Highly Enantioselective Rhodium-Catalyzed Hydrogenation of Dehydroamino Acids with New Chiral Bisphosphinates

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Asymmetric synthesis based on transition metal catalyzed processes has attracted a great deal of interest because of its high efficiency for the preparation of enantiomerically pure compounds. The development of efficient chiral transition metal complexes has focused mainly on the design and synthesis of new chiral ligands. Many chiral bisphosphines have been invented to facilitate enantioselective catalytic reactions, and unique properties of chiral ligands are strongly associated with their ligand frameworks such as biaryl chirality with BINAP and chiral phosphalane with DuPhos. Recently, we have reported a new chiral 1,4-bisphosphine, (2R,2′R)-bis(diphenylphosphino)-1(R,1′R)-dicyclopentane (1) [(1R,1′R,2R,2′R)-BICP] (Figure 1) for the effective rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)-acrylic acids.2 This new chiral phosphine has four stereogenic centers, and contains two cyclopentane rings in its backbone which greatly restrict its conformational flexibility. A recent work by Chan et al.3m also concurs with our observation that increasing ligand rigidity is the key for the development of highly enantioselective reactions. 

In contrast to many chiral phosphines reported in the literature, phosphinates used in metal complexes for asymmetric reactions are generally rather poor ligands with few exceptions.3 While phosphinates are less electron donating than phosphines, they can be excellent ligands for asymmetric hydrogenation.4 and hydrocyanation reactions.5 Clearly, it is worthwhile to search for new chiral phosphinates with new chiral scaffolds. Taking advantage of the relatively rigid bicyclopentane backbone of BICP, we made the corresponding chiral phosphinite, (25S′S)-bis(diphenylphosphino)-1(1R′,1′R)-dicyclopentane (abbreviated (1R,1′R,2S,2′S)-BICPO) (Figure 1), from (1R,1′R)-bicyclopentyl-(2S,2′S)-diol. Highly enantioselective hydrogenation of dehydroamino acids catalyzed by rhodium complexes with this ligand is reported herein. Our goal is not simply to create another asymmetric catalytic system for hydrogenation of dehydroamino acids—a well-studied reaction—the impact of this study is to enhance fundamental understanding of those factors in chiral ligand design by exploring a variety of chiral ligand motifs.

The phosphinite ligand (2, (1R,1′R,25S,2′S)-BICPO) is easily made from chiral (1R,1′R)-bicyclopentyl-(2S,2′S)-diol 3 in high yield as illustrated in Scheme 1.

The cationic Rh(I) complex [Rh(COD)(BICPO)]BF₄, prepared in situ by mixing [Rh(COD)]₂BF₄ with 1.1 molar equiv of (1R,1′R,25S,2′S)-BICPO under an inert atmosphere, is a highly effective catalyst for the hydrogenation of α-acetoamidodinamic acid at ambient temperature under 1 atm of H₂. Table 1 summarizes the results of hydrogenation of α-acetoamidocinnamic acid under a variety of experimental conditions. The reaction medium significantly affects the catalytic activity and enantioselectivity of the product. Unlike our early observation on the additive effect of triethylamine with the BICP catalyst,2 the enantioselectivity and reactivity of the hydrogenation decreased drastically in the presence of a catalytic amount of triethylamine (Rh₂Et₃N = 1:1:50). For example, α-acetoamidocinnamic acid was completely reduced with 89.1% ee in THF in the absence of Et₃N, while only 30% was reduced with 30.9% ee with a catalytic amount of Et₃N under 1 atm of H₂ (entry 3 vs 2, entry 5 vs 4). Asymmetric hydrogenation in alcoholic solvents (entries 6 and 8) gave better selectivities than in THF (entry 2) and CH₂Cl₂ (entry 1). Among several common alcohol solvents, the highest enantioselectivity (97.4% ee, 5) for the hydrogenation of α-acetoamidodinamic acid was achieved in PrOH under 1 atm of H₂ at ambient temperature (entry 9). The best result (96.1% ee, 100% conversion) for the hydrogenation of α-acetoamidocinnamic acid was obtained when (1R,1′R,25S,2′S)-BICPO

![Figure 1](image_url)

Figure 1.

slightly lower enantioselectivity (83.5% ee) to give acetoamidocinnamic acid was reduced completely with \( \text{R}^{-} \) using (1′R,1′S,2R,2′R)-BICPO (Scheme 1). A new bisphosphinite, \( \text{R}^{-} \) being the catalyst, the enantioselectivity with \( \text{Rh} \) (COD)Cl was less effective than the cationic one described above (entry 11).

A neutral rhodium catalyst formed in situ from \( \text{Rh}(\text{COD})\text{Cl} \) (0.5 mol %) was used as the catalyst precursor. The reaction was carried out at rt under 1 atm of \( \text{H}_2 \) for 24 h with the best chiral bisphosphines or bisphosphinites,\(^3j,m,8\), comparable with enantioselectivities attained previously with \( \text{Rh} \) catalysts, the enantioselectivity with \( \text{Rh}(\text{COD})\text{Cl} \) (0.5 mol %) was used as the catalyst precursor.

was used in \( \text{iPrOH} \) under 1 atm of \( \text{H}_2 \) at 0°C (entry 10). A neutral rhodium catalyst formed in situ from \( \text{Rh}(\text{COD})\text{Cl} \) (0.5 mol %) was used as the catalyst precursor. The reaction was carried out at rt under 1 atm of \( \text{H}_2 \) for 24 h with the best chiral bisphosphines or bisphosphinites,\(^3j,m,8\), comparable with enantioselectivities attained previously with \( \text{Rh} \) catalysts, the enantioselectivity with \( \text{Rh}(\text{COD})\text{Cl} \) (0.5 mol %) was used as the catalyst precursor.

Four stereogenic carbon centers are contained within our ligand system, which is fundamentally distinct from either axially dissymmetric \( \text{BINAP} \), planar chiral phosphines, or other diphosphines with two stereogenic centers in their backbone. The absolute configurations at the 2,2′-positions are opposite in BICPO (1) and BICPO (2), but in the asymmetric hydrogenation of \( \alpha \)-acetoamidinocinnamic acid, both gave the same amino acid: (S)-N-acetylphenylalanine. These results suggest that these reactions, promoted by a seven-membered \( \text{Rh} \) complex and a nine-membered \( \text{Rh} \) complex, may proceed via different pathways. It is apparent that there must be careful matching of the catalyst chiral environment to the substrate in order to obtain high selectivity. To further understand the relationship between the absolute configuration of BICPO (2) and the product stereochemistry, the absolute configurations of the 2,2′-positions of diol (1R,1′R,2S,2′S)-3 was converted into (1R,1′R,2R,2′R)-4 via a Mitsunobu reaction.\(^7\) A new bisphosphinite, (1R,1′R,2R,2′R)-5, having the same configuration as the original (1R,1′R,2R,2′R)-BICPO was made (Scheme 2). Using (1R,1′R,2R,2′R)-5 as the ligand under the best conditions for hydrogenation with (1R,1′R,2S,2′S)-2, \( \alpha \)-acetoamidinocinnamic acid was reduced completely with slightly lower enantioselectivity (83.5% ee) to give (R)-N-acetylphenylalanine as the product.

\( \text{Scheme 1} \)

\( \text{Scheme 2} \)

\( \text{Table 1. Rh-Catalyzed Asymmetric Hydrogenation of } \alpha \text{-Acetamidocinnamic Acid}^{a} \)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>Et(_3\text{N}) (%)</th>
<th>Con. (%)(^b)</th>
<th>ee (%)(^b)</th>
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<td>CICH(_2)CH(_2)Cl</td>
<td>100</td>
<td>88.2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>100</td>
<td>89.1</td>
<td></td>
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<tr>
<td>3</td>
<td>THF</td>
<td>50</td>
<td>30</td>
<td>30.9</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>100</td>
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<tr>
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<td>MeOH</td>
<td>50</td>
<td>67.9</td>
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<tr>
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<tr>
<td>8</td>
<td>BuOH</td>
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</tr>
<tr>
<td>10(^e)</td>
<td>( \text{iPrOH} )</td>
<td>100</td>
<td>96.1</td>
<td></td>
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<tr>
<td>11(^{d})</td>
<td>( \text{iPrOH} )</td>
<td>86.6</td>
<td>63.9</td>
<td></td>
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</table>

\(^a\) The reaction was carried out at rt under 1 atm of \( \text{H}_2 \) for 24 h (substrate (0.5 mmol, 0.125 M); \( \text{Rh}(\text{COD})\text{BF}_4 \cdot \text{ligand} \) = \( 1:0.01:0.01 \)). \(^b\) Determined by GC using a Chirasil-VALIIIFSOT column on the corresponding methyl ester. \(^d\) The absolute configuration was determined by comparing the optical rotation with the reported value. \(^e\) Reaction was carried out at 0°C. \(^f\) [\( \text{Rh}(\text{COD})\text{Cl} \) (0.5 mol %)] was used as the catalyst precursor.

transition metals. However, compared with the potential nine-membered chelated bidentate ligands reported by Grubbs,3b Miyano,3 and Kumada,10 our newbishphosphites 2 and 3 display the highest reactivities and enantioselectivities in the rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids.

Conclusions

The mechanism of asymmetric hydrogenation of dehydroamino acids has been examined intensively.11 It is generally accepted that a chiral ligand which can form a rigid ligand–metal complex is essential for effective chiral recognition. The most difficult part of research in asymmetric catalysis is to find effective new ligand scaffolds. Our study shows that the new class of nine-membered chelated complexes with rhodium, gave remarkably high selectivities for the hydrogenation of dehydroamino acids. The key element of this system is that the two cyclopentane rings in the backbone restrict the conformational flexibility of the nine-membered ring, and the four stereogenic carbon centers in the backbone dictate the orientation of four P-phenyl groups. Other chiral ligands based on this framework are under study and will be reported in due course.

Experimental Section

General. All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. Toluene, benzene, and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl under nitrogen. Methanol, ethanol, and 2-propanol were distilled from Mg under nitrogen. Column chromatography was performed using EM Silica gel 60 (230–400 mesh). α-Acetamidoacrylic acid and its methyl ester were purchased from Aldrich and used as received. All other substrates, β-isopropyl-α-acetoamidoacrylic acid,12 β-aminobenzamidonic acid,13 methyl 2-chloro-9,9-dicyclopentyl-(2

Notes

Selected data are given below.

(2R,2'R)-Dicyclopentyl-(2R,2'R)-diol (4). Under nitrogen, to a solution of diol 2 (2.5 g, 14.7 mmol), benzoic acid (7.26 g, 59.4 mmol), and triphenylphosphine (15.6 g, 59.5 mmol) in THF (50 mL) was added diethyl azodicarboxylate (59 mL, 59.7 mmol) dropwise at 0°C. After stirring overnight, the reaction mixture was treated with the catalyst and the residue was chromatographed on silica gel to afford the benzoxo ester. The diol was directly used for hydrolysis. A mixture of NaOMe, which was made from sodium (3.35 g, 0.15 mol) and MeOH (560 mL), and benzoic ester in MeOH was stirred overnight at room temperature. After evaporation of MeOH, the residue was diluted with ether and then was added with 10% aqueous hydrochloric acid. The mixture was extracted with methylene chloride, the combined organic layer was dried over sodium sulfate. After evaporation of solution, the residue was purified by chromatography on silica gel. Diod 4 was obtained as a solid (1.0 g, 40% total yield) : [α]D 20 = -54.0 (c, 1.07, CHCl 3) ; [α]D 20 = 1.30 (c, 1.11, CHCl 3) ; [α]D 20 = 74.2 (c, 1.11, CHCl 3) ; [α]D 20 = 1.24, 28.27, 21.62 (m), 53.8 m/z 538, 461, 383, 353, 337, 201, 185, 151, 135, 77; HRMS calcd for C34H36O2P2 (M+1 - OH) 153.1279, found 153.1238.

(2R,2'R)-Bis(dihydroporphosphinoxy)-(1R,1'R)-dicyclopeptane (5). This compound was made in a similar fashion as phosphine 2 (1.20 g, 74.4% yield) : [α]D 20 = 74.8–74.0 (m, 8 H), 7.35–7.27 (m, 12 H), 4.11–4.09 (m, 2 H), 1.86–1.77 (m, 4 H), 1.50–1.45 (m, 12 H), 1.30 (m, 12 H), 0.87–0.81 (m, 12 H), 0.71–0.65 (m, 12 H). The mixture was concentrated and the residue was chromato- graphed on silica gel to afford the benzoxo ester. The benzoxo ester was directly used for hydrolysis. A mixture of NaOMe, which was made from sodium (3.35 g, 0.15 mol) and MeOH (560 mL), and benzoic ester in MeOH was stirred overnight at room temperature. After evaporation of MeOH, the residue was diluted with ether and then was added with 10% aqueous hydrochloric acid. The mixture was extracted with methylene chloride, the combined organic layer was dried over sodium sulfate. After evaporation of solution, the residue was purified by chromatography on silica gel. Diod 4 was obtained as a solid (1.0 g, 40% total yield) : [α]D 20 = -54.0 (c, 1.07, CHCl 3) ; [α]D 20 = 1.30 (c, 1.11, CHCl 3) ; [α]D 20 = 74.2 (c, 1.11, CHCl 3) ; [α]D 20 = 1.24, 28.27, 21.62 (m), 53.8 m/z 538, 461, 383, 353, 337, 201, 185, 151, 135, 77; HRMS calcd for C34H36O2P2 (M+1 - OH) 153.1279, found 153.1238.

General Procedure for Asymmetric Hydrogenation. In a glovebox, to a solution of [Rh(COD)2]BF 4 (5.0 mg, 0.012 mmol) in MeOH (10 mL) was added catalyst and diol 2 (0.15 mL of 0.1 M solution in toluene, 0.015 mmol). After stirring for 30 min, the dehydroamino acid (1.2 mmol) was added. The hydrogenation was performed at room temperature under 1 atm of hydrogen for 24 h. The reaction mixture was treated with CH 3N 2 and then concentrated in vacuo. The residue was passed through a short silica gel column to remove the catalyst. The enantiomeric excess was measured by GC using a chiral column. The absolute configuration of products was determined by comparing the observed rotation with the reported value.

Determination of Enantiomeric Excess. Chiral capillary GC used the following: column, Chirasil-VAL III FSOT; dimensions, 25 m x 0.25 mm (i.d.); carrier gas, He (1 mL/min). The racemic products were obtained by hydrogenation of substrates with an achiral catalyst. The following is the retention time for the racemic products.

N-Acetylphenylalanine methyl ester (2) (capillary GC, 150°C, isothermal) (R) t R = 14.66 min, (S) t S = 16.23 min; [α]D 20 = 74.8–74.0 (m, 8 H), 7.35–7.27 (m, 12 H), 4.11–4.09 (m, 2 H), 1.86–1.77 (m, 4 H), 1.50–1.45 (m, 12 H), 1.30 (m, 12 H), 0.87–0.81 (m, 12 H), 0.71–0.65 (m, 12 H). The mixture was concentrated and the residue was chromato- graphed on silica gel to afford the benzoxo ester. The benzoxo ester was directly used for hydrolysis. A mixture of NaOMe, which was made from sodium (3.35 g, 0.15 mol) and MeOH (560 mL), and benzoic ester in MeOH was stirred overnight at room temperature. After evaporation of MeOH, the residue was diluted with ether and then was added with 10% aqueous hydrochloric acid. The mixture was extracted with methylene chloride, the combined organic layer was dried over sodium sulfate. After evaporation of solution, the residue was purified by chromatography on silica gel. Diod 4 was obtained as a solid (1.0 g, 40% total yield) : [α]D 20 = -54.0 (c, 1.07, CHCl 3) ; [α]D 20 = 1.30 (c, 1.11, CHCl 3) ; [α]D 20 = 74.2 (c, 1.11, CHCl 3) ; [α]D 20 = 1.24, 28.27, 21.62 (m), 53.8 m/z 538, 461, 383, 353, 337, 201, 185, 151, 135, 77; HRMS calcd for C34H36O2P2 (M+1 - OH) 153.1279, found 153.1238.

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δ 5.93 (br, 1H), 4.62 (m, 1H), 3.72 (s, 3H), 1.98 (s, 3H), 1.70–1.50 (m, 3H), 1.04 (d, J = 6.63 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H).

**N-Acetyl-p-fluorophenylalanine methyl ester** (capillary GC, 180 °C, isothermal) (R) t₁ = 5.02 min, (S) t₂ = 5.28 min; 1H NMR (CDCl₃) δ 7.07–6.95 (m, 4H), 5.92 (br, 1H), 4.88–4.83 (m, 1H), 3.72 (s, 3H), 3.16–3.03 (m, 2H), 1.95 (s, 3H).

**N-Acetyl-o-chlorophenylalanine methyl ester** (capillary GC, 180 °C, isothermal) (R) t₁ = 9.32 min, (S) t₂ = 9.78 min.

**N-Acetyl-3-(2-naphthyl)alanine methyl ester**: (capillary GC, 190 °C, isothermal) (R) t₁ = 27.88 min, (S) t₂ = 29.30 min; 1H NMR (CDCl₃) δ 7.32–7.30 (m, 1H), 7.17–7.12 (m, 3H), 6.30–6.30 (br, 1H), 4.90–4.84 (m, 1H), 3.67 (s, 3H), 3.30–3.24 (m, 1H), 1.92 (s, 3H); 13C NMR (CDCl₃) δ 172.05, 169.71, 134.33, 134.08, 131.16, 129.51, 128.42, 126.78, 52.29, 35.32, 22.84, 0.89; MS m/z 258 (M⁺ + 37Cl), 256 (M⁺ + 35Cl), 226, 224, 216, 214, 198, 196, 161, 156, 154, 125, 118, 102, 91, 88; HRMS calcld for C₁₂H₁₄ClNO₃ 255.0662 (M⁺), found 255.0655.

**N-Acetyl-3-(2-thienyl)alanine methyl ester** (capillary GC, 170 °C, isothermal) (R) t₁ = 7.21 min, (S) t₂ = 7.54 min; 1H NMR (CDCl₃) δ 7.20–7.00 (m, 1H), 6.00–5.97 (br, 1H), 4.90–4.84 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.02 (dd, J = 2.23 Hz, J = 5.73 Hz, 2H), 1.94 (s, 3H).

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**Supporting Information Available:** Spectroscopic data for compounds 2–4 and details for the determination of enantiomeric excess (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

**Notes**