Highly Enantioselective Rh-Catalyzed Hydrogenations with a New Chiral 1,4-Bisphosphine Containing a Cyclic Backbone

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The design and synthesis of chiral phosphine ligands have played a significant role in the development of transition metal catalyzed asymmetric reactions.[1] Over 1000 chiral bisphosphines[2] have been made, and several industrial processes have used their transition metal complexes as catalysts for the production of enantiomerically pure compounds (e.g., syntheses of L-DOPA,[3] L-menthol,[4] and carbapenems[4]). While high selectivities were observed in many reactions using chiral bisphosphines, such as DIPAMP,[5] DIOP,[6] Chiraphos,[7] Skewphos,[8] BPPM,[9] DEGphos,[10] BINAP,[11] Duphos,[12] BPE,[12] and others,[13] there are a variety of reactions where these ligands are not efficient in their activity and selectivity. The search for new well-designed chiral ligands is therefore still an important goal in the field of asymmetric catalysis. Herein we report the synthesis and application of a new chiral 1,4-bisphosphine, (2*R*,2′*R*)-bis(diphenylphosphino)-(1*R*,1′*R*)-dicyclopentane (**1**) (abbreviated (*R*,*R*)-BICP) (Figure 1) in the rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)-acrylic acids. The key feature of this ligand is that it contains two cyclopentane rings in its backbone which are present to restrict its conformational flexibility. We hypothesize this conformational rigidity leads to high enantioselectivity in asymmetric reactions. *The four stereogenic carbon centers in the backbone of this phosphine dictate the orientation of P-phenyl groups. This structure is fundamentally different from either axially dissymmetric BINAP or bisphosphines with two stereogenic carbon centers in their backbones such as Chiraphos and BPPM.*

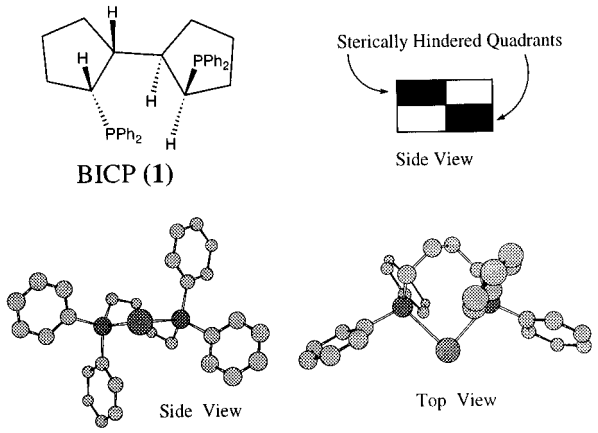

Figure 1.

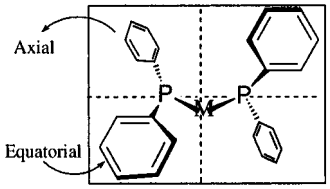

Figure 2.

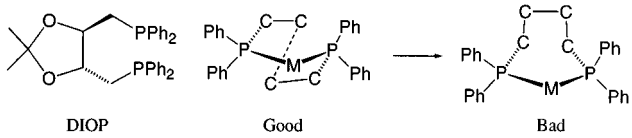

Figure 3.

The enantioselectivity achieved with many asymmetric transition metal catalysts bearing chiral C_2 symmetric bisphosphines can be rationalized by using a simple quadrant diagram (Figure 2).[3] Good asymmetric catalysts generally have their ligands effectively shielding two diagonal quadrants. The absolute configuration of the ligand dictates which two quadrants are blocked. The extent to which the quadrants are blocked has a strong influence on the reaction enantioselectivity.

A breakthrough in asymmetric catalysis came with DIOP, a C_2 symmetric chiral bisphosphine prepared from tartaric acid.[6] This landmark ligand has been used in a number of transition metal catalyzed asymmetric reactions.[1] The enantioselectivity with DIOP, however, is not as good in many asymmetric reactions as some other chiral bisphosphines (e.g., BINAP[4]). A possible explanation for this observation is that the seven-membered chelate ring of DIOP bound to a transition metal is too conformationally flexible (the transfer of backbone chirality to the phenyl groups on the phosphine goes through a methylene group). Figure 3 illustrates the conformational ambiguities in DIOP metal complexes which could result in the erosion of enantioselectivities.[14]

Since achieving conformationally unambiguous coordination geometry between transition metals and chiral ligands is important in the development of efficient ligand systems, we have designed the chiral 1,4-bisphosphine **1** by introducing rings into the backbone. Molecular modeling (MM2 calculations based on the CAChe program) shows that the preferred conformation of transition metal complexes of **1** is a highly skewed seven-membered ring (Figure 1). The two axial phenyls stay back and parallel to two methylene groups. The two equatorial phenyls protrude into the P−M−P in-plane coordina-

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Scheme 1

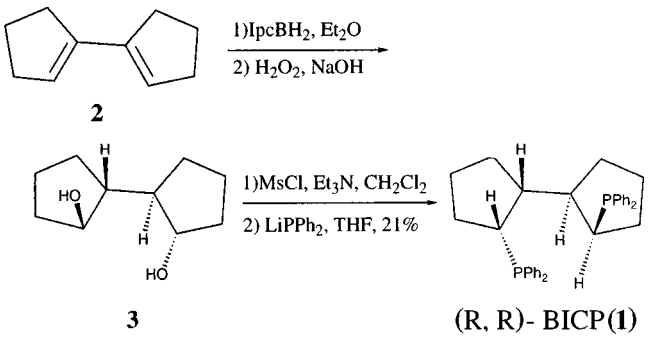
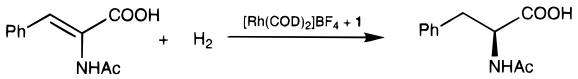


Table 1. Optimization of the Asymmetric Hydrogenation of α-Acetamidocinnamic Acid[a]



entry	solvent	Et_3N (%)	ee (%)[b]
1	EtOH	0	89.2
2	EtOH	50	93.3
3[c]	EtOH	50	83.6
4	$ClCH_2CH_2Cl$	50	93.4
5	THF	50	96.8
6[d]	THF	5	95.1

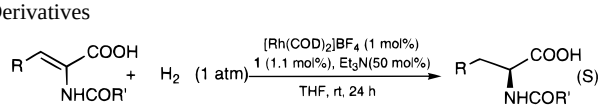
[a] The reaction was performed at room temperature under 1 atm of H_2 for 24 h [substrate (0.5 mmol, 0.125 M)/$[Rh(COD)_2]BF_4$/ligand(**1**) = 1:0.01:0.011]. The reaction went in quantitative yield. [b] Determined by GC using a Chirasil-VAL III FSOT column on the corresponding methyl ester. The *S* absolute configuration was determined by comparing the optical rotation with the reported value.[12] [c] $[Rh(COD)Cl]_2$ (0.5 mol %) was used as the catalyst precursor. [d] A ratio of $[Rh(COD)_2]BF_4$ (0.1 mol %)/ligand **1** (0.11 mol %)/Et_3N (5 mol %) was used.

tion sites. The edge-face array of phenyl groups with **1**·metal is similar to other effective chiral bidentate phosphines (e. g., BINAP and Chiraphos).

The bisphosphine ligand **1** ((*R,R*)-BICP) was synthesized from readily available 1,1′-dicyclopentene (**2**),[15] as shown in Scheme 1. Asymmetric hydroboration of **2** using (+)-monoisopinocampheylborane [(+) $IpcBH_2$] followed by oxidation with H_2O_2[16] gave the desired chiral diol **3** (100% ee after recrystallization from ether/hexanes),[17] which was then converted to the dimesylate in high yield. Subsequent reaction of the dimesylate with lithium diphenylphosphide afforded the bisphosphine **1**.[18]

Hydrogenation of α-acetamidocinnamic acid was performed at room temperature and 1 atm of hydrogen in the presence of the catalyst formed *in situ* from $[Rh(COD)_2]BF_4$ and bisphosphine **1** (1:1.1). Table 1 shows the results of hydrogenation of α-acetamidocinnamic acid under a variety of conditions. The addition of a catalytic amount of triethylamine (Rh/**1**/Et_3N = 1:1.1:50) to the reaction gave a higher enantiomeric excess than those run without triethylamine (entry 2 vs 1). This effect may be due to a conformational change in the chiral Rh complex, since the carboxylate anion generated from the substrate and triethylamine has a greater affinity for the metal than the corresponding acid.[9a,19,20] The enantioselectivity in the hydrogenation[21] was found to be highly dependent on the nature of the Rh complex. When a neutral Rh complex was used as the catalyst precursor, the enantioselectivity decreased dramatically (entry 3). The highest selectivity (96.8%, *S*) for the hydrogenation of α-acetamidocinnamic acid was obtained in THF at 1 atm of H_2 in the presence of triethylamine (entry 5), while changing substrate/catalyst ratio had a little effect on the enantioselectivities (entry 6 vs 5).

Table 2. Asymmetric Hydrogenations of Dehydroamino Acid Derivatives



entry	substrate	ee (%)[a]
1	R = H, R′ = CH_3	97.5[b]
2	R = Ph, R′ = CH_3	96.8[b]
3	R = Ph, R′ = Ph	99.0[b]
4	R = *p*-OAc-*m*-OMePh, R′ = CH_3	98.2[c]
5	R = *m*-BrPh, R′ = CH_3	97.0[b]
6	R = *p*-OMePh, R′ = CH_3	99.0[c]
7	R = *i*-Pr, R′ = CH_3	92.6[b]

[a] The *S* absolute configurations were determined by comparing optical rotations with reported values.[7,12] [b] The ee(%) values were determined by GC using a Chirasil-VAL III FSOT column on the corresponding methyl ester. The reaction went in quantitative yield. [c] The ee(%) values were determined by HPLC using a Diacel Chiralcel OJ column on the corresponding methyl ester.

This methodology is useful for the asymmetric synthesis of chiral amino acids. Table 2 shows the enantioselectivity (chemical yields of ∼100%) of some amino acids obtained by hydrogenation of α-(acylamino)acrylic acids under the optimum conditions. For the four typical substrates (entries 1−4), ee values (96.8−99%) with ligand **1** are higher than or comparable to those achieved with other chiral bisphosphine ligands (e.g., DIOP, 64−84%;[6] BPPM, 83−98%;[9] Chiraphos, 83−99%;[7] BINAP, 67−100%;[11a] DIPAMP, 94−96%;[5] Et-Duphos, 99−99.4% for the methyl ester of the first two substrates[12b]). α-Benzamidocinnamic acid gave higher enantioselectivity than the corresponding acetamido derivative (entry 3 vs 2).[11b] High enantioselectivity (98.2% ee) was obtained for the synthesis of an L-DOPA precursor (entry 4). *o*-Bromophenylalanine, which was obtained in 97% ee (entry 5), can be used in Pd-catalyzed cross-coupling for the synthesis of various amino acid derivatives.[12d] The enantioselectivity for an alkyl-substituted substrate (entry 7) is slightly lower than other substrates (entries 1−6).

In conclusion, the new chiral 1,4-bisphosphine BICP (**1**) is an excellent ligand for the Rh(I)-catalyzed asymmetric hydrogenation of several α-(acylamino)acrylic acids. This ligand and the structurally related compounds, are expected to have many applications in asymmetric catalysis. These investigations are in progress and will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of compound **1** and **3** (3 pages). See any current masthead page for ordering and Internet access instructions.

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(16) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074. The absolute configuration was assigned according to the known asymmetric hydroboration of trisubstituted olefins (e.g., methylcyclopentene) by (+)-$IpcBH_2$.

(17) The enantiomeric excess of the chiral diol **3** was determined by GC using a Supelco γ-DEX225 column.

(18) The bisphosphine was isolated by column chromatography on silica gel after conversion to a bisborane complex. Decomplexation under acidic conditions afforded the pure bisphosphine. Data for the bisphosphine **1**: ^1H NMR ($CDCl_3$, 360 MHz) δ 7.52−7.27 (m, 20 H), 2.53 (m, 2 H), 2.27 (m, 2 H), 1.93(m, 2 H), 1.72 (m, 2 H), 1.70−1.43 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 139−127 (Ph), 45.9 (d, *J* = 12.1 Hz), 45.8 (d, *J* = 12.0 Hz), 40.34 (d, *J* = 14.0 Hz), 30.9 (m), 23.8 (m); ^{31}P NMR ($CDCl_3$) δ −14.6. This phosphine was also fully characterized as its borane complex.

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(20) Under similar conditions, addition of triethylamine did not improve the enantioselectivity for hydrogenation of methyl α-acetamidocinnamate using this ligand system. This result implies that the interaction between the free carboxyl group and triethylamine is important.

(21) Hydrogen pressure and reaction temperature have almost no effect on the enantioselectivity of this asymmetric hydrogenation.