sturmer, R.; Borner, A. *J. Org. Chem.* **1998**, *63*, 8031. (e) Borner, A.; Holz, J.; Voss, G.; Sturmer, R. DE 48 084 (18.06.1997). (f) Holz, J.; Heller, D.; Sturmer, R.; Borner, A. *Tetrahedron Lett.* **1999**, *40*, 7059. During the preparation of our full paper, RajanBabu reported synthesis and applications of some ligands reported in our paper: (g) Yan, Y.-Y.; RajanBabu, T. V. *Org. Letter* **2000**, *2*, 199. (h) Yan, Y.-Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900.

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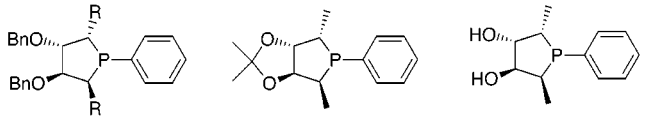
reoisomers of the 1,4-diols of our chiral hydroxyl phospholanes are also available from D-mannitol, which could potentially lead to opposite asymmetric induction in the catalytic process.[7]

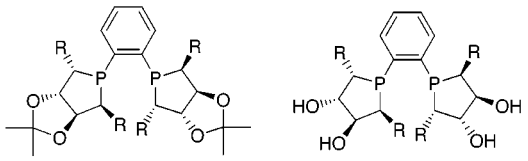
Our new hydroxyl phospholanes accelerate the Baylis−Hillman reaction, which we believe is due to the secondary interactions between the hydroxyl group and the enolate intermediate formed during the reaction. We are also pleased to see that Rh(I) complexes of our new bisphospholanes **5** afforded efficient catalysts for the highly enantioselective hydrogenation of various unsaturated substrates such as dehydroamino acid derivatives, itaconic acid derivatives, enamides, and enol acetates. Another significant finding is that the hydrogenation reaction can be carried out in water with high ee (e.g., itaconic acid, >99% ee).



**1a** R = $CH_3$
**1b** R = Bn

**2**

**3**



**4a** R = $CH_3$
**4b** R = Et



**5a** R = $CH_3$
**5b** R = Et

## Results and Discussion

**1. Ligand Preparation.** There have been extensive studies in preparing hydroxyl phosphines.[8] The key step is removal of the O-protecting group in the presence of phosphine. Most of the known O-protective groups have serious drawbacks due to attack by phosphide ions or to problematic deprotection in the presence of incorporated phosphine groups.[9] Because Kagan's (*S*)-1,2-bis(diphenylphosphino)butane-4-ol was protected via benzyl ether[8f] and (*R*,*R*)-1,4(diphenylphosphino)butane-2,3-diol was protected via isopropylidene ketal,[8b,8 g−h] we started both synthetic routes simultaneously for the purpose of comparison. The synthetic route is illustrated in Scheme 1. For the benzyl ether protection route, commercially available D-mannitol was selectively converted into the 1,2:5,6-di-*O*-isopropylidene derivative followed by O-benzylation of the remaining alcoholic groups affording 3,4-di-*O*-benzyl ether **7**.[10] Acidic cleavage of the acetal protective groups followed by selective tosylation of the two primary hydroxymethyl groups and subsequent reduction with $LiAlH_4$ furnished the 1,4-diol **8**.[6d,11] In basic medium, the ditosylate underwent an intramolecular $S_N2$ reaction leading to diepoxide **9** with retention of configuration at C2 and C5.[7] Regioselective ring-opening by attack of PhMgBr in the presence of CuI gave the 1,4-diol **10** in high yield.[12] Cyclic sulfate **11** was obtained using esterification with thionyl chloride followed by oxidation with $RuCl_3/NaIO_4$.[13] Nucleophilic attack of **11** with phenylphosphine in the presence of *n*-BuLi afforded **1** as a colorless oil in high yield. For further purification, phospholane **1** was converted in situ into the corresponding phosphine borane adducts by treatment with a 1 M THF solution of $BH_3$.[14] After flash chromatography, the phosphines were liberated with 1,4-diazabicyclo[2,2,2]-octane (DABCO) in toluene to afford the desired phospholane **1**.[14] In the ketal route, selective hydrolysis of 1,2:3,4:5,6-triacetonide D-mannitol gave 3,4-*O*-isopropylidene D-mannitol **12**[7] as a white solid that was transferred into the ketal phosphine **2**.

In our experiments, all attempts to cleave the *O*-benzyl ether groups of the **1a**−borane adduct failed. In the presence of excess $BCl_3$[15] or $BF_3{\cdot}Et_2O$,[16] the **1a**−borane adduct was debenzylated to give the derivatives bearing one hydroxyl and one benzyl ethyl groups. The corresponding phosphine oxide of **1a** was formed under hydrogenation conditions [$Pd(OH)_2/C$, 30 atm of $H_2$ or $H_2NNH_2{\cdot}H_2O$, Pd/C in $CH_3OH$ or ethanol with reflux].[17] High temperature (50 °C) and $H_2$ pressure (40 atm) led to cleavage of the benzyl ether and reduction of the phenyl group attached to phosphine to a cyclohexanyl group. Although *O*-benzyl ether protection afford the monophosphine **1** in high yield, we cannot get the desired hydroxyl phosphine **3** from **1a**. In contrast, the isopropylidene group in **2** was smoothly removed by acid-catalyzed hydrolysis (methanesulfonic acid/$CH_3OH$, refluxing).[8b] Based on these results, we selected the isopropylidene protection strategy in the preparation of hydroxyl phosphines. Compared with preparation of **8**, synthesis of the diol **15** is much easier because there is no need to run column chromatography in all of the steps.

The bisphospholanes **4** and **5** were synthesized using a similar procedure for preparation of **3**. The phosphine compounds **4** were formed as crystalline materials and purified by recrystallization from ether/methanol. Compounds **4** are air stable (e.g., their $^{31}P$ NMR spectra remain the same after 4 days). The easier synthesis and air-stability of phosphines **4** and **5** are attractive for the practical applications of these chiral phosphines.

**2. Asymmetric Catalytic Baylis−Hillman Reaction.** The Baylis−Hillman reaction is a convenient

(7) (a) Merver, Y. L.; Dureault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J.-C. *Heterocycles* **1987**, *25*, 541. (b) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron*: *Asymmetry* **1994**, *5*, 927.

(8) (a) Ward, J.; Borner, A.; Kagan, H. B. *Tetrahedron*: *Asymmetry* **1992**, *3*, 849. (b) Borner, A.; Ward, J.; Kortus, K.; Kagan, H. B. *Tetrahedron*: *Asymmetry* **1993**, *4*, 2219. (c) Borner, A.; Kadyrov, R.; Michalik, M.; Heller, D. *J. Organomet. Chem*. **1994**, *470*, 237. (d) Borner, A.; Holz, J.; Ward, J.; Kagan, H. B. *J. Org. Chem*. **1993**, *58*, 6814. (e) Lopusinski, A.; Bernet, B.; Linden, A.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 94. (f) Borner, A.; Ward, J.; Ruth, W.; Holz, J.; Kless, A.; Heller, D.; Kagan, H. B. *Tetrahedron* **1994**, *50*, 10419. (g) Descheneaux, R.; Stille, J. *J. Org. Chem*. **1985**, *50*, 2299. (h) Tamao, K.; Nakamura, K.; Yamaguchi, S.; Shiro, M.; Saito, S. *Chem. Lett*. **1996**, 1007.

(9) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley & Sons: New York, 1991.

(10) (a) Jurczak, J.; Bauer, T.; Chmielewski, M. *Carbohydr. Res*. **1987**, *164*, 493. (b) Zou, W.; Szarek, W. A. *Carbohydr. Res*. **1994**, *254*, 25.

(11) Fitremann, J.; Dureault, A.; Depezay, J.-C. *Tetrahedron* **1995**, *51*, 9581.

(12) Ghosh, A. K.; Mckee, S. P.; Thompson, W. J. *Tetrahedron Lett*. **1991**, *32*, 5729.

(13) (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett*. **1989**, *30*, 655. (b) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc*. **1988**, *110*, 7538.

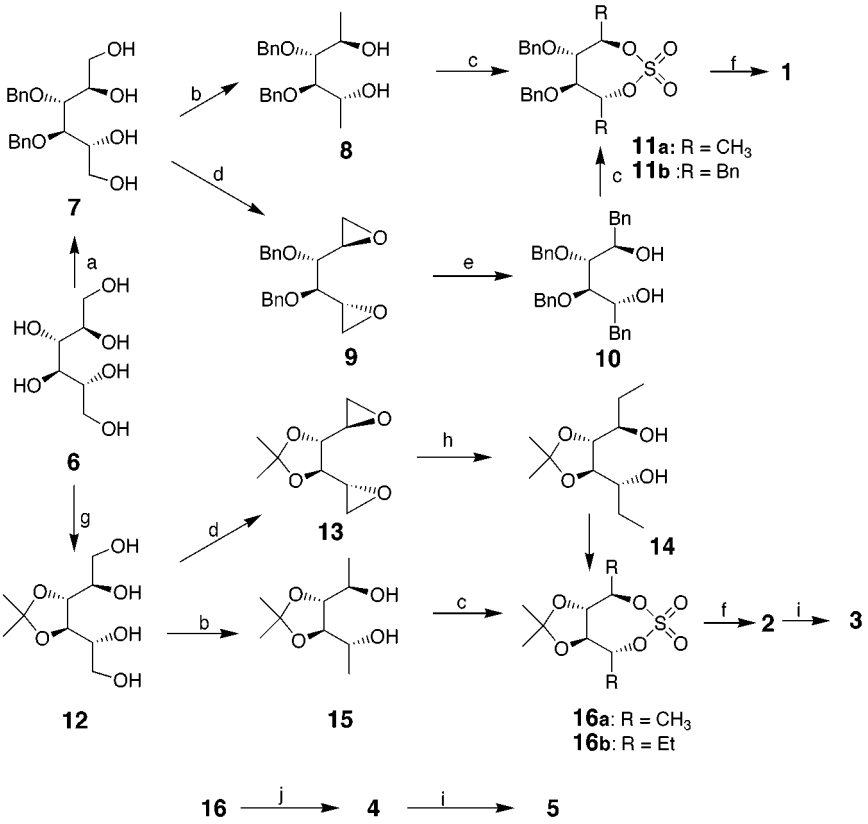
(14) Ohff, M.; Holz, J.; Quirmbach, M.; Borner, A. *Synthesis* **1998**, 1391.

(15) Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett*. **1981**, *22*, 899.

(16) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem*. **1979**, *44*, 1661.

(17) (a) Bieg, T.; Szeja, W. *Synthesis* **1986**, 317. (b) Otvos, L.; Beres, J.; Sagi, G.; Tomoskozi, I.; Gruber, L. *Tetrahedron Lett*. **1987**, *28*, 6381.

**Scheme 1**[a]

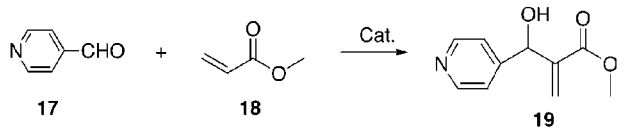



[a] Key: (a) (i) $(CH_3)_2C(OCH_3)_2$, PTS, DMSO, rt, (ii) BnBr, KOH, DMSO, rt, (iii) 70% HOAc−$H_2O$, 40 °C; (b) (i) TsCl, pyridine, 0 °C, (ii) $LiAlH_4$, THF, (c) (i) $SOCl_2$, $Et_3N$, $CH_2Cl_2$, 0 °C, (ii) $NaIO_4$, $RuCl_3 \cdot xH_2O$, 0 °C; (d) (i) TsCl, pyridine, 0 °C, (ii) $K_2CO_3$, $CH_3OH$; (e) CuI, PhMgBr, THF, −40 °C; (f) (i) $PhPH_2$, *n*-BuLi, THF, (ii) *n*-BuLi, THF; (g) (i) acetone, $H_2SO_4$, (ii) 70% HOAc−$H_2O$, 40 °C; (i) CuI, $CH_3MgBr$, THF, −40 °C, (ii) $CH_3OH$, $H_2O$, $CH_3SO_3H$, refluxing; (j) (i) 1,2-$H_2PC_6H_4PH_2$, *n*-BuLi, THF, (ii) *n*-BuLi, THF.

method for the preparation of β-hydroxy-α-methylene ketones, nitriles, and esters via the condensation of an aldehyde and corresponding α,β-unsaturated derivatives.[18] The reaction products bearing polyfunctional groups are very useful for various organic transformations. Recently, much effort has been focused on the development of an enantioselective Baylis−Hillman reaction.[19] However, only limited success has been reported. A significant drawback is the requirement of high pressure with a tertiary amine catalyst,[20] and low reactivity is observed with both amine and phosphine catalysts.[21]

The first step of the Baylis−Hillman reaction was proposed as a Michael addition of tertiary amines or phosphines to the activated alkene forming a transient zwitterionic enolate.[22] If this intermediate is stabilized by interaction of an intramolecular hydrogen bond, the reactivity increases.[23] Based on this assumption, we tested our hydroxyl phospholanes in the Baylis−Hillman reaction using 4-pyridinecarboaldehyde and methyl acrylate as the reactants.

**Table 1. Asymmetric Catalytic Baylis−Hillman Reaction**[a]




| entry | catalyst | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **1a** | 70 | 29 | 19 (+) |
| 2 | **1b** | 94 | 18 | 2 (−) |
| 3 | **3** | 9 | 83 | 17 (+) |
| 4 | **20** | 31 | 56 | 18 (+) |

[a] The reaction was carried out at rt by mixing 1 mmol of 4-pyridinecarbonaldehyde, 1 mL of methyl acrylate, and 10% catalyst under $N_2$ atmosphere. [b] Isolated yield. [c] % ee was determined by GC using a Supelco Chiral 1000 column.

The reaction was carried out by mixing the reactants and phosphines under inert atmosphere in the absence of solvent. The phospholane **1a** catalyzed this reaction with low conversion and moderate ee (19%) (Table 1, entry 1). When the methyl group in **1a** was replaced with a benzyl group (**1b**), the ee dropped to 2% (entry 2). With

(18) For the recent progress of Baylis−Hillman reaction, see a review: Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.

(19) (a) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun*. **1998**, 2533. (b) Barrett, A. G. M.; Kamimura, A. *J. Chem. Soc., Chem. Commun*. **1995**, 1755. (c) Ciganek, E. *Org. React*. **1997**, *51*, 201. (d) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc*. **1997**, *119*, 4317.

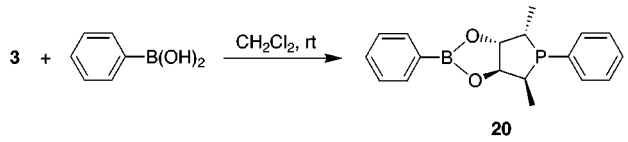
(20) (a) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1241. (b) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.

(21) Hayase, H.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun*. **1998**, 1271.

(22) (a) Drewes, S. E.; Nijamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun*. **1993**, *23*, 2807. (b) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem*. **1990**, *3*, 285. (c) Bode, M. L.; Kaye, P. T. *Tetrahedron Lett*. **1991**, *32*, 5611. (d) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371.

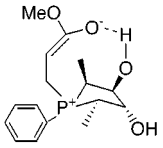
(23) (a) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun*. **1988**, *18*, 1565. (b) Ailey, M.; Marko, I. E.; Ollis, W. D.; Rasmussen, P. R. *Tetrahedron Lett*. **1990**, *31*, 4509. (c) Basavaiah, D.; Sarma, P. K. S. *Synth. Commun*. **1990**, *20*, 1611.

**Scheme 2**




**20**

the hydroxyl phospholane **3** as the catalyst, the reaction was accelerated significantly [83% isolated yield in 9 h (entry 3) vs 29% isolated yield in 70 h (entry 1)]. Unfortunately, the enantioselectivity was not enhanced with the hydroxyl phospholane **3**. This rate acceleration may be explained by the hydrogen-bonding interaction between a hydroxyl group and an enolate formed in the reaction.




We also made the boron analogue (**20**) of phospholane **3** by mixing phenylboronic acid in methylene chloride at −78 °C (Scheme 2).[24] The product was used directly as the catalyst after removing the solvent under vacuum. We expected to achieve rate acceleration through secondary interaction between the substrate and boron Lewis acid. Indeed, a moderate rate acceleration was achieved with **20** compared with **1a** (entry 4).

**3. Asymmetric Hydrogenation of Dehydroamino Acid Derivatives.** The demand of making enantiomerically pure α-amino acids has led to the development of effective chiral diphosphine−rhodium catalysts for hydrogenation of α-(acylamino)acrylates.[1,25] This reaction has been extensively investigated, and high enantioselectivities have been achieved using many chiral diphosphine−Rh catalysts. Thus, the hydrogenation of these enamides has become a standard test reaction for new chiral phosphine ligands. Using chiral chelating hydroxyl phosphines as ligands, we have evaluated their effectiveness in Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylates (Table 2 and Table 3).

The cationic Rh(I) complexes [Rh(COD)(phosphine)]X (X = $PF_6$, $BF_4$, $SbF_6$, and OTf) were prepared in situ by mixing the corresponding $Rh(COD)_2X$ with 1.1 molar equiv of bisphospholane ligands under inert atmosphere. Surprisingly, the isopropylidene-protected phospholane **4a** does not work in the hydrogenation reaction. Under 3 atm of $H_2$, no product was detected by chiral GC after 12 h. This is likely due to the steric hindrance of the isopropylidene group in the two fused trans-five-membered rings, which blocks the substrate binding site to the Rh. However, Rh complex with the corresponding hydroxyl phospholane **5a** is an excellent hydrogenation catalyst.[4] The more sterically hindered Et-phospholane **5b** provided slightly higher enantiomeric excess compared with Me-phospholane **5a** (Table 2, entries 2 and 4). Furthermore, both acid and ester derivatives were hydrogenated with high enantioselectivities. Changing solvents (entries 4 and 8−11) and counteranions (entries 4−7) has no significant effect on the enantioselectivity. The enantioselectivities obtained with these hydroxyl phospholanes are comparable to those achieved with Rh-DuPhos catalysts and higher than those reported with a Rh-RoPhos catalyst.[26]

Extremely high enantioselectivities have been achieved in hydrogenation of dehydroamino acid and ester derivatives with the Rh−**5b** catalyst (Table 3). The catalyst can tolerate substrates with thio (entries 11 and 12) and halogen groups (entries 3, 4, and 7−10). A wide array of ring-substituted phenylalanine derivatives were formed with high enantioselectivity regardless of the substituent or substitution position. The 2-naphthyl (entries 13 and 14) as well as *N*-benzoyl derivatives (entries 15 and 16) were also hydrogenated with high enantioselectivities (>99% ee).

**4. Asymmetric Hydrogenation of Itaconic Acid in Aqueous Medium.** Enantioselective hydrogenation of itaconic acid and its dimethyl ester was carried out (Table 4). The Rh-Et-phospholane **5b** catalyst gave superior enantioselectivities for both the acid and dimethyl ester compared with Rh-Me-phospholane **5a**. The mixture of $Rh(COD)_2PF_6$ (2.1 mg, 0.0045 mmol) and 0.1 mL of 0.05 M **5b** (0.005 mmol) in methanol was stirred for several minutes followed by addition of 3 mL of water. A clear yellowish solution was formed, which indicates that the Rh(I)−**5b** complex is soluble in water. In this 97%/3% water/MeOH solution, itaconic acid was hydrogenated smoothly with 100% conversion and >99% ee. It is exciting that this hydrogenation reaction can be carried out in water without any decrease of enantioselectivity. Further modification of the new hydroxyl phosphines will focus on creating more water-soluble catalysts so two-phase catalytic systems can be generated.

**5. Asymmetric Hydrogenation of Enamides and Enolacetates.** In many cases, high enantioselectivity and reactivity are achieved only on electron-deficient olefins. In contrast, electron-rich olefins such as simple enamides and enolacetates are generally poor substrates for asymmetric hydrogenation with most known systems.[27] Since enamides and enolacetates upon asymmetric hydrogenation can be converted to enantiomerically pure amines and alcohols, it would be extremely desirable to have a general and efficient method for this transformation. Therefore, we have investigated the hydrogenation of several enamides with rhodium−**5b** complex. The results of these studies are listed in Table 5. While high enantioselectivities were obtained, relatively low reaction rates were observed compared with DuPhos, PennPhos, and BICP.[26]

To further expand the utility of this asymmetric hydrogenation, we have examined enantioselective hydrogenation of cyclic enamide **29** and some enolacetates

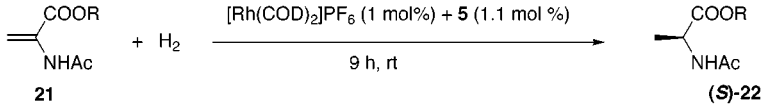
(24) Fields, L. B.; Jacobsen, E. N. *Tetrahedron*: *Asymmetry* **1993**, *4*, 2229.

(25) (a) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. (b) Koenig, K. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 3.

(26) (a) Borner, A.; Kless, A.; Kempe, R.; Heller, D.; Holz, J.; Baumann, W. *Chem. Ber.* **1995**, *128*, 767. (b) Borns, S.; Kadyrov, R.; Heller, D.; Baumann, W.; Spannenberg, A.; Kempe, R.; Holz, J.; Borner, A. *Eur. J. Inorg. Chem.* **1998**, 1291. (c) Borns, S.; Kadyrov, R.; Heller, D.; Baumann, W.; Holz, J.; Borner, A. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1425. (d) Kadyrov, R.; Borner, A.; Selke, R. *Eur. J. Inorg. Chem.* **1999**, 705.

(27) (a) Chan, Y. Ng C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952. (c) Uematsu, N.; Fuji, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (d) Burk, M. J.; Wang, Y. M.; Lee, R. J. *J. Am. Chem. Soc.* **1996**, 118, 5241. (e) Zhang, F.-Y.; Pai, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808. (f) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590. (g) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679.

**Table 2. Rhodium Catalyzed Asymmetric Hydrogenation of Dehydroamino Acid 21[a]**

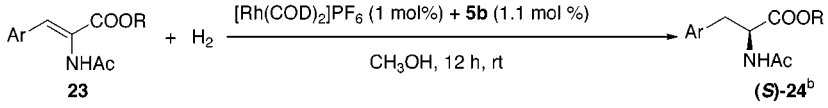



21 (*S*)-22

| entry | substrate | cat. | ligand | solvent | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **21a**, R = H | $Rh(COD)_2PF_6$ | **5a** | MeOH | >99[c] |
| 2 | **21b**, R = $CH_3$ | $Rh(COD)_2PF_6$ | **5a** | MeOH | 98 |
| 3 | **21a** | $Rh(COD)_2PF_6$ | **5b** | MeOH | >99[c] |
| 4 | **21b** | $Rh(COD)_2PF_6$ | **5b** | MeOH | >99 |
| 5 | **21b** | $Rh(COD)_2SbF_6$ | **5b** | MeOH | >99 |
| 6 | **21b** | $Rh(COD)_2BF_4$ | **5b** | MeOH | >99 |
| 7 | **21b** | $Rh(COD)_2OTf$ | **5b** | MeOH | >99 |
| 8 | **21b** | $Rh(COD)_2PF_6$ | **5b** | *i*-PrOH | >99 |
| 9 | **21b** | $Rh(COD)_2PF_6$ | **5b** | $CH_2CL_2$ | >99 |
| 10 | **21b** | $Rh(COD)_2PF_6$ | **5b** | THF | >99 |
| 11 | **21b** | $Rh(COD)_2PF_6$ | **5b** | toluene | >99 |

[a] The reaction was carried out at rt under 3 atm of $H_2$ for 9 h. The catalyst was prepared in situ by stirring a solution of $Rh(COD)_2X$ (X = $PF_6$, $SbF_6$, $BF_4$, OTf) and **5** in a solvent (3 mL) [[substrate (0.5 mmol, 0.167 M)/[Rh]/**5** = 1:0.01:0.011]]. The reaction went with 100% conversion. [b] The *S* absolute configuration was assigned by comparison of optical rotation with reported data.[6c] Enantiomeric excesses were determined by chiral GC using a Chirasil-VAL III FSOT column. [c] % ee was determined on the corresponding methyl ester.

**Table 3. Asymmetric Hydrogenation of Dehydroamino Acid Derivatives by a Cationic Rhodium−5b Complex[a]**




23 (*S*)-24[b]

| entry | substrate | ee[c] (%) |
|---|---|---|
| 1 | Ar = Ph, R = H | >99[d] |
| 2 | Ar = Ph, R = $CH_3$ | >99 |
| 3 | Ar = *p*-F-Ph, R = H | >99[d] |
| 4 | Ar = *p*-F-Ph, R = $CH_3$ | >99 |
| 5 | Ar = *p*-MeO-Ph, R = H | 99[d,e] |
| 6 | Ar = *p*-MeO-Ph, R = $CH_3$ | >99[e] |
| 7 | Ar = *m*-Br-Ph, R = H | 99[d] |
| 8 | Ar = *m*-Br-Ph, R = $CH_3$ | >99 |
| 9 | Ar = *o*-Cl-Ph, R = H | 98[d] |
| 10 | Ar = *o*-Cl-Ph, R = $CH_3$ | 98 |
| 11 | Ar = 2-thienyl, R = H | >99[d] |
| 12 | Ar = 2-thienyl, R = $CH_3$ | >99 |
| 13 | Ar = 2-naphthyl, R = H | >99[d] |
| 14 | Ar = 2-naphthyl, R = $CH_3$ | >99 |
| 15 | Ar = Ph, R = H, *N*-benzoyl | >99[d] |
| 16 | Ar = Ph, R = $CH_3$, *N*-benzoyl | >99 |

[a] The reaction was carried out at rt under 3 atm of $H_2$ for 12 h. The catalyst was made in situ by stirring a solution of $Rh(COD)_2PF_6$ and the ligand **5b** in methanol (3 mL) [[substrate (0.5 mmol, 0.167 M)/[Rh]/**5b** = 1:0.01:0.011]]. The reaction went with 100% conversion. [b] The *S* absolute configuration was assigned by comparison of optical rotation with reported data.[6c] [c] Enantiomeric excesses were determined by chiral GC using a Chirasil-VAL III FSOT column. [d] Determined on the corresponding methyl ester. [e] The % ee was determined by HPLC using a Daicel Chiralcel OJ column.

**30**−**32**. Under the same reaction conditions used for hydrogenation of acyclic enamide substrates, hydrogenation of cyclic enamide **29** gave the corresponding *N*-acetylamine with 96.2% ee. Enolate **30** was hydrogenated with 94.5% ee (48 h, 100% conversion). While enolates **31** and **32** were hydrogenated with high enantioselectivities, low conversions [**31** (37%) and **32** (31%)] were achieved after 48 h.

## Summary

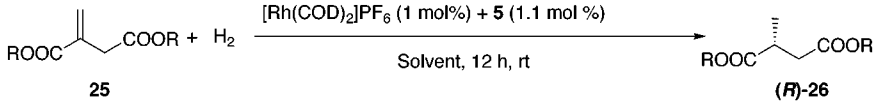
We have derived a practical route to synthesize chiral hydroxyl mono- and bisphospholanes and developed a highly enantioselective catalyst for asymmetric hydrogenation of dehydroamino acids and their derivatives, itaconic acid and its derivatives, enamides, and enolacetates. The Rh−**5** complex can be used in water to hydrogenate water-soluble substrates (e.g., itaconic acid) without decrease of enantiomeric excesses. We also observed that hydrogen-bonding interactions can accelerate the Baylis−Hillman reaction. The readily accessible chiral hydroxyl phosphines are likely to be useful for many asymmetric catalytic reactions.

## Experimental Section

**General Methods.** All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. All reagents were obtained from Aldrich and used directly. Toluene, diethyl ether, tetrahydrofuran, and hexanes were distilled from sodium benzophenone ketyl under nitrogen. Methylene chloride was distilled from $CaH_2$. Methanol and isopropyl alcohol were distilled from Mg under nitrogen. The phenylphosphine was purchased from Strem, and 1,2-bis(phosphino)benzene was prepared by $LiAlH_4$ reduction of 1,2-phenylenebis(phosphorodichloridite) from Digital Specialty Chemicals, Inc. (Canada).

Melting points were determined in sealed capillary tubes under nitrogen and are uncorrected. GC analyses were carried out on a Helwett-Packard 6890 gas chromatograph using chiral

**Table 4. Asymmetric Hydrogenation of Itaconic Acid Derivatives by a Rhodium−5 Complex[a]**

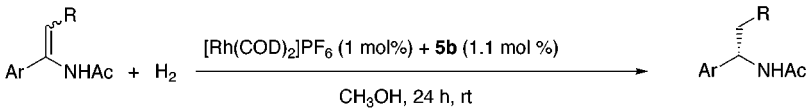



**25** **(*R*)-26**

| entry | substrate | ligand | solvent | ee[b] (%) |
|---|---|---|---|---|
| 1 | **25a**, R = H | **5a** | MeOH | 96[c] |
| 2 | **25b**, R = $CH_3$ | **5a** | MeOH | 98 |
| 3 | **25a** | **5b** | MeOH | >99[c] |
| 4 | **25b** | **5b** | MeOH | >99 |
| 5 | **25b** | **5b** | MeOH/$H_2O$ (9:1) | >99[c] |
| 6 | **25b** | **5b** | MeOH/$H_2O$ (5:5) | >99[c] |
| 7 | **25a** | **5b** | MeOH/$H_2O$ (5:5) | >99 |
| 8 | **25a** | **5b** | MeOH/$H_2O$ (3:97) | >99 |

[a] The reaction was carried out at rt under 10 atm of $H_2$ for 12 h. The catalyst was prepared in situ by stirring a solution of $Rh(COD)_2PF_6$ and the ligand **5** in a solvent (3 mL) [[substrate (0.5 mmol, 0.167 M)/[Rh]/**5** = 1:0.01:0.011]]. The reaction went with 100% conversion. [b] The *R* absolute configuration was assigned by comparison of optical rotation with reported data. Enantiomeric excesses were determined by chiral GC using a gama-225 column. [c] % ee was determined on the corresponding methyl ester.

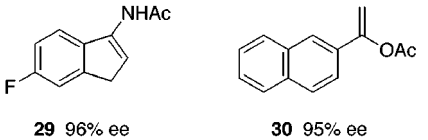
**Table 5. Asymmetric Hydrogenation of Enamides by a Rhodium−5b complex[a]**




**27** **(*S*)-28**[b]

| entry | substrate | ee[c] (%) |
|---|---|---|
| 1 | Ar = Ph, R = H | 96 |
| 2 | Ar = *p*-MeO-Ph, R = H | 95 |
| 3 | Ar = *p*-$F_3C$-Ph, R = H | 98 |
| 4 | Ar = *p*-Cy-Ph, R = H | 98 |
| 5 | Ar = 2-naphthyl, R = H | 99[d] |
| 6 | Ar = *p*-MeO-Ph, R = $CH_3$ | 92[d] |
| 7 | Ar = *p*-$F_3C$-Ph, R = $CH_3$ | 91 |

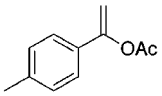
[a] The reaction was carried out at rt under 10 atm of $H_2$ for 24 h. The catalyst was prepared in situ by stirring a solution of $Rh(COD)_2PF_6$ and **5b** in methanol (3 mL) [[substrate (0.5 mmol, 0.167 M)/[Rh]/**5b** = 1:0.01:0.011]]. The reaction went with 100% conversion. [b] The *S* absolute configuration was assigned by comparison of optical rotation with reported data. [c] % ee was determined by chiral GC using a Supelco Chiral Select 1000 (0.25 mm × 15 m) column. [d] % ee was determined by HPLC using a (*R*, *R*)-Poly Whelk-O1 column.



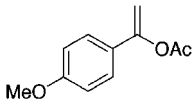

**29** 96% ee




**30** 95% ee




**31** 95% ee




**32** 93% ee

capillary columns: Chirasil-Val III FOST (dimensions: 25 m × 0.25 mm) for dehydroamino acid derivatives; Chiral Select 1000 column (dimensions: 15 m × 0.25 mm) for enamides, enolates, and Baylis−Hillman products; $\gamma$-225 (dimensions: 30 m × 0.25 mm) for itaconic acid derivatives. HPLC analysis was carried out on a Waters 600 chromatograph with an (*R*,*R*)-Poly Whelk-O1 column from Regis Technologies, Inc. [particle size: 5.0 $\mu$m. column dimensions: 25 cm (length) × 0.46 cm (i.d.)] for enamide derivatives; Daicel Chiralcel OJ column for dehydroamino acid derivatives. $^1H$, $^{13}C$, and $^{31}P$NMR were recorded on Bruker WM 360 spectrometer. Chemical shifts were reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard or 85% $H_3PO_4$ as the external standard, respectively. Optical rotation was obtained on a Perkin-Elmer 241 polarimeter.

**Synthesis of Chiral 1,4-Diols.** The diols **8**, **14**, and **15** were prepared according to reported procedures.[6d,7]

**(2*R*,3*R*,4*R*,5*R*)-1,6-Diphenyl-3,4-di-*O*-benzylhexane-2,3,4,5-tetrol (10).** To a suspension of CuI (2.09 g, 10.8 mmol) in dry THF (40 mL) was added 21.6 mL of PhMgBr (1.0 M in THF, 21.6 mmol) over 30 min at −40 °C. The mixture was stirred for an additional 30 min before a solution of diepoxide **9** (1.75 g, 5.37 mmol) in THF (20 mL) was added. After being stirred at −40 °C for 4 h and then at room temperature for additional 1 h, the reaction mixture was quenched with 50 mL of saturated $NH_4Cl$ aqueous solution. The aqueous layer was separated and extracted with 3 × 30 mL of $CH_2Cl_2$. The combined organic layer was dried over $Na_2SO_4$ and evaporated. The residue was further purified via a silica gel column eluted with hexanes/EtOAc (8:2) to give a colorless oil (2.51 g) in 97% yield: $[\alpha]^{24}_D = -6.8$ (*c* 1.02, $CHCl_3$); $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.53−7.34 (m, 20H), 4.87−4.75 (m, 4H) 4.40−4.34 (m, 2H), 3.91−3.85 (m, 2H), 3.12 (dd, *J* = 3.74, 13.78 Hz, 2H), 3.0 (br, 2H), 2.84 (dd, *J* = 8.9, 17.78 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 138.43, 137.34, 129.33, 128.49, 128.45, 128.37, 128.04, 126.37, 79.72, 72.96, 72.25, 40.16; HRMS calcd for $C_{32}H_{34}O_4Na$ ($MNa^+$) 505.2355, found 505.2391.

**Synthesis of 1,4-Diol Cyclic Sulfates.** Cyclic sulfate **11a** was prepared according to the literature.[6d]

**(4*R*,5*S*,6*S*,7*R*)-5,6-Bis(benzyloxy)-4,7-dibenzyl[1,3,2]-dioxathiepane 2,2-Dioxide (11b).** To a solution of diol **10** (2.41 g, 5.0 mmol) and $Et_3N$ (1.4 mL, 10.0 mmol) in $CH_2Cl_2$ (30 mL) was added dropwise a solution of $SOCl_2$ (0.5 mL, 6.0 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with 30 mL of brine. The separated aqueous layer was then extracted with 3 × 30 mL of $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$, evaporated, and then dried via vacuum pump for 20 min. The residue was dissolved in 20 mL of $CCl_4$, 20 mL of $CH_3CN$, and 30 mL of water. $RuCl_3 \cdot xH_2O$ (25 mg) and $NaIO_4$ (1.33 g, 6.0 mmol) were added at 0 °C, and the mixture was stirred for 30

min. Brine (50 mL) was added, and the aqueous solution was extracted with ether (3 × 50 mL). The combined extracts were dried over $Na_2SO_4$ and evaporated. The residue was purified by a silica gel column eluted with hexanes/EtOAc (9:1) to give sulfate **11b** as a white solid (2.58 g) in 95% yield: mp 81−3 °C; $[\alpha]^{24}_D = -4.5$ (*c* 1.0, $CHCl_3$); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.53−7.35 (m, 20H), 5.02−4.97 (m, 4H), 4.94−4.91 (m, 2H), 3.92−3.88 (m, 2H), 3.55−3.50 (m, 2H), 3.02−2.95 (m, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 136.97, 135.06, 129.35, 128.56, 128.43, 128.06, 127.50, 126.97, 83.31, 82.62, 75.45, 37.47; HRMS calcd for $C_{32}H_{32}O_6SNa$ ($MNa^+$) 567.1817, found 567.1762.

**(4*R*,5*S*,6*S*,7*R*)-5,6-*O*-(1-Methylethylidene)-4,7-dimethyl-[1,3,2]dioxathiepane 2,2-Dioxide (16a).** Cyclic sulfate **16a** was prepared according to the procedure for **11b** in 96% yield: mp 70−1 °C; $[\alpha]^{24}_D = +9.4$ (*c* 1.01, $CHCl_3$); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.45−4.40 (m, 2H), 4.05−4.00 (m, 2H), 1.56 (d, $J$ = 7.6 Hz, 6H), 1.40 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 110.64, 81.16, 80.45, 26.69, 18.35; HRMS calcd for $C_9H_{16}O_6SNa$ 275.0565, found 275.0568.

**(4*R*,5*S*,6*S*,7*R*)-5,6-*O*-(1-Methylethylidene)-4,7-diethyl-[1,3,2]dioxathiepane 2,2-Dioxide (16b).** Cyclic sulfate **16b** was prepared according to the similar procedure for **11b** in 97% yield: mp 58−9 °C; $[\alpha]^{24}_D = +35.2$ (*c* 1.07, $CHCl_3$); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.27−4.22 (m, 2H), 4.07−4.04 (m, 2H), 2.01−1.88 (m, 4H), 1.41 (s, 6H), 1.08 (t, $J$ = 7.39 Hz, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 110.58, 86.06, 79.36, 26.76, 25.53, 9.16; HRMS calcd for $C_{11}H_{20}O_6SNa$ 303.0878, found 303.0888.

**General Synthetic Procedure for Making Chiral Phosphines. Phosphine 1a.** To a stirred solution of phenylphosphine (220.2 mg, 2.0 mmol) in THF (50 mL) was added dropwise *n*-BuLi (1.6 M *n*-hexane solution, 1.25 mL, 2.0 mmol) via a syringe at −78 °C. The resulting yellow solution was warmed to room temperature and stirred for 2 h. The mixture was then cooled to −78 °C, and cyclic sulfate **11a** (0.78 g, 2.0 mmol) in THF (30 mL) was added over 10 min. The resulting brown solution was warmed to room temperature and stirred for 4 h. After the solution was cooled back to −78 °C, *n*-BuLi (1.6 M solution in *n*-hexane, 1.25 mL, 2.0 mmol) was added and the reaction mixture was stirred for additional 20 h at room temperature followed by addition of $BH_3$−THF complex (1 M solution in THF, 3.0 mL, 3.0 mmol) at 0 °C. After the solution was stirred overnight, the solvent was evaporated under reduced pressure and 30 mL of water was added. The aqueous solution was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layer was dried over $Na_2SO_4$ and concentrated to afford the crude phospholane−borane product. Purification was performed by a silica gel column eluted with hexanes/EtOAc (9:1) to give **1a**-borane adduct as a white solid (767 mg, 92%): mp 90−2 °C; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.96−7.91 (m, 2H), 7.43−7.24 (m, 13H), 4.65−4.53 (m, 4H), 4.10−3.95 (m, 2H), 2.87−2.81 (m, 2H), 1.29 (dd, $J$ = 7.33, 15.82 Hz, 3H), 0.94 (dd, $J$ = 7.38, 14.21 Hz, 3H), 1.23−0 (br, 3H, $BH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 137.91, 137.50, 134.26 (d, $J$ = 9.15 Hz), 130.96, 128.37−126.29 (m), 83.61 (d, $J$ = 2.71 Hz), 72.35 (d, $J$ = 24.54 Hz), 35,83 (dd, $J$ = 25.6, 33.8 Hz), 9,04 (t, $J$ = 7.33 Hz); $^{31}$P NMR ($CDCl_3$) $\delta$ 37.1 (br); HRMS calcd for $C_{26}H_{32}O_2PB$ 417.2269, found 417.2281.

The **1a**−borane adduct was dissolved in 20 mL of toluene, and 2 equiv of DABCO was added. The resulting mixture was heated at 50 °C for 8 h. After removal of the solvent, the residue was passed through a silica gel plug eluted with hexane/ethyl acetate (9:1) to give phosphine **1a** as a colorless oil: $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.56−7.52 (m, 2H), 7.17−7.06 (m, 13H), 4.45−4.32 (m, 4H), 3.86−3.82 (m, 2H), 2.75−2.67 (m, 2H), 1.15 (dd, $J$ = 7.57, 14.88 Hz, 3H), 0.68 (dd, $J$ = 7.42, 17.2 Hz, 3H); $^{31}$P NMR ($CDCl_3$) $\delta$ 5.95.

**Phosphine 1b.** The phosphine **1b** was prepared according to the procedure for the synthesis of **1a**.

**1b**−$BH_3$ adduct in 87% yield: mp 78−81 °C; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 8.28−8.22 (m, 2H), 7.71−7.15 (m, 18H), 4.59−4.49 (m, 4H), 4.11−3.97 (m, 2H), 3.50−3.18 (m, 4H), 2.79−2.76 (m, 2H), 1.30−0 (br, 3H, $BH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.03, 137.82, 137.36, 134.32, 134.21, 131.27, 128.54−125.97 (m), 80.65 (d, $J$ = 49.17 Hz), 72.25 (d, $J$ = 18.1 Hz), 43.23 (dd, $J$ = 31.60, 60.68 Hz), 29.81 (d, $J$ = 7.15 Hz); $^{31}$P NMR ($CDCl_3$) $\delta$ 34.20; HRMS calcd for $C_{38}H_{40}O_2PB$ 569.2895, found 569.2862.

**1b** was liberated according to the procedure for **1a**: $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.90−7.80 (m, 2H), 7.50−7.20 (m, 18H), 4.28−4.21 (m, 4H), 4.08−3.98 (m, 2H), 3.35−3.20 (m, 4H), 2.70−2.61 (m, 2H); $^{31}$P NMR ($CDCl_3$) $\delta$ −0.31.

**Phosphine 2.** To a stirred solution of phenylphosphine (440.4 mg, 4.0 mmol) in THF (80 mL) was added dropwise *n*-BuLi (1.6 M *n*-hexane solution, 2.5 mL, 4.0 mmol) via a syringe at −78 °C. Then the resulting pale yellow solution was stirred for 2 h at room temperature. After the mixture was cooled to −78 °C, cyclic sulfate **16a** (1.01 g, 4.0 mmol) in THF (40 mL) was added over 10 min. The resulting yellow solution was warmed to room temperature and stirred for 4 h. After the solution was cooled to −78 °C, *n*-BuLi (1.6 M solution in *n*-hexane, 2.5 mL, 4.0 mmol) was added, and the reaction mixture was stirred for an additional 20 h at room temperature. The color of the reaction mixture changed from orange yellow to red and then became colorless. After removal of the solvent under reduced pressure, the residue was dissolved in 40 mL of ethyl ether, and 30 mL of brine was added. The aqueous layer was then washed with 3 × 30 mL of ethyl ether. The combined organic layer was dried over $Na_2SO_4$ and concentrated to afford a colorless oil. This oily compound (**2**) was further purified by a short silica gel column eluted with hexane/ether (9:1) (850 mg in 80% yield): $^1$H NMR (360, MHz, $CDCl_3$) $\delta$ 7.72−7.27 (m, 5H), 4.60−4.32 (m, 2H), 2.70−2.51 (m, 2H), 1.52 (s, 6H), 1.38−1.32 (m, 3H), 0.70−0.52(m, 3H); $^{31}$P NMR ($CDCl_3$) $\delta$ 50.2; HRMS calcd for $C_{15}H_{21}O_2P$ 265.1357, found 265.1370.

**Phosphine 3.** The phosphine (**2**) (528 mg, 2.0 mmol) obtained above was dissolved in 50 mL of methanol and 2 mL of water. To this solution was added 0.05 mL of methanesulfonic acid, and the resulting mixture was refluxed for 10 h. The solvent was removed under reduced pressure, and the residue was dissolved in 50 mL of methylene chloride. A saturated aqueous solution of $NaHCO_3$ (30 mL) was added, and the two layers were separated. The aqueous layer was washed with 3 × 40 mL of methylene chloride. The combined organic layers were dried over $Na_2SO_4$ and concentrated to give a white solid **3**: mp 57−9 °C; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.94−7.89 (m, 2H), 7.48−7.41 (m, 3H), 4.36−4.22 (m, 2H), 3.05−2.93 (m, 1H), 2.82−2.73 (m, 1H), 2.11 (br, 2H), 1.29 (dd, $J$ = 7.46, 15.6 Hz, 3H), 0.92 (dd, $J$ = 7.38, 14.3 Hz, 3H); $^{31}$P NMR ($CDCl_3$) $\delta$ 4.69; HRMS calcd for $C_{12}H_{17}O_2P$ 225.1044, found 225.1042.

**Phosphine 4a.** To a stirred solution of 1,2-bis(phosphino)-benzene (1.24 g, 8.72 mmol) in THF (200 mL) was added dropwise *n*-BuLi (1.6 M *n*-hexane solution, 10.9 mL, 17.4 mmol) via a syringe at −78 °C. Then the resulting yellow solution was stirred for 2 h at room temperature. After the mixture was cooled to −78 °C, cyclic sulfate **16a** (4.39 g, 17.4 mmol) in THF (50 mL) was added over 10 min. The solution was then warmed to room temperature and stirred for 4 h. The mixture was cooled to −78 °C, and *n*-BuLi (1.6 M solution in *n*-hexane, 11.0 mL, 17.5 mmol) was added. After the mixture was cooled at room temperature for another 20 h, the solvent was removed under reduced pressure. The residue was dissolved in 50 mL of ethyl ether and washed with 50 mL of brine. The aqueous layer was then extracted with 3 × 40 mL ethyl ether. The combined organic layer was dried over $Na_2SO_4$ and concentrated to afford a colorless crystalline solid. Recrystallization from $Et_2O$/MeOH gave the pure product (3.42 g, 87% yield): mp 67−9 °C; $[\alpha]^{24}_D = +287.2$ (*c* 0.85 $CHCl_3$); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.38−7.33 (m, 4H), 4.46−4.36 (m, 4H), 2.89−2.82 (m, 2H), 2.56−2.51 (m, 2H), 1.47 (s, 6H), 1.42 (s, 6H), 1.33−1.28 (m, 6H), 0.73−0.69 (m, 6H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 140.53, 130.59, 129.00, 117.44, 81.41, 80.51 (t, $J$ = 6.5 Hz), 27.34, 27.30, 25.05 (t, $J$ = 10.3 Hz), 24.20, 13.74 (t, $J$ = 19.6 Hz), 12.15; $^{31}$P NMR (145 MHz, $CDCl_3$) $\delta$ 45.1; HRMS calcd for $C_{24}H_{37}O_4P_2$ ($MH^+$) 451.2167, found 451.2164.

**Phosphine 5a.** Compound **4a** (451 mg, 1.0 mmol) was dissolved in 100 mL of methanol and 2 mL of water. To this solution 0.05 mL of methanesulfonic acid was added, and the resulting mixture was heated at reflux for 10 h. After removal

of the solvent, the residue was passed through a short silica gel plug by eluting with EtOAc/MeOH (95:5) to give pure compound **5a** as a colorless syrup (352 mg, 95% yield): $[\alpha]^{24}_D$ = + 373.1 (*c* 0.98 $CH_3OH$); $^1H$ NMR (360 MHz, $CD_3OD$) $\delta$ 8.42−8.07 (m, 2H), 7.72−7.69 (m, 2H), 5.28 (br, 4H), 4.24−4.17 (m, 4H), 3.31−3.28 (m, 2H), 3.16−3.13 (m, 2H), 1.37−1.30 (m, 6H), 0.94−0.88 (m, 6H); $^{13}C$ NMR (90 MHz, $CD_3OD$) $\delta$ 136.6 (t, $J$ = 3.4 Hz), 133.7, 133.6, 80.2, 80.0, 37.3, 35.4 (d, $J$ = 10.0 Hz), 11.6 (d, $J$ = 6.5 Hz), 10.8; $^{31}P$ NMR (145 MHz, $CD_3OD$) $\delta$ 11.9 (br); HRMS calcd for $C_{18}H_{29}O_4P_2$ ($MH^+$) 371.1541, found 371.1523.

**Phosphine 4b.** Diethyl phosphine **4b** was prepared according to the procedure for the synthesis of **4a.** Recrystallization of crude **4b** from $Et_2O$/MeOH gave the pure product as a colorless crystal in 83% yield: mp 55−7 °C; $[\alpha]^{24}_D$ = +142.3 (*c* 0.84 $CHCl_3$); $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.41−7.32 (m, 4H), 4.50−4.37 (m, 4H), 2.62−2.61 (m, 2H), 2.22−2.20 (m, 2H), 2.19−2.17 (m, 2H), 1.50−1.44 (m, 2H), 1.47 (s, 6H), 1.32−1.30 (m, 2H), 0.99−0.95 (m, 6H), 0.88−0.86 (m, 2H), 0.79−0.75 (m, 6H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 141.3, 131.1, 129.2, 117.1, 82.3, 81.4 (t, $J$ = 6.1 Hz), 33.0, 32.8 (t, $J$ = 9.6 Hz), 27.4, 27.3, 21.4, 21.1 (t, $J$ = 14.2 Hz), 14.6, 13.1 (t, $J$ = 5.1 Hz).; $^{31}P$ NMR (145 MHz, $CDCl_3$) $\delta$ 34.5; HRMS calcd for $C_{28}H_{44}O_4P_2$ 507.2793, found 507.2777.

**Phosphine 5b.** Hydroxyl phospholane **5b** was prepared as a colorless syrup according to the procedure for the synthesis of **4b** (94% yield): $[\alpha]^{24}_D$ = +195.4 (*c* 0.75 $CH_3OH$); $^1H$ NMR (360 MHz, $CD_3OD$) $\delta$ 8.30−8.20 (m, 2H), 7.71−7.67 (m, 2H), 5.30 (br, 4H), 4.40−4.33 (m, 4H), 3.26−3.11 (m, 2H), 2.96−2.85 (m, 2H), 1.95−1.91 (m, 2H), 1.76−1.72 (m, 2H), 1.37−1.27 (m, 4H), 0.93 (t, $J$ = 7.35 Hz, 6H), 0.87 (t, $J$ = 7.26 HZ, 6H); $^{13}C$ NMR (90 MHz, $CD_3OD$) $\delta$ 137.1 (t, $J$ = 3.4 Hz), 133.3, 133.2, 78.0, 77.4, 42.3 (d, $J$ = 15.7 Hz), 39.6, 21.2 (d, $J$ = 13.3 Hz), 19.7, 14.2 (d, $J$ = 10.8 Hz), 13.5 (d, $J$ = 10.8 Hz); $^{31}P$ NMR (145 MHz, $CD_3OD$) $\delta$ 5.65 (br); HRMS calcd for $C_{22}H_{36}O_4P_2$ 427.2167, found 427.2165.

**General Procedure for Asymmetric Baylis−Hillman Reaction.** The mixture of 4-pyridinecarbonaldehyde (110 mg, 1 mmol) and 1 mL of methyl acrylate was degassed three times by a freeze−pump−thaw method. The resulting solution was transferred into another Schlenk tube, which contained the phosphine catalyst (0.1 mmol). The solution was stirred at room temperature, and the methyl acrylate was removed under vacuum. The residue was purified by a silica gel column eluted with hexanes/ethyl acetate (1:2). The enantiomeric excess was measured by GC with a chiral capillary column.

**General Procedure for Asymmetric Hydrogenation.** To a solution of $[Rh(COD)_2]PF_6$ (2.1 mg, 0.0045 mmol) in methanol (3 mL) in a glovebox was added bisphospholane **5** (0.10 mL of 0.05 M solution in methanol, 0.005 mmol). After the mixture was stirred for 10 min, substrate (0.5 mmol) was added. The hydrogenation was performed at room temperature under 3−10 atm of $H_2$ for 12−48 h. After carefully releasing the hydrogen, the reaction mixture was passed through a short silica gel column to remove the catalyst. For hydrogenation of dehydroamino acids and itaconic acid, the methanol was removed under vacuum. A portion of the residue was dissolved in THF and then treated with a diazamethane in ether to provide the corresponding methyl ester. The enantiomeric excesses were measured by GC or HPLC directly. The absolute configuration of products was determined by comparing the observed rotation with the reported value. When water was used as the solvent for hydrogenation of dimethyl itaconate, the product was extracted with 3 × 3 mL $Et_2O$ and dried over $Na_2SO_4$. For hydrogenation of the itaconic acid, the solvent was removed and a portion of the residue was treated with a diazamethane solution in THF.

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