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Novel, Tunable, and Efficient Chiral Bisdihydrobenzooxaphosphole Ligands for Asymmetric Hydrogenation

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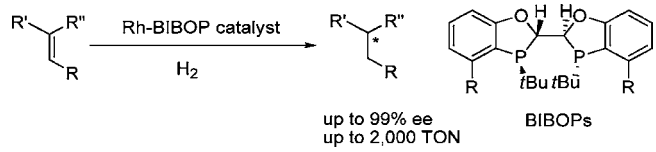
ABSTRACT



A series of novel, efficient, air-stable, and tunable chiral bisdihydrobenzooxaphosphole ligands (BIBOPs) were developed for rhodium-catalyzed hydrogenations of various functionalized olefins such as α-arylenamides, α-(acylamino)acrylic acid derivatives, *β*-(acylamino)acrylates, and dimethyl itaconate with excellent enantioselectivities (up to 99% ee) and reactivities (up to 2000 TON).

The development of efficient chiral phosphorus ligands has played a central role toward the rapid development in the field of asymmetric hydrogenation.[1] Structurally novel, sterically or electronically tunable, and operationally convenient chiral phosphorus ligands remain of great interest in further broadening the scope of asymmetric hydrogenation as well as in the discovery of new efficient transition metal catalyzed asymmetric reactions.[2] We herein report a series of novel and air-stable *P*-chiral bisdihydrobenzooxaphosphole ligands (BIBOPs, Figure 1) and their excellent applications in rhodium-catalyzed hydrogenation of various functionalized olefins. Notable features of these ligands are their rigid and unique bisdihydrobenzo[*d*][1,3]oxaphosphole core structures and the tunability by variation of the substituents at the 4,4′-positions. Molecular modeling of their rhodium complexes on a CAChe model[3] has shown a rigid and well-defined chiral environment as well as the potentially strong influence of R groups at the 4,4′-positions. We predicted that

(1) For representative reviews, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; p 1. (c) Brown, J. M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 121. (d) Krépy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1. (e) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.

(2) For recent representative examples, see: (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (b) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100. (c) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. (d) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889. (e) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425. (f) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197. (g) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612. (h) Ostermeier, M.; Priess, J.; Helmchen, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 612. (i) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348. (j) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943. (k) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509. (l) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966. (m) Wu, S.; Zhang, W.; Zhang, Z.; Zhang, X. *Org. Lett.* **2004**, *6*, 3565. (n) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2004**, *6*, 3585. (o) Imamoto, T.; Oohara, N.; Takahashi, H. *Synthesis* **2004**, 1353. (p) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646. (q) Cheng, X.; Zhang, Q.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1118. (r) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934. (s) Chen, W.; McCormack, P. J.; Mohammed, K.; Mbafor, W.; Roberts, S. M.; Whittall, J. *Angew. Chem., Int. Ed.* **2007**, *44*, 4141. (t) Imamoto, T.; Saitoh, Y.; Koide, A.; Ogura, T.; Yoshida, K. *Angew. Chem., Int. Ed.* **2007**, *44*, 8636.

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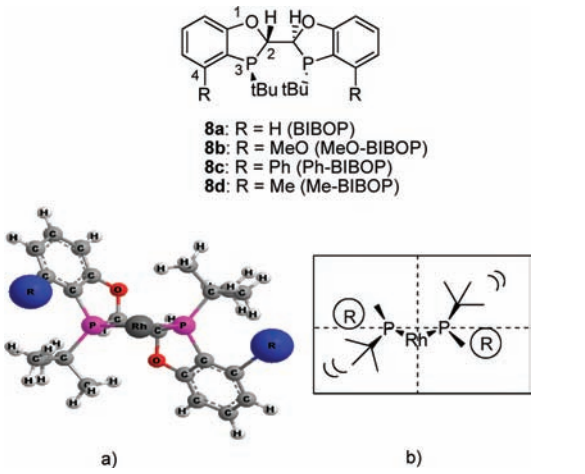
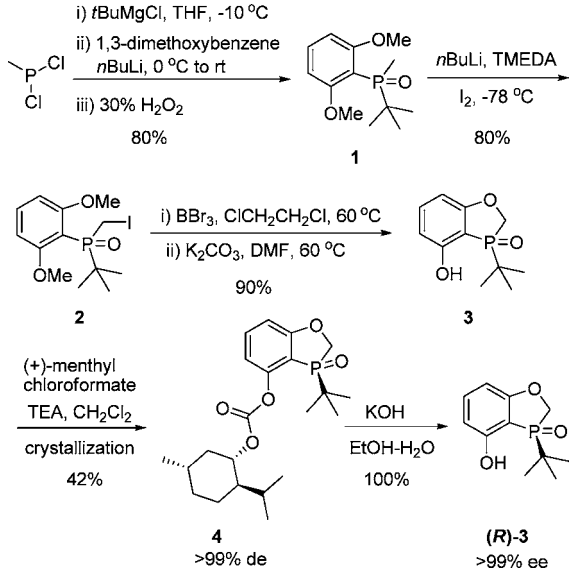


Figure 1. Chiral bisdihydrobenzo[*d*][1,3]oxaphosphole ligands (BIBOPs): (a) a CAChe model of the Rh−R−BIBOP complex with the MM3 force field and (b) a tunable quadrant diagram.

the steric and electronic variations of R groups could have a great impact on the efficiencies of their rhodium complexes when applied in asymmetric hydrogenation (Figure 1).

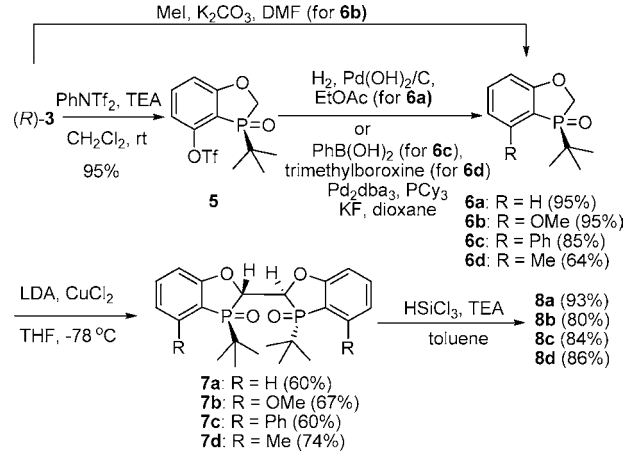
Synthesis of a series of BIBOP ligands (**8a**−**d**) was derived from the same chiral intermediate, 3-*tert*-butyl-2,3-dihydrobenzo[*d*][1,3]oxaphosphol-4-ol oxide ((*R*)-**3**, Scheme 1). Preparation of racemic **3** was accomplished from methyldichlorophosphine in four steps. Reaction of methyldichlorophosphine with *t*-butylmagnesium chloride and 2,6-dimethoxyphenyllithium followed by oxidation with H_2O_2 provided phosphine oxide **1** in 80% yield. Iodination of **1** was accomplished by deprotonation with *n*BuLi followed by addition of I_2 to form iodo compound **2** in 80% yield. Demethylation with boron tribromide as the reagent followed by cyclization with K_2CO_3 as the base in DMF afforded racemic **3** in 90% yield over two steps. Efficient resolution of **3** was successfully accomplished by converting to its menthyl carbonate. The diastereomerically pure isomer **4** was isolated in 42% yield after single crystallization, and its absolute configuration was confirmed by its X-ray structure.[4] Basic hydrolysis of carbonate **4** afforded enantiomerically pure compound (*R*)-**3** quantitatively. Utilizing this synthetic route, we have prepared both (*R*)-**3** and (*S*)-**3** in kilogram quantity.

Scheme 1. Synthesis of Chiral 3-*tert*-Butyl-2,3-dihydrobenzo[*d*][1,3]oxaphosphol-4-ol Oxide ((*R*)-**3**)



With (*R*)-**3** in hand, we were able to install different substituents (H, OMe, Ph, or Me) at the 4 position by simple functionalizations (Scheme 2). Thus, **6a** was obtained by converting (*R*)-**3** to its triflate **5** followed by hydrogenolysis in 90% overall yield. Methylation of (*R*)-3 using MeI and potassium carbonate provided **6b** in 95% isolated yield. The phenyl-substituted product **6c** was formed by Suzuki coupling from **5** and phenylboronic acid in 85% yield. Similarly, the methyl-substituted compound **6d** was prepared in 64% yield from the triflate and trimethyl boroxine. Homocouplings of **6a**−**d**, mediated with LDA and $CuCl_2$ as the reagents,[5] afforded **7a**−**d** in 60−74% isolated yields as single isomeric coupling products. It is noteworthy that the deprotonation of **6a**−**d** with LDA is highly selective, and the bulkiness of the *tert*-butyl group only allowed deprotonation to occur on the opposite face of the ring, which stereospecifically set the configurations at the 2,2′-positions. Reduction of **7a**−**d** with $HSiCl_3$[6] provided a series of BIBOP ligands as white

Scheme 2. Syntheses of BIBOP Ligands



(3) Molecular simulations were performed on CAChe 6.1 with a MM3 force field.

(4) Crystallographic data for compound **4** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-750224). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

(5) Maryanoff, C. A.; Maryanoff, B. E.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 5839.

solids in satisfactory yields. The air stability of these ligands in the solid state is notable. BIBOP (**8a**) was exposed in air for one month without observation of oxidation side product. This stability provides a great deal of operational convenience.

After synthesis of the ligands, a series of rhodium complexes Rh[(nbd)(**8a**−**d**)]BF_4 were prepared. The stereoconfiguration of the ligand core was further confirmed by the X-ray structure of the Rh[(nbd)((2*R*,2′*R*,3*R*,3′*R*)-BIBOP)]BF_4 complex (Figure 2).[7] The rhodium complexes

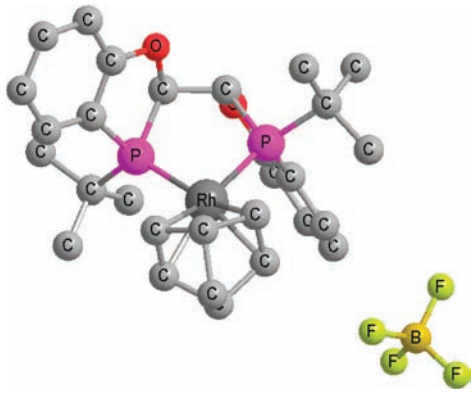
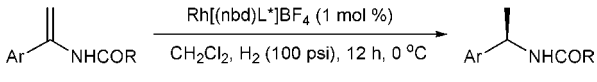


Figure 2. X-ray crystal structure of Rh[(nbd)((2*R*,2′*R*,3*R*,3′*R*)-BIBOP)]BF_4 (the H atoms are omitted).

were then applied as catalysts for hydrogenation of α-arylenamides.[8,9] The hydrogenations were run at 0 °C in dichloromethane in the presence of 1 mol % rhodium complex under 100 psi of hydrogenation for 12 h. As shown in Table 1, the rhodium complexes with different ligands provided

Table 1. Rh-Catalyzed Asymmetric Hydrogenation of α-Arylenamides[a]



9a-i **10a-i**

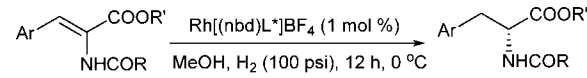
entry	L*	substrate	Ar	R	ee [%][b]
1	**8a**	**9a**	Ph	Me	99
2	**8b**	**9a**	Ph	Me	92
3	**8c**	**9a**	Ph	Me	49
4	**8d**	**9a**	Ph	Me	4
5	**8a**	**9b**	*p*-MeO-Ph	Me	99
6	**8a**	**9c**	*p*-Br-Ph	Me	99
7	**8a**	**9d**	*p*-CF_3−Ph	Me	>99
8	**8a**	**9e**	*m*-Me-Ph	Me	>99
9	**8a**	**9f**	3-thiophenyl	Me	>99
10	**8a**	**9g**	2-naphthyl	Me	98
11	**8a**	**9h**	*p*-Br-Ph	CF_3	98
12	**8a**	**9i**	*p*-MeO-Ph	*t*Bu	99

[a] Conditions: see Supporting Information for experimental details. [b] The *R* absolute configuration was assigned by comparison of optical rotation with reported data. The enantiomeric excesses were determined by chiral GC (Varian CP-Chiralsil-L-Val) or HPLC (chiralpak AD-H).

dramatically different efficiencies in hydrogenation of *N*-(1-phenylvinyl)acetamide (entries 1−4). While BIBOP provided almost perfect enantioselectivity (99% ee), MeO-BIBOP (**8b**) and Ph-BIBOP (**8c**) led to the diminished selectivities (92% ee and 49% ee). Surprisingly, Me-BIBOP (**8d**) was inefficient, leading to only 4% ee. These dramatic results strongly demonstrated the sensitivity of the substituents of the ligand at 4,4′-positions on stereoselectivity. With the Rh[(nbd)(**8a**)]BF_4 complex as the catalyst, a variety of α-aryl enamides were hydrogenated to provide very high enantioselectivities (98% to >99% ee, entries 5−12). A thiophenyl and a 2-naphthyl substrate were also reduced to afford the products in >99% ee and 98% ee, respectively. High enantioselectivities were also achieved on a trifluoroacetyl enamide and a pivaloyl enamide (entries 11−12). To further test the reactivity of the Rh−BIBOP system on hydrogenation of α-arylenamides, *N*-(1-(4-(trifluoromethyl)phenyl)-vinyl)acetamide (**9d**) was subjected to hydrogenation at rt for 12 h under 100 psi H_2 in the presence of Rh-[(nbd)(**8a**)]BF_4 (0.05 mol %, 2000 TON), and the desired product (*R*)-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)acetamide was obtained in >99% ee and in quantitative yield.

The rhodium complexes were also applied as catalysts for hydrogenations of α-(acylamino)acrylic acid derivatives,[8] and the results are shown in Table 2. The hydrogenations were

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of α-(Acylamino)acrylic Acid Derivatives[a]



11a-p **12a-p**

entry	L*	substrate	Ar	R, R′	ee [%][b]
1	**8a**	**11a**	Ph	*t*Bu, Me	99
2	**8b**	**11a**	Ph	*t*Bu, Me	93
3	**8c**	**11a**	Ph	*t*Bu, Me	20
4	**8d**	**11a**	Ph	*t*Bu, Me	93
5	**8a**	**11b**	H	Me, Me	>99
6	**8a**	**11c**	Ph	Me, Me	97
7	**8a**	**11d**	*p*-F-Ph	Me, Me	97
8	**8a**	**11e**	*p*-MeO-Ph	Me, Me	96
9	**8a**	**11f**	*m*-Br-Ph	Me, Me	98
10	**8a**	**11g**	*o*-Cl-Ph	Me, Me	97
11	**8a**	**11h**	2-thiophenyl	Me, Me	99
12	**8a**	**11i**	2-naphthyl	Me, Me	96
13	**8a**	**11j**	Ph	*N*-morpholine, Me	98
14	**8a**	**11k**	Ph	Me, H	98[c]

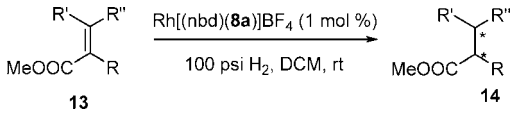
[a] Conditions: see Supporting Information for experimental details. [b] The *R* absolute configuration was assigned by comparison of optical rotation with reported data. The enantiometric excesses were determined by chiral GC (Varian CP-Chiralsil-L-Val) or Chiral HPLC (chiral-AGP or chiralpak AD-H). [c] The ee of acid **12k** was determined on corresponding methyl ester by treatment with $TMSCHN_2$.

performed at 0 °C in methanol in the presence of 1 mol % rhodium complex under 100 psi of hydrogenation for 12 h. Hydrogenation of 3-phenyl-2-pivalamidoacrylate (**11a**) with four chiral rhodium catalysts once again provided very

different enantioselectivities (Table 2, entries 1−4), demonstrating the importance in developing chiral ligands with tunable electronic and steric properties. The Rh-BIBOP catalyst led to the product with the highest enantioselectivity (99% ee). With the same catalyst, an array of α-(acetylamino)acrylic acid derivatives (entries 5−12) were hydrogenated with very good enantioselectivities (96→99% ee's). An excellent ee was also achieved on a urea substrate (entry 13). (*Z*)-2-Acetamido-3-phenylacrylic acid was hydrogenated to provide the corresponding chiral acid in 98% ee (entry 14). Again, the reactivity of the Rh-BIBOP catalyst was tested on hydrogenation of methyl 2-acetamido-3-(4-fluorophenyl)acrylate (**11d**). At 0.05 mol % catalyst loading (2000 TON), the hydrogenation product was obtained with 97% ee in quantitative yield.

The Rh-BIBOP catalyst was also applied for hydrogenation of methyl β-(acetylamino)acrylates and dimethyl itaconate (Table 3).[8] Both (*Z*)- and (*E*)-methyl β-(acetylamino)acrylates were hydrogenated to provide the corresponding chiral β-amino acid derivative with the same configuration and excellent enantioselectivities (99% ee's). Dimethyl itaconate was also hydrogenated to afford the corresponding chiral ester in 94% ee.

Table 3. Asymmetric Hydrogenation of (*Z*)- or (*E*)-Methyl β-(acetylamino)acrylate and Dimethyl Itaconate with Rh[(nbd)(**8a**)]BF_4 as the Catalyst[a]



entry	substrate	R, R′, R″	ee [%][b]	config
1	**13a** (*Z*)	H, NHAc, Me	99	*R*
2	**13b** (*E*)	H, Me, NHAc	99	*R*
3	**13c**	CH_2COOMe, H, H	94	*S*

[a] The reactions were run in dichloromethane under 50 psi H_2 for 12 h in the presence of 1 mol % Rh[(nbd)(**8a**)]BF_4 as the catalyst. [b] The absolute configuration was assigned by comparison of optical rotation with reported data. The enantiomeric excesses were determined by chiral GC (betadex-225) or chiral HPLC (Kromasil 3-CelluCoat RP).

In conclusion, we have designed and developed a series of novel, efficient, and tunable bisdihydrobenzooxaphosphole ligands which have shown excellent enantioselectivities and reactivities for rhodium-catalyzed hydrogenations of various functionalized olefins such as α-arylenamides, α-(acylamino)acrylic acid derivatives, β-(acylamino)acrylates, and dimethyl itaconate. BIBOP (**8a**) is proven to be a general ligand that has provided high enantioselectivities for a range of functionalized olefins. The ease of synthesizing both enantiomers and the excellent air stability for handling make BIBOP a practical ligand for producing chiral products such as chiral amines, chiral α-amino acid derivatives, chiral β-amino acid derivatives, and chiral esters by asymmetric hydrogenation. Additionally, the substituent effect at the 4,4′-positions of the ligand on asymmetric hydrogenation was also demonstrated. Further applications of these ligands in asymmetric catalysis are under investigation, and progress will be reported in due course.

Acknowledgment. We thank Dr. Andre White (Boehringer Ingelheim) for solving X-ray structures.

Supporting Information Available: Experimental details and NMR spectra of the new compounds, general hydrogenation procedures, and chiral separation methods of hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 2788.

(7) Crystallographic data for Rh[(nbd)((2*R*,2′*R*,3*R*,3′*R*)-BIBOP)]BF_4 have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-750225). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

(8) For a recent overview on rhodium-catalyzed hydrogenation of various functionalized olefins, see ref 1a.

(9) We have recently reported an efficient and practical method for the synthesis of α-arylenamides, see: Tang, W.; Capacci, A.; Sarvestani, M.; Wei, X.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.*, DOI: 10.1021/jo9022594.