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An *ortho*-Substituted BIPHEP Ligand and Its Applications in Rh-Catalyzed Hydrogenation of Cyclic Enamides

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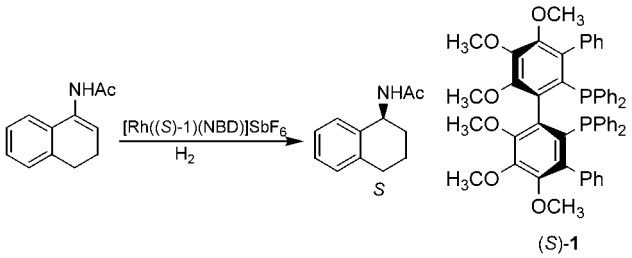
ABSTRACT



(*S*)-**1**

An *ortho*-substituted BIPHEP ligand, *o*-Ph-hexaMeO-BIPHEP (1), is designed and synthesized. Compared with chiral biaryl phosphines without *ortho* substituents such as BINAP and MeO-BIPHEP, *o*-Ph-hexaMeO-BIPHEP shows higher enantioselectivities in Rh-catalyzed hydrogenation of cyclic enamides.

Ligand design has played a central role in developing highly efficient metal-catalyzed asymmetric reactions. Although many effective bisphosphine ligands have been reported, the development of new efficient phosphines remains of great importance. Chiral biaryl bisphosphines such as BINAP,[1] BIPHEMP,[2] and MeO-BIPHEP[2] (Figure 1) are very effective ligands for many metal-catalyzed asymmetric reactions. Structural variation of these ligands can lead to new chiral catalysts with special properties. Some ligands such as Bitianp,[3] TetraMe-Bitiop,[3] P-Phos,[4] and Segphos[5] have been reported through modification of related biaryl phosphines. Recently, we also developed biaryl TunaPhos ligands, a series of BIPHEP ligands with systematic variations of bite angles, and demonstrated that they are superior for some asymmetric reactions.[6] In this paper, we like to report a new chiral BIPHEP ligand with *ortho* substituents, (3,3′-diphenyl-4,4′,5,5′,6,6′-hexamethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine) (abbreviated *o*-Ph-hexaMeO-BIPHEP, **1**) and its applications in Rh-catalyzed hydrogenation of cyclic enamides. To the best of our knowledge, chiral BIPHEP ligands with substituents at 3,3′-positions have not been systematically examined. We envision that the introduction of phenyl groups at 3,3′-positions in **1** can have a strong influence on the conformation of P-aryl rings and high enantioselectivity in asymmetric hydrogenation is possible.

The quadrant diagram has been used to describe the effectiveness of Rh-chiral phosphine catalysts (Figure 2).[1c,7] Generally, the two equatorial P-aryl rings exert the greater

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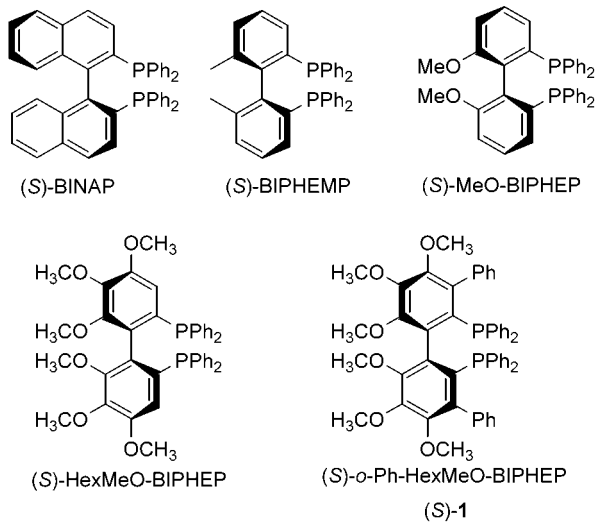


Figure 1. Chiral atropisomeric bisphosphines.

steric influence on two diagonal quadrants while the two axial P-aryl rings stay relatively open in the other two quadrants. Hence, the orientation and rotation of the two equatorial

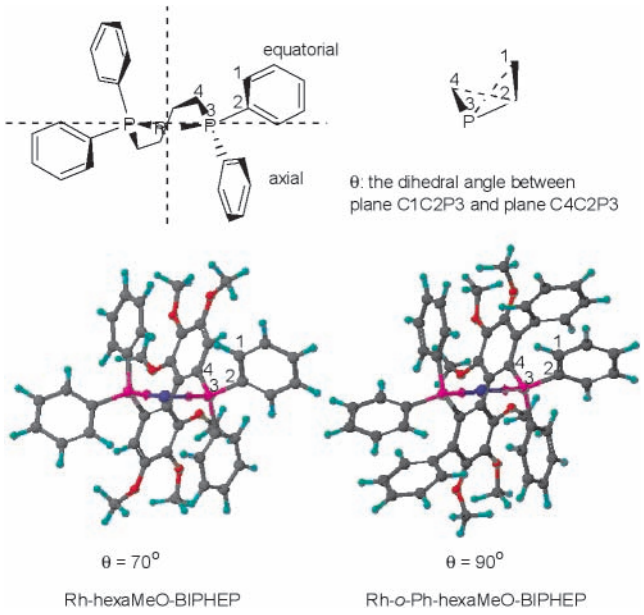
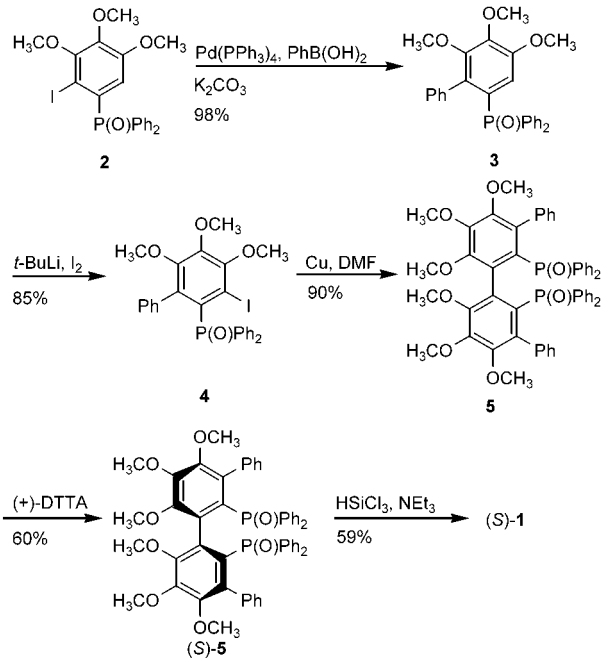


Figure 2. MM2 Calculations based on the CAChe program.

P-aryl rings will be crucial for chiral differentiation. We believe that the rotation of two equatorial P-phenyl rings in the Rh-*o*-Ph-hexaMeO-BIPHEP complex could be restricted through the introduction of the two phenyl rings at 3,3′-positions. Molecular simulation (based on the CAChe MM2 calculations) shows that the two equatorial P-phenyl rings of Rh-*o*-Ph-hexaMeO-BIPHEP are almost parallel to the phenyl rings at 3,3′-positions. The two equatorial P-phenyl rings protrude out of the two diagonal quadrants to an extent greater than that of the Rh-hexaMeO-BIPHEP complex, in which hydrogen atoms are at 3,3′-positions (θ = dihedral angle between plane C1C2P3 and plane C4C2P3; $\theta = 90°$ for the Rh-*o*-Ph-hexaMeO-BIPHEP complex; $\theta = 70°$ for the Rh-hexaMeO-BIPHEP complex). Consequently, a better chiral differentiation can be achieved.

Synthesis of ligand **1** is illustrated in Scheme 1. With the

Scheme 1. Synthesis of the (*S*)-*o*-Ph-hexaMeO-BIPHEP Ligand



known iodide compound **2** as the starting material,[2b] (2-phenyl-3,4,5-trimethoxyphenyl)diphenylphosphine oxide **3** was synthesized via a Suzuki coupling in 98% yield. Deprotonation of **3** with *t*-BuLi followed by quenching with I_2 produced an iodination product **4** in 85% yield. Copper-mediated Ullmann coupling of **4** led to the formation of the bisphosphine oxide **5** in 90% yield. Resolution of racemic **5** was effectively carried out by using (+)-(2*R*,3*R*)-2,3-*O*-ditoluoyltartric acid ((+)-DTTA) as the resolving agent. The configuration of the optically pure (+)-**5** was assigned as *S* by comparing the hydrogenation results of ligand **1** with those of MeO-BIPHEP and hexaMeO-BIPHEP. Reduction of the bisphosphine oxide (*S*)-**5** with trichlorosilane provided (*S*)-**1**.

Ligand (*S*)-**1** was used for hydrogenation of cyclic enamides. Asymmetric hydrogenation of cyclic enamides is potentially important for the synthesis of biologically active chiral aminotetralines and aminoindanes.[8] For example, sertraline is a chiral aminotetraline compound and a major

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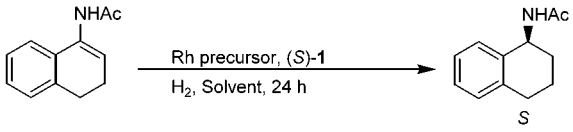
antidepressant drug.[9] However, synthesis of this drug via asymmetric hydrogenation has not been realized. To the best of our knowledge, only a few catalytic systems have been efficient in the metal-catalyzed asymmetric hydrogenation of cyclic enamides (e.g., the Rh-PennPhos[10] and Rh-BPE[11] systems). In our study, *N*-(3,4-dehydro-1-naphthyl)acetamide was chosen as the substrate for optimizing the reaction conditions (Table 1). The catalyst was prepared in situ by mixing a solution of a Rh precursor and a phosphine ligand. Under the initial hydrogenation pressure of 30 atm at room temperature and with a ratio of substrate/Rh/(*S*)-**1** of 100:1:1.1, different Rh precursors led to different results in enantioselectivities (entries 1−5). Cationic Rh precursors gave better enantioselectivities than did a neutral Rh precursor, and $Rh(NBD)_2SbF_6$ was selected as the desired precursor. A slight improvement of the enantioselectivity was observed when the reaction was carried out at a lower hydrogen pressure (entry 5 vs 6). A small solvent effect was also found in the reaction (entries 6−10). Both THF and CH_2Cl_2 proved to be good solvents for this hydrogenation process. When the hydrogenation was carried out at 0 °C, a further improved enantioselectivity was observed (entry 11). The best ee (98%) was achieved when the hydrogenation was carried out at −20 °C under 25 psi of hydrogen in CH_2Cl_2 (entry 12). This result was comparable with the best results obtained with the Rh-PennPhos system.[10] To demonstrate the importance of the *o*-phenyl groups of (*S*)-**1** on the enantioselectivity of the product, we investigated the reaction with some other chiral ligands under the same conditions (entries 13−17). Compared with the *o*-Ph-hexaMeO-BIPHEP ligand **1**, significantly lower enantioseletivities (55−65%) were observed with other chiral biaryl phosphines without *ortho* substituents, such as hexaMeO-BIPHEP, MeO-BIPHEP, and BINAP. These results clearly indicated the strong influence of *o*-phenyl groups of (*S*)-**1** on the enantioselectivity of the reaction. When DIOP was used as the ligand, a low ee was obtained. Under the same reaction condition, no reaction was observed with Me-DuPhos as the ligand.

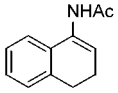
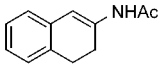
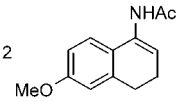
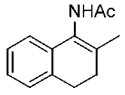
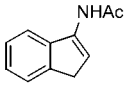
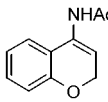
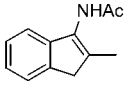
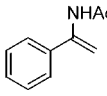
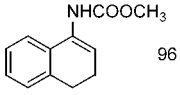
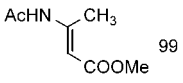
Table 1. Optimization of the Reaction Conditions for Rh-catalyzed Hydrogenation of a Cyclic Enamide



entry[a]	Rh precursor	ligand	H_2 press.	solvent	*T* (°C)	ee[b] (%)
1	$Rh(COD)_2SbF_6$	(*S*)-**1**	30 atm	CH_3OH	rt	92
2	$Rh(NBD)_2BF_4$	(*S*)-**1**	30 atm	CH_3OH	rt	81
3	$Rh(COD)_2PF_6$	(*S*)-**1**	30 atm	CH_3OH	rt	90
4	$[Rh(COD)Cl]_2$	(*S*)-**1**	30 atm	CH_3OH	rt	50
5	$Rh(NBD)_2SbF_6$	(*S*)-**1**	30 atm	CH_3OH	rt	93
6	$Rh(NBD)_2SbF_6$	(*S*)-**1**	25 psi	CH_3OH	rt	94
7	$Rh(NBD)_2SbF_6$	(*S*)-**1**	25 psi	THF	rt	95
8	$Rh(NBD)_2SbF_6$	(*S*)-**1**	25 psi	toluene	rt	90
9	$Rh(NBD)_2SbF_6$	(*S*)-**1**	25 psi	CH_2Cl_2	rt	95
10	$Rh(NBD)_2SbF_6$	(*S*)-**1**	25 psi	EtOAc	rt	93
11	$Rh(NBD)_2SbF_6$	(*S*)-**1**	25 psi	CH_2Cl_2	0	97
12	$Rh(NBD)_2SbF_6$	(*S*)-**1**	25 psi	CH_2Cl_2	−20	98
13	$Rh(NBD)_2SbF_6$	(*S*)-hexaMeO-BIPHEP	25 psi	CH_2Cl_2	−20	65
14	$Rh(NBD)_2SbF_6$	(*S*)-MeO-BIPHEP	25 psi	CH_2Cl_2	−20	67
15	$Rh(NBD)_2SbF_6$	(*R*)-BINAP	25 psi	CH_2Cl_2	−20	55[c]
16	$Rh(NBD)_2SbF_6$	(+)-DIOP	25 psi	CH_2Cl_2	−20	13[c]
17[d]	$Rh(NBD)_2SbF_6$	(*R*,*R*)-Me-DuPhos	25 psi	CH_2Cl_2	−20	N/A

[a] The reaction was complete in quantitative yield. The catalyst was made in situ by stirring a solution of Rh precursor and phosphine ligand in the solvent for 30 min [substrate/Rh/L* = 100/1/1.1]. The configuration of the product is *S*. [b] Enantiomeric excesses were determined by chiral GC using Supelco chiral Select 1000 (0.25 mm × 30 m) column. [c] The configuration of the major product is *R*. [d] No reaction.

Table 2. Hydrogenation of Enamides Catalyzed by Rh-*o*-Ph-HexaMeO-BIPHEP System

entry[a]	substrate	ee (%)[b]	entry	substrate	ee (%)[b]
1		98	6		45
2		98	7[c]		37
3		96	8		66
4		99	9		70
5		96	10		99

[a] The reaction was carried out at −20 °C under 25 psi of H_2 in CH_2Cl_2 with catalyst [Rh((S)-**1**)(NBD)]SbF_6/substrate = 1:200. The reaction was complete unless otherwise specified. The configuration of chiral amine products is *S*. [b] Enantiomeric excesses were determined by chiral GC using Supelco chiral Select 1000 (0.25 mm × 30 m) column. [c] Conversion 83%.

To test the catalytic efficiency of Rh-*o*-Ph-hexaMeO-BIPHEP system for hydrogenation of cyclic enamides, the catalyst precursor [Rh((*S*)-**1**)(NBD)]SbF_6 was prepared. With this catalyst precursor, up to 2,000 turnovers for hydrogena-

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(9) For a racemic route to sertraline, see: William, M.; Quallich, G. *Chem Ind. (London)* **1990**, *10*, 315. For an asymmetric route, see: (a) Quallich, G. J.; Woodall, T. M. *Tetrahedron* **1992**, *48*, 10239. (b) Corey, E. J.; Grant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373. (c) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246. (d) Lautens, M.; Rovis, T. *Tetrahedron* **1999**, *55*, 8967. (d) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233. (e) Chen, C.-Y.; Reamer, R. A. *Org. Lett.* **1999**, *1*, 293. (f) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 1111. (g) Yun, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 767.

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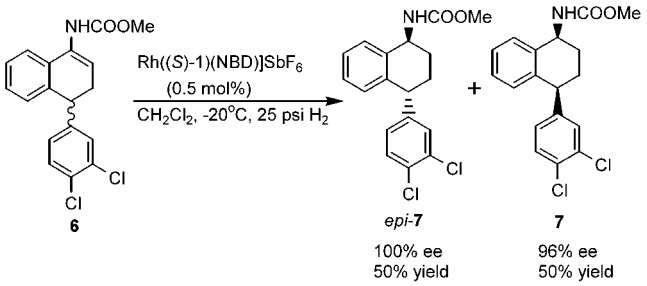
tion of *N*-(3,4-dehydro-1-naphthyl)acetamide and 95% ee were obtained. Under the optimized conditions, a variety of enamides have been hydrogenated with the Rh-*o*-Ph-hexaMeO-BIPHEP system (Table 2). Excellent enantioselectivities (96−98%) were observed on hydrogenation of cyclic enamides derived from α-tetralones and α-indanones (entries 1−5). A tetrasubstituted five-membered cyclic enamide also gave a high ee with complete conversion (entry 4). An excellent ee was also achieved on the hydrogenation of an (*E*)-*β*-dehydroamino acid ester (entry 10). However, the ee obtained for the enamide derived from *β*-tetralone was low (45%, entry 6). The system also showed only moderate ee's on the hydrogenation of other cyclic and acyclic enamides (entries 7−9).

Because a cyclic carbamate substrate gave an excellent ee (entry 5), we tested a racemic carbamate **6** for hydrogenation under the same reaction conditions (Scheme 2). The carbamate **6** was converted smoothly into the *cis* product **7** in 50% yield with 96% ee and the *trans* product *epi*-**7** in 50% yield with 100% ee. According to the literature procedure,[12] LAH reduction of **7** can directly lead to the formation of enantiomerically enriched sertraline.

In conclusion, we have designed and synthesized the first BIPHEP ligand with substituents at 3,3′-positions, *o*-Ph-hexaMeO-BIPHEP. This ligand has been successfully applied in Rh-catalyzed hydrogenation of cyclic enamides and carbamates. High ee's and turnovers have been realized. The importance of the *o*-phenyl groups of the ligand on the enantioselectivity of the reaction has also been demonstrated by comparing the hydrogenation results of the corresponding chiral ligands without *ortho* substituents. Further study will be focused on the synthesis and applications of other *ortho*-substituted BIPHEP or BINAP ligands and progress will be reported in due course.

Scheme 2. Hydrogenation of a Racemic Cyclic Carbamate



Acknowledgment. This work was supported by the National Institute of Health.

Supporting Information Available: Experimental details, spectroscopic data, and analytical conditions of the ligand and hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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