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

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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 C2-symmetric diphosphines are of
special interest due to their effectiveness in many
asymmetric reactions.2 Ligands such as DIP,3 DIPAMP,4
Chiraphos,5 Skewphos,6 BPPM,7 DEGPhos,8 BINAP,9
DiPhos,10,11 BPE,10,11 and PPh3 are some
representative examples of 1,2-, 1,3-, and 1,4-diphos-
phines which form a five-, six-, and seven-membered ring
with transition metals. Due to the limitation of existing
ciral 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-

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(i) Oliver, J. D.; Riley, D. P. Organometallics, 1983, 2, 1032.
(l) Oliver, J. D.; Riley, D. P. Organometallics, 1983, 2, 1032.
(o) Oliver, J. D.; Riley, D. P. Organometallics, 1983, 2, 1032.
an intramolecular SN2 reaction gives ditosylation (5–6) shown in Scheme 1. Cheap, commercially available D-mannitol was used as the starting material. D-mannitol 4 was used as the starting material. D-mannitol 4 was first converted to 3,4-iso-\(\text{ipropylidene-D-mannitol} 5\) followed by dibenylation (5 → 6) and ditosylation (6 → 7). Transesterification of 7 followed by an intramolecular Sn2 reaction gives 8 with inversion of configuration of the two stereogenic centers. Redu}
Asymmetric Hydrogenation of Enamides 11 Catalyzed by a Rhodium-3 Complex

Table 2

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>R</th>
<th>Rh</th>
<th>ee (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>C6H5</td>
<td>H</td>
<td>[Rh(COD)Cl]2</td>
<td>97.8</td>
</tr>
<tr>
<td>2</td>
<td>C6H5</td>
<td>H</td>
<td>[Rh(COD)2]SbF6</td>
<td>98.3</td>
</tr>
<tr>
<td>3</td>
<td>p-CF3C6H4</td>
<td>H</td>
<td>[Rh(COD)Cl]2</td>
<td>97.6</td>
</tr>
<tr>
<td>4</td>
<td>p-CF3C6H4</td>
<td>H</td>
<td>[Rh(COD)2]SbF6</td>
<td>98.7</td>
</tr>
<tr>
<td>5</td>
<td>m-CH3C6H4</td>
<td>H</td>
<td>[Rh(COD)Cl]2</td>
<td>98.5</td>
</tr>
<tr>
<td>6</td>
<td>m-CH3C6H4</td>
<td>H</td>
<td>[Rh(COD)2]SbF6</td>
<td>98.8</td>
</tr>
<tr>
<td>7</td>
<td>p-CH3C6H4</td>
<td>H</td>
<td>[Rh(COD)Cl]2</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>8</td>
<td>p-CH3C6H4</td>
<td>H</td>
<td>[Rh(COD)2]SbF6</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>9</td>
<td>2-naphthyl</td>
<td>H</td>
<td>[Rh(COD)Cl]2</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>10</td>
<td>2-naphthyl</td>
<td>H</td>
<td>[Rh(COD)2]SbF6</td>
<td>99.0%</td>
</tr>
<tr>
<td>11</td>
<td>C6H5</td>
<td>CH3</td>
<td>[Rh(COD)2]SbF6</td>
<td>97.3</td>
</tr>
<tr>
<td>12</td>
<td>C6H5</td>
<td>isopropyl</td>
<td>[Rh(COD)2]SbF6</td>
<td>99.0</td>
</tr>
<tr>
<td>13</td>
<td>C6H5</td>
<td>Bn</td>
<td>[Rh(COD)2]SbF6</td>
<td>98.6%</td>
</tr>
<tr>
<td>14</td>
<td>p-CF3C6H4</td>
<td>CH3</td>
<td>[Rh(COD)2]SbF6</td>
<td>98.3</td>
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<tr>
<td>15</td>
<td>p-MeOC6H4</td>
<td>CH3</td>
<td>[Rh(COD)2]SbF6</td>
<td>98.0%</td>
</tr>
<tr>
<td>16</td>
<td>2-naphthyl</td>
<td>CH3</td>
<td>[Rh(COD)2]SbF6</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

* The reaction was carried out at rt under 10 bar of H2 for 48–60 h. The catalyst was made in situ by stirring a solution of a Rh precursor and the bisphosphine ligand 3 in 3 mL of methanol ([substrate (0.25 mmol, 0.083 M) [Rh(II)] / 3 = 1:0.020:0.022)]. The reaction went with >99% conversion unless stated otherwise.

* 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. * Enantiomeric excesses were determined by chiral HPLC using a (S,S)-whelk-O1 column. * With 20% conversion based on GC analysis.

11–13 with 3 are highly enantioselective for hydrogenation of 11a in MeOH. Increasing H2 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 CH2Cl2 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). It has been suggested that such effects are the results of conformational changes of the metal complex in different solvents. 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 substrates 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 2). An important feature of the Rh-3 (R,S,S,R)-DIOP* catalyst is its high enantioselectivity for hydrogenation of an α-aryl enamine 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. 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. Rh, S, Rh-DIOP* and its derivatives can be prepared easily from the readily available D-mannitol 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 (CH2Cl2) was distilled from Mg under nitrogen. Gas chromatography was carried out on an Hewlett-Packard 6890 gas chromatograph using a Chiral Select 1000 column (Dimensions: 15 m × 0.25 mm), carrier gas: He (1 mL/min). HPLC analysis was carried out on a Waters 600 chromatograph with an (S,S)-Whelk-O1 column from Regis Technologies, Inc. (particle size: 5.0 μm, column dimensions: 25 cm (length) × 0.46 cm (i.d.).

Synthesis of 3,4-O-Isopropylidene-(3S,4S)-di-hydroxy-(25S,5S)-hexanediol Bis(methanesulfonate) 10. To a solution of 3,4-O-Isopropylidene-(3S,4S)-di-hydroxy-(25S,5S)-hexanediol Bis(methanesulfonate) 10 (2.2 g, 11.6 mmol) and triethylamine (4.9 mL, 34.8 mmol) in CH2Cl2 (30 mL) was added dropwise a solution of methanesulfonyl chloride (2.0 mL, 25.8 mmol) in CH2Cl2 (10 mL) at 0 °C. After 30 min at 0 °C, the reaction mixture was stirred for an additional 30 min at room temperature and then quenched by saturated aqueous NH4Cl solution. The aqueous layer was extracted with CH2Cl2 and the combined organic solution was dried over Na2SO4. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel eluting with CH2Cl2/EtOAc (9/1) to give a colorless oil 3.85 g in 96% yield: [α]22 D = –1.32° (c = 1.04, CHCl3); 1H NMR (CDCl3, 300 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); 13C NMR (CDCl3, 75 MHz) δ 110.14, 78.19, 76.26, 38.53, 26.75, 17.63; HRMS calcd for C11H22O8S2Na (MNa+) 347.0834 and found 347.0834 and 369.0654. Summary of 3,4-O-Isopropylidene-(3S,4S)-di-hydroxy-(2R,5R)-bis(diphenylphosphino)hexane 3a ([R,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).

Notes


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-(3S,4S)-dihydroxy-(2S,5S)-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 NH₄Cl solution. The aqueous layer was extracted with CH₂Cl₂ and the combined organic solution was dried over anhydrous Na₂SO₄. 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: [α]D25 = +41.8° (c = 0.88, toluene); ¹H NMR (CDCl₃, 360 MHz) δ 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); ¹³C NMR (CD₂Cl₂, 90 MHz) δ 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, J₁ = 12.0 Hz J₂ = 6.8 Hz), 31.33 (d, J = 14.3 Hz), 27.05, 10.74 (d, J = 17.6 Hz); ³¹P NMR (CDCl₃) δ = −6.3 ppm; HRMS calcd for C₁₃H₁₃O₂P₂ (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

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