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

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ABSTRACT



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-BIPHEP² (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 Segphos⁵ have been

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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

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; $\theta = 90^{\circ}$ for the Rh-o-Ph-hexaMeO-BIPHEP complex; $\theta = 70^{\circ}$ 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

calculations) shows that the two equatorial P-phenyl rings



known iodide compound 2 as the starting material,^{2b} (2phenyl-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 I₂ produced an iodination product **4** in 85% yield. Coppermediated 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 (+)-(2R,3R)-2,3-Oditoluoyltartric 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-PennPhos¹⁰ and Rh-BPE¹¹ 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

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

NHAc				NHAc		
(-	Rh precursor, (<i>S</i>)- H ₂ , Solvent, 24 h	1	→ 〔	s s]
en- try ^a	Rh precursor	ligand	H ₂ press.	solvent	Т (°С)	ee ^b (%)
1	Rh(COD) ₂ SbF ₆	(<i>S</i>)- 1	30 atm	CH ₃ OH	rt	92
2	$Rh(NBD)_2BF_4$	(S)- 1	30 atm	CH ₃ OH	rt	81
3	$Rh(COD)_2PF_6$	(S)- 1	30 atm	CH ₃ OH	rt	90
4	[Rh(COD)Cl] ₂	(S)- 1	30 atm	CH ₃ OH	rt	50
5	Rh(NBD) ₂ SbF ₆	(S)- 1	30 atm	CH_3OH	rt	93
6	$Rh(NBD)_2SbF_6$	(S)- 1	25 psi	CH ₃ OH	rt	94
7	$Rh(NBD)_2SbF_6$	(S)- 1	25 psi	THF	rt	95
8	$Rh(NBD)_2SbF_6$	(<i>S</i>)-1	25 psi	toluene	rt	90
9	Rh(NBD) ₂ SbF ₆	(S)- 1	25 psi	CH_2Cl_2	rt	95
10	Rh(NBD) ₂ SbF ₆	(<i>S</i>)-1	25 psi	EtOAc	rt	93
11	$Rh(NBD)_2SbF_6$	(<i>S</i>)-1	25 psi	CH_2Cl_2	0	97
12	Rh(NBD) ₂ SbF ₆	(S)- 1	25 psi	CH_2Cl_2	-20	98
13	Rh(NBD) ₂ SbF ₆	(S)-hexaMeO- BIPHEP	25 psi	CH ₂ Cl ₂	-20	65
14	Rh(NBD) ₂ SbF ₆	(S)-MeO- BIPHEP	25 psi	CH_2Cl_2	-20	67
15	Rh(NBD)2SbF6	(R)-BINAP	25 psi	CH_2Cl_2	-20	55 ^c
16	$Rh(NBD)_2SbF_6$	(+)-DIOP	25 psi	CH_2Cl_2	-20	134
17^d	Rh(NBD) ₂ SbF ₆	(<i>R</i> , <i>R</i>)-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.

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 precur

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sor, and Rh(NBD)₂SbF₆ 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 CH₂Cl₂ 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 CH₂- Cl_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-PhhexaMeO-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 2.
 Hydrogenation of Enamides Catalyzed by

 Rh-o-Ph-HexaMeO-BIPHEP System



^{*a*} The reaction was carried out at -20 °C under 25 psi of H₂ in CH₂Cl₂ with catalyst [Rh((S)-1)(NBD)]SbF₆/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)]SbF₆ was prepared. With this catalyst precursor, up to 2,000 turnovers for hydrogena-

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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

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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.

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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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