A Novel Chiral Ferrocenyl Phosphine Ligand from Sugar: Applications in Rh-Catalyzed Asymmetric Hydrogenation Reactions

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ABSTRACT

A new chiral ferrocenyl diphosphine ligand 3 was synthesized from readily available D-mannitol. Rh-complex with this ligand showed high enantioselectivity and reactivity in the asymmetric hydrogenation of dehydroamino acid derivatives and itaconic acid derivatives. Up to over 99% ee and 10 000 TON were achieved with this catalytic system.

An increasing number of chiral compounds and enantiomerically pure drugs are prepared through transition metal-catalyzed asymmetric reactions.1 Since the reactivity and stereoselectivity of an asymmetric transformation are highly dependent on the structure of the chiral ligand coordinated to the transition metal, the design and synthesis of efficient chiral ligands are important in this area and have attracted a great deal of attention from both academia and industry.2 For many years, the ferrocene moiety has been extensively explored as a backbone of chiral phosphine ligands due to its easy modifiability and highly electron donating property. In addition, the ferrocene-derived ligands generally crystallize readily and are relatively air stable compared to their nonferrocenyl analogues. These features are beneficial for purification and usage of the ligands. Excellent results have been achieved with ferrocene-based ligands in asymmetric hydrogenation. JosiPhos,3 TRAP4 and FERRIPHOS5 are some examples of these ligands. Recently, we also reported a C2-symmetric ferrocene-linked seven-membered phosphane ligand (f-Binaphane) and illustrated its high enantioselectivity for the hydrogenation of imine substrates.6 DuPHOS and BPE type ligands have proven to be versatile in asymmetric hydrogenation reactions and these ligands have the five-membered trans-2,5-disubstituted phospholane motif. Some other polysubstituted phospholanes were also reported to be efficient ligands for asymmetric catalysis.7 However, few good ligands have been reported with both the ferrocene backbone and the five-membered phospholane moiety. Ligand 1 (Figure 1) has the combination of a ferrocene linker...
and trans-2,5-disubstituted phospholanes and shows significantly lower enantioselectivities in hydrogenation reactions compared to its DuPHOS and BPE analogues. Herein, we wish to report the synthesis of a new chiral ferrocenyl polysubstituted phospholane ligand, (3aS,3aS,4S,4S,6S,6S,6aS,6aS)-5,5′-[1,1′-ferrocenyl]bis[tetrahydro-2,2,4,6-tetramethyl-4H-phosphol[3,4-d]-1,3-dioxole] (3) and its excellent applications in asymmetric hydrogenation reactions.

Burk and co-workers synthesized the ferrocenyl analogue of DuPHOS (ligand 1) by using a flexible and more electron-donating 1,1′-ferrocenyl bridge as a linker between two phosphorus atoms. These catalysts exhibited excellent catalytic activity for the hydrogenation of various olefins and carbonyl groups, but a decrease in the enantioselectivity was observed. Recently, both Marinetti and Burk prepared new ferrocenyl bisphosphetane ligands (FerroTANE), which had shown superior utility in the asymmetric hydrogenation of dehydroamino acids with this new class of ligands. It is noteworthy that changing the steric bulk on the 2,4-disubstituted phospholane ligands 2 resulted in a marked increase in enantioselectivity in the Rh-2 catalyzed hydrogenation of α-(N-acetamido)acrylate (69% ee (S) and 94% ee (R), respectively). A similar trend was also observed in the Rh-1 catalytic system for hydrogenation of the same substrate. We reasoned that an appropriate bulky chiral phosphorus heterocycle might have a better asymmetric induction than a less bulky heterocycle. On the basis of this assumption, we envisioned that the ferrocene-bridged polysubstituted phospholane ligand (3) might be an excellent ligand. It was thought that the increased steric hindrance and rigidity of this ketal phospholane may result in high enantioselectivity.

The synthetic route to ligand 3 is shown in Scheme 1. The key intermediate 1,4-diol cyclic sulfate 7 was prepared according to the reported method from the commercially available and inexpensive D-mannitol. The 1,1′-bis(phosphino)ferrocene 8 was prepared from ferrocene through a two-step procedure. Nucleophilic attack of 7 with 8 in the presence of n-BuLi afforded ligand 3. This new ligand can be easily isolated by running it through a short silica gel plug followed by recrystallization to afford orange crystals, which are air-stable in the solid state.

The Rh(I)-catalyzed hydrogenation of dehydroamino acids and their ester derivatives was investigated with ligand 3. The catalyst was prepared in situ by mixing [Rh(COD)2]OTf and ligand 3 in a solvent. The commercially available α-(N-acetamido)acrylate 9a was initially chosen to screen the reaction conditions. The results are shown in Table 1.

Table 1. Rh(I)-3 Catalyzed Asymmetric Hydrogenation of α-(N-acetamido)acrylate

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>solvent</th>
<th>pressure of H2 [psi]</th>
<th>time [h]</th>
<th>ee [%]</th>
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<tbody>
<tr>
<td>1a</td>
<td>1a</td>
<td>MeOH</td>
<td>60</td>
<td>6</td>
<td>64</td>
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<td>1b</td>
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<td>2a</td>
<td>MeOH</td>
<td>60</td>
<td>18</td>
<td>69</td>
</tr>
<tr>
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<td>2b</td>
<td>MeOH</td>
<td>60</td>
<td>18</td>
<td>94</td>
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<tr>
<td>3</td>
<td>3</td>
<td>CH2Cl2</td>
<td>45</td>
<td>0.5</td>
<td>99.4</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>THF</td>
<td>45</td>
<td>0.5</td>
<td>99.2</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>toluene</td>
<td>45</td>
<td>0.5</td>
<td>98.8</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>THF</td>
<td>15</td>
<td>0.5</td>
<td>99.9</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>toluene</td>
<td>15</td>
<td>0.5</td>
<td>99.6</td>
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</table>

* See Experimental Section for details. The absolute configuration was assigned by comparison of optical rotation with reported data. Enantiomeric excesses were determined by chiral GC (Chirasil-VAL III FSOT). These results are from ref 8; (Rh(I)COD)OTf was used as catalyst precursor.

Excellent enantioselectivities (up to 99.9% ee) were observed for this reaction under all tested conditions. This result is superior to those obtained with the analogous ligands 1

Figure 1.
entries 1–6). A small solvent effect was seen and THF gave the best results. Toluene was not a favorable choice because it did not provide sufficient solubility for the majority of the substrates tested. Low hydrogen pressure was favorable for achieving higher enantioselectivity (Table 2, entries 2–4). The reaction was complete at ambient H₂ pressure within 30 min, which suggests that this catalytic system is highly efficient.

Table 2. Rh(I)-3 Catalyzed Asymmetric Hydrogenation of α-Dehydroamino Acid Derivatives

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>solvent</th>
<th>conversion [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9b R = Ph, R' = Me</td>
<td>MeOH</td>
<td>97</td>
<td>9b</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>THF</td>
<td>99.0</td>
<td>9c</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>THF</td>
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<td>CH₂Cl₂</td>
<td>CH₂Cl₂</td>
<td>98.9</td>
<td>9f</td>
</tr>
<tr>
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<td>Toluene</td>
<td>99.5</td>
<td>9d</td>
</tr>
<tr>
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<td>9g</td>
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<td>&gt;99.9</td>
<td>9h</td>
<td></td>
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<tr>
<td>9</td>
<td>THF</td>
<td>THF</td>
<td>99.0</td>
<td>9i</td>
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<td>98.8</td>
<td>9l</td>
</tr>
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<td>THF</td>
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<td>9m</td>
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<td>98.7</td>
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<td>THF</td>
<td>THF</td>
<td>97.8</td>
<td>9n</td>
</tr>
</tbody>
</table>

To further investigate the catalytic efficiency of the Rh(I)-3 system, the pure catalyst precursor [Rh(COD)]PF₆ (11) was isolated. α-(N-Acetamido)acrylate (9a) was subject to 3 atm of H₂ in the presence of 0.01 mol % of [Rh(COD)]-PF₆ in THF. (S)-10a was obtained in 100% yield within 12 h as a single enantiomer detected by GC (>99.9% ee). Thus, a high turnover number of 10 000 can be achieved in this system.

Hydrogenation of itaconic acid derivatives was also explored with the Rh(I)-3 catalytic system. Good to excellent results (up to >99% ee) were achieved for itaconic acid (12a) and its derivatives 12b and 12c (Figure 2).

In conclusion, a new chiral polysubstituted bisphospholane ligand possessing a ferrocenyl backbone was prepared. The bulky ketol substituent on both of the phospholane rings results in a significant improvement on the enantioselectivity of Rh-catalyzed hydrogenation of dehydroamino acid derivatives compared to its disubstituted phospholane and phosphetane analogues. Hydrogenation of selected itaconic acid derivatives also gave high ee values. More detailed studies on this type of substrate as well as other utilities of this ligand in asymmetric catalysis are in process.

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Table 2 summarizes the results of Rh(I)-3 catalyzed hydrogenation of various trisubstituted α-dehydroamino acid derivatives 9d–m. All the reactions went to completion in 1 h at ambient H₂ with excellent ee values observed (up to over 99.9%). A tetrasubstituted dehydroamino acid 9n was also explored, while the ee value (87.3%) was a little lower than those for the trisubstituted substrates (Table 2, entry 19). The overall enantioselectivities for the Rh(I)-3 catalyzed hydrogenation of dehydroamino acid derivatives were excellent and these results compare favorably to other C₂-symmetric ferrocenyl bisphosphine ligands reported to date.

(11) A great activity enhancement was observed in Ru-catalyzed transfer hydrogenation of ketones by introducing a ketal functionality at the rear end of the ligand presumably due to remote dipole effects: Nordin, S. J. M.; Roth, P.; Turnau, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. Chem. Eur. J. 2001, 7, 1431.
Supporting Information Available: Experimental procedures and spectroscopic data for 3 and 11, and general procedure for asymmetric hydrogenation of dehydroamino acid derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.
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