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Rhodium-hydroxyl bisphospholane catalyzed highly enantioselective hydrogenation of dehydroamino acids and esters

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Abstract

A chiral hydroxyl bisphospholane, 1,2-bis[(2*S*,3*S*,4*S*,5*S*)-3,4-dihydroxyl-2,5-dimethylphospholanyl]benzene (**4**), was synthesized from readily available D-mannitol. Its Rh(I) complex catalyzes asymmetric hydrogenation of dehydroamino acids and their ester derivatives with excellent enantioselectivities (98 to >99% ee).

Transition metal-catalyzed asymmetric hydrogenation reaction is one of the most efficient methods for preparing a wide range of enantiomerically pure compounds.[1] Development of efficient chiral catalysts depends on the design and synthesis of new chiral ligands. Recently, we introduced several classes of structurally innovative bisphosphines based on chiral 1,4-diols with four stereogenic centers[2] (e.g. BICP and PennPhos) which have shown excellent enantioselectivities in Rh- and Ru-catalyzed hydrogenation of olefins and ketones. 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 acids.[2a] Herein, we report the synthesis of bisphospholane **4** bearing four hydroxyl groups from D-mannitol and its application in asymmetric hydrogenation of dehydroamino acids and ester derivatives.

Burk et al. have developed Me-DuPhos **1** and its rhodium(I) complex has shown broad utilities for catalytic asymmetric hydrogenation.[3] We proposed to make chiral hydroxy bisphosphines such as **4** and monophosphines to achieve the following significant goals: (1) to introduce a secondary interaction site between hydroxy groups and substrates;[4] (2) to link the hydroxyl groups toward a polymer chain or water soluble groups; and (3) to gain benefit of easier ligand synthesis from readily available materials. Since D-mannitol is commonly used as a chiral auxiliary or ligand backbone, we have learned from recent literature that the Borner[5] and Brown[6] groups have independently pursued the synthesis of chiral phospholane from D-mannitol during the course of our study. The so-called RoPhos **2** developed by Borner is an excellent ligand for Rh-catalyzed asymmetric hydrogenation reactions. Borner's results prompted us to disclose our finding with the chiral hydroxy bisphosphine **4**, a more amenable ligand for structural modification compared with **2** (Scheme 1).

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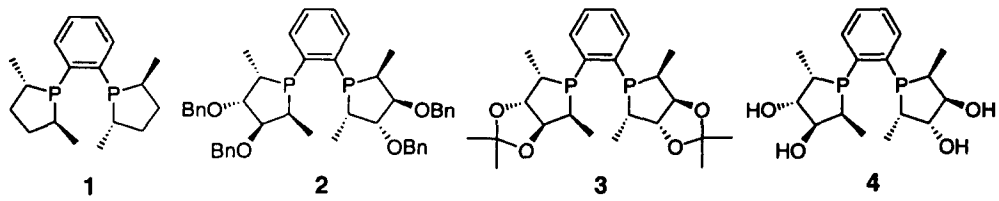
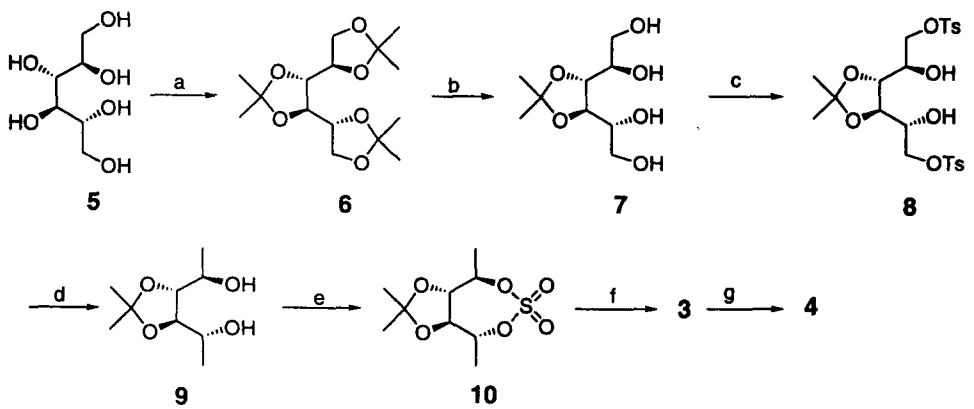


Scheme 1.

Our synthetic route to **4** is shown in Scheme 2. A cheap commercially available D-mannitol **5** was used as the starting material, which was fully protected to give the triacetonide **6** in 81% yield. Selective conversion of **6** into the 3,4-*iso*-propylene D-mannitol **7** was done according to a literature procedure.[7] Both primary hydroxyl groups were converted via tosylation and subsequent reduction with $LiAlH_4$ into methyl groups. Cyclic sulfate **10** was obtained using esterification with thionyl chloride followed oxidation with $RuCl_3/NaIO_4$.[8] Nucleophilic attack of **10** with 1,2-diphosphinobenzene in the presence of *n*-BuLi affords **3** as a white solid in 85% yield. Finally, bisphospholane **3** was hydrolyzed in the presence of methanesulfonic acid to give **4** in 90% yield.[9] Compared with ligand **2**, the synthesis of the corresponding 1,4-diol for **3** is much easier and there is no need to do BH_3 protection and run column chromatography to obtain **3**. Furthermore, we cannot obtain **4** from **2** by a deprotection procedure.[10]

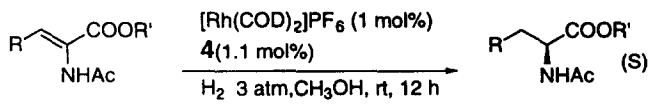


Scheme 2. (a) Acetone, H_2SO_4; 81%. (b) AcOH, H_2O, 40°C, 2.5 h; 78%. (c) TsCl, pyridine, 0°C, 4 h. (d) $LiAlH_4$, THF; 75% from **7**. (e) (i) $SOCl_2$, Et_3N, CH_2Cl_2; (ii) $NaIO_4/RuCl_3$; 90% from **9**. (f) (i) 1,2-$H_2PC_6H_4PH_2$, *n*-BuLi; (ii) *n*-BuLi, THF, 85%. (g) CH_3OH, H_2O, CH_3SO_3H, refluxing, 90%

The phospholanes **3** and **4** were used in Rh-catalyzed hydrogenation of dehydroamino acids and their ester derivatives. The catalyst was prepared in situ by mixing $Rh(COD)_2PF_6$ and the ligand in methanol. Surprisingly, the *iso*-propylene protected phospholane **3** does not work for the hydrogenation reaction. After 12 h under 3 atm of H_2, the substrate was recovered quantitatively. That is likely due to the steric hinderance of the *iso*-propylene group in the two fused *trans* five–five membered rings, which blocks substrate binding site to the Rh center. However, Rh complex with the corresponding hydroxyl bisphospholane **4** is an excellent hydrogenation catalyst (Table 1). High enantioselectivities (98 to >99% ee) have been achieved for hydrogenation of many dehydroamino acids and their ester derivatives. These results are comparable to those achieved with Rh-Me-DuPhos (**1**)[3] and higher than the ee's reported with a Rh (**2**) catalyst (only 93 and 96% ee were obtained for substrates in entries 3 and 4 of Table 1, respectively).[5]

In summary, we have derived a practical route to synthesize a chiral hydroxyl bisphospholane **4** and developed a highly enantioselective catalyst for asymmetric hydrogenation of dehydroamino acids

Table 1
Asymmetric hydrogenation of dehydroamino acid derivatives[a]



Entry	Substrate	% ee [b]
1	R = H, R^1 = H	>99[c]
2	R = H, R^1 = CH_3	98.3
3	R = Ph, R^1 = H	>99[c]
4	R = Ph, R^1 = CH_3	>99
5	R = *p*-F-C_6H_4, R^1 = H	98.5[c]
6	R = *p*-F-C_6H_4, R^1 = CH_3	98.4
7	R = *p*-MeO-C_6H_4, R^1 = H	98.1[c,d]
8	R = *p*-MeO-C_6H_4, R^1 = CH_3	98.3[d]
9	R = 2-thienyl, R^1 = H	>99[c]
10	R = 2-thienyl, R^1 = CH_3	>99

a. The reaction was carried out at rt under 3 atm of H_2 for 12 h in 3 mL of methanol with 100% conversion [substrate (0.5 mmol):[$Rh(COD)_2$]PF_6:ligand **4** = 1:0.01:0.011]. b. The *S* absolute configurations were determined by comparing optical rotations with reported values. The %ee was measured by GC using a Chiral-VAL III FSOT column. c. Determined on the corresponding methyl ester. d. The %ee was determined by HPLC using a Chiral OJ column.

and ester derivatives. The readily accessible chiral hydroxyl phosphines can be very useful for many asymmetric catalytic reactions. We are preparing many derivatives of the chiral hydroxy bisphosphine **4** as well as chiral hydroxy monophosphines and testing them for a variety of organic transformations.

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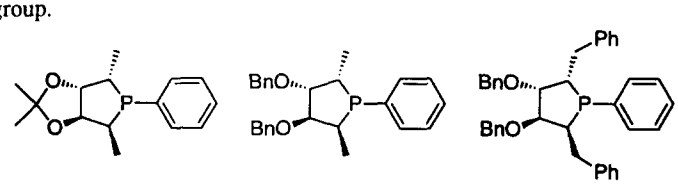
9. Selective data for compounds **3** and **4**. Compound **3**: ^{1}H NMR ($CDCl_3$): δ 7.38–7.33 (m, 4H, aromatic), 4.46–4.36 (m, 4H), 2.89–2.82 (m, 2H), 2.56–2.51 (m, 2H), 1.47 (s, 6H), 1.42 (s, 6H), 1.33–1.28 (m, 6H), 0.73–0.69 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 140.53, 130.59, 129.00, 117.44, 81.41, 80.51 (t, J_{PC}=6.5 Hz), 27.34, 27.30, 25.05 (t, J_{PC}=10.3 Hz), 24.20, 13.74 (t, J_{PC}=19.6 Hz), 12.15; ^{31}P NMR ($CDCl_3$): δ 45.1 ppm. HRMS calcd for $C_{24}H_{37}O_4P_2$ (MH^+): 451.2167; found: 451.2164. Compound **4**: ^{1}H NMR (CD_3OD): δ 8.42–8.07 (m, 2H, aromatic), 7.72–7.69 (m, 2H, aromatic), 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 (CD_3OD): δ 136.6 (t, J_{PC}=3.4 Hz), 133.7, 133.6, 80.2, 80.0, 37.3, 35.4 (d, J_{PC}=10.0 Hz), 11.6 (d, J_{PC}=6.5 Hz), 10.8. ^{31}P NMR (CD_3OD): δ 11.9 (broad) ppm. HRMS calcd for $C_{18}H_{29}O_4P_2$ (MH^+): 371.1541; found: 371.1523.
10. We have made several chiral monophospholanes from D-mannitol (e.g. **11** to **13**) and tried many methods to cleave the protecting groups. The *iso*-propylene group in **11** was smoothly removed by an acid catalyzed hydrolysis. However, the borane adduct of **12** was just selectively debenzylated when BCl_3 or $BF_3 \cdot Et_2O$ was used as the reagent to give the derivatives bearing one hydroxyl and one benzyl ether group. The corresponding phosphine oxide of **12** also gave selectively debenzylated products under mild hydrogenation conditions (10% $Pd(OH)_2$/C). The hydrogenation reaction done under high temperature (50°C) and pressure of H_2 (40 atm) not only cleaved the benzyl ether but also reduced the phenyl to cyclohexyl group.



11 **12** **13**