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Novel and Efficient Chiral Bisphosphorus Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation

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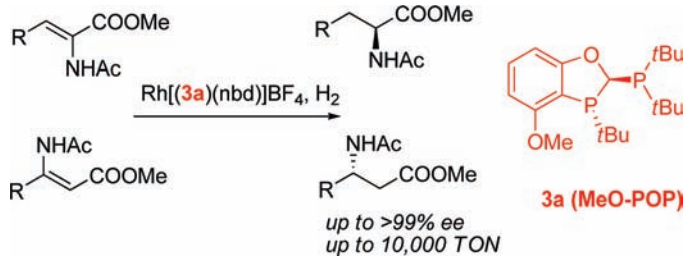
ABSTRACT



A series of structurally novel, operationally convenient, and efficient chiral 2-phosphino-2,3-dihydrobenzo[*d*][1,3]oxaphosphole ligands was developed. Applications of ligands 3a and 3b in rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)acrylates and *β*-(acylamino)acrylates provided excellent enantioselectivities (up to >99% ee) and reactivities (up to 10 000 TON).

The design of structurally novel, operationally convenient, and efficient chiral phosphorus ligands remains of great importance for further development in the area of asymmetric hydrogenation as well as in the search for new efficient metal-catalyzed asymmetric reactions.[1,2] Chiral 1,1-bisphosphorus ligands (Structure **A**, Figure 1) have recently gained increased attention[3] with the development of some notable ligands such as MiniPhos[4] and trichickenfootphos.[5] However, some of these ligands are still synthetically challenging and current methods are either applied for only one enantiomer[4] or require a preparative HPLC purification.[5] Additionally, handling of these ligands is operationally inconvenient due to their oily or air-sensitive nature.[4,5] In terms of structure, most chiral 1,1-bisphosphorus ligands possess a methylene group which links the two phosphorus centers.[6] Interestingly,

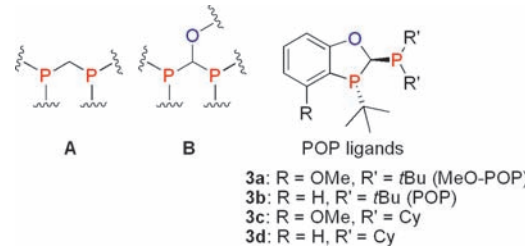


Figure 1. (**A**) 1,1-Bisphosphorus ligand; (**B**) 1-oxy-1,1-bisphosphorus ligand; (**3a**−**d**) novel 2-phosphino-2,3-dihydrobenzo-[*d*][1,3]oxaphosphole ligand (POPs).

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(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.

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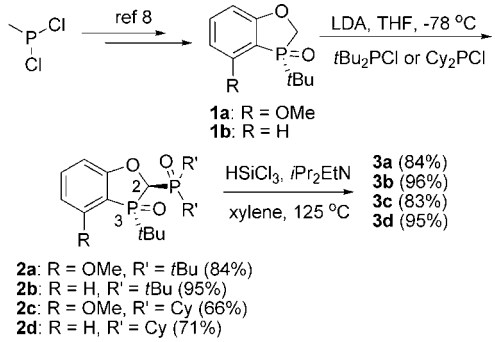
chiral ligands containing a 1-oxy-1,1-bisphosphorus unit **B** have rarely been reported.[7] We herein describe the synthesis of a series of structurally unique and operationally convenient chiral 2-phosphino-2,3-dihydrobenzo[*d*][1,3]oxaphosphole ligands **3a**−**d** (POPs**)** which contain the unique substructural unit (**B**) and their excellent applications in rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)acrylates and *β*-(acylamino)acrylates.

We have recently reported a series of efficient BIBOP ligands for asymmetric hydrogenation during which we developed the scalable syntheses of chiral 3-*tert*-butyl-2,3-dihydrobenzo[*d*][1,3]oxaphosphole intermediates (**1a**−**b**, Scheme 1).[8] This allowed us to synthesize an array of chiral

Scheme 1. Ligand Synthesis



2-phosphino-2,3-dihydrobenzo[*d*][1,3]oxaphosphole ligands **3a**−**d** (POPs) in only two steps from **1a**−**b**. Thus, deprotonation of **1a** or **1b** with LDA followed by phosphinylation with di(*tert*-butyl)chlorophosphine or dicyclohexylchlorophosphine then treatment with H_2O_2 provided diphosphine oxides **2a**−**d** in 66−95% yield. No diastereomeric products were observed during these reactions, indicating a stereospecific phosphinylation at the 2 position. Reduction of **2a**−**d** with $HSiCl_3/iPr_2EtN$[9] as the reagents in xylene provided the desired diphosphorus ligands **3a**−**d** in satisfactory yields. No racemization or epimerization was observed during the reductions. Ligand **3a** (MeO-POP) was reoxidized to the diphosphine oxide **2a** with H_2O_2,[10] showing >99% enantiomeric purity by chiral HPLC.[11] The stability of ligand **3a** as a white crystalline solid was also tested by exposure to air at rt. No detectable oxidation was observed by ^{31}P NMR analysis after four hours and only ∼5% oxidation side-product was detected after one week. The good stability of **3a** in air offers great operational convenience for handling.

The rhodium complexes Rh[(**3a**−**d**)(nbd)]BF_4 were also prepared from ligands **3a**−**d** by reacting with Rh[$(nbd)_2$]BF_4. The absolute configuration and the relative stereochemistry of ligands **3a**−**d** between the chiral phosphorus center and the adjacent chiral carbon center were unambiguously confirmed from the X-ray structure of Rh[(*ent*-**3a**)(nbd)]BF_4 (Figure 2).[12] Study of the X-ray structure revealed that the

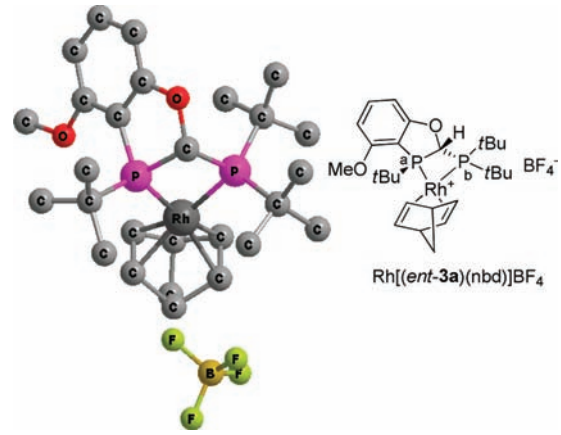


Figure 2. X-ray structure of Rh[(*ent*-**3a**)(nbd)]BF_4 [the H atoms are omitted for clarity, selected bond lengths (Å) 2.281 (Rh−P(a)), 2.337 (Rh−P(b)); selected bond angle (deg) 73.7 (P(a)−Rh−P(b))]

rhodium atom has a stronger coordination bond with the chiral phosphorus center (P(a)) than with the phosphorus

(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) Wu, S.; Zhang, W.; Zhang, Z.; Zhang, X. *Org. Lett.* **2004**, *6*, 3565. (n) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2004**, *6*, 3585. (m) Imamoto, T.; Oohara, N.; Takahashi, H. *Synthesis* **2004**, 1353. (nn) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646. (o) Cheng, X.; Zhang, Q.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1118. (p) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934. (q) Chen, W.; McCormack, P. J.; Mohammed, K.; Mbafor, W.; Roberts, S. M.; Whittall, J. *Angew. Chem., Int. Ed.* **2007**, *44*, 4141. (r) Imamoto, T.; Saitoh, Y.; Koide, A.; Ogura, T.; Yoshida, K. *Angew. Chem., Int. Ed.* **2007**, *44*, 8636.

(3) (a) Jackson, M.; Lennon, I. C. *Tetrahedron Lett.* **2007**, *48*, 1831. (b) Dai, Q.; Li, W.; Zhang, X. *Tetrahedron* **2008**, *64*, 6943.

(4) (a) Yamanio, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988. (b) Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118.

(5) (a) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966. (b) Wu, H.-P.; Hoge, G. *Org. Lett.* **2004**, *6*, 3645. (c) Gridnev, I. D.; Imamato, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 2560.

(6) Other than methylene group, a few chiral 1,1-bisphosphorus ligands with carbocycle, oxygen, or nitrogen linkers were reported, see: (a) Marinetti, A.; Le Menn, C.; Ricard, L. *Organometallics* **1995**, *14*, 4983. (b) Calabrò, G.; Drommi, D.; Bruno, G.; Faraone, F. *Dalton Trans.* **2004**, 81. (c) Payne, N. C.; Stephan, D. W. *J. Organomet. Chem.* **1981**, *221*, 203.

(7) No bisphosphorus ligands containing a 1-oxy-1,1-bisphosphorus unit **B** can be found on SciFinder. An unconfirmed nonchiral structure containing 1-amino-1,1-bisphosphorus unit was recently reported, see: Aluri, B. R.; Kindermann, M. K.; Jones, P. G.; Dix, I.; Heinicke, J. *Inorg. Chem.* **2008**, *47*, 6900.

(8) Tang, W.; Qu, B.; Capacci, A. G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 176.

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

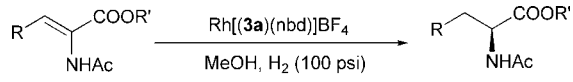
(10) Oxidation of chiral phosphine with H_2O_2 is generally stereospecific with retention at the P center, see ref 9 and Luckenbach, R. *Tetrahedron Lett.* **1976**, *24*, 2017.

(11) See Supporting Information for details.

atom (P(b)) connecting with two *tert*-butyl groups (Figure 2). A similar coordination pattern has been observed for the reported Rh[(trichickenfootphos)(cod)]BF_4 complex.[5a] It is noteworthy that the rhodium complexes Rh[(**3a**−**d**)(nbd)]BF_4 have also shown great stability in air, which again provides a great deal of operational convenience. For example, no decomposition of Rh[(**3a**)(nbd)]BF_4 was observed according to NMR after exposure to air for 24 h.

Rh[(**3a**−**d**)(nbd)]BF_4 were applied as catalysts for hydrogenation of α-(acylamino)acrylates. The hydrogenations were carried out at rt in methanol under 100 psi of hydrogen (Table 1). Screening of the four chiral rhodium complexes revealed

Table 1. Asymmetric Hydrogenation of α-(Acylamino)acrylic Acid Derivatives with the Rh-**3a** Catalyst[a]



4a-j **5a-j**

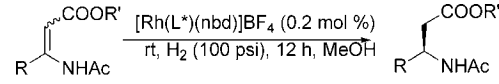
entry	R, R′	s/c ratio[b]	t (h)	ee [%][c]
1	Ph, H (**4a**)	500	1	99
2	Ph, H (**4a**)	10 000	24	99
3	H, Me (**4b**)	5000	6	98
4	Ph, Me (**4c**)	2000	6	99
5	*p*-F-Ph, Me (**4d**)	2000	6	>99
6	*p*-MeO-Ph, Me (**4e**)	2000	6	>99
7	*m*-Br-Ph, Me (**4f**)	2000	6	>99
8	*o*-Cl-Ph, Me (**4g**)	2000	6	98
9	1-naphthyl, Me (**4h**)	2000	6	>99
10	2-naphthyl, Me (**4i**)	2000	6	>99
11	Me, Me (**4j**)	2000	6	98

[a] Reactions were run at rt in MeOH under 100 psi H_2, see Supporting Information for experimental details. [b] s/c ratios were not fully optimized. [c] *S* 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 betadex-225) or Chiral HPLC (chiralpak AD-H). The ee of hydrogenation product **5a** was determined on corresponding methyl ester by treatment with $TMSCHN_2$.

that the Rh-**3a** catalyst provided the best and almost perfect enantioselectivity for hydrogenation of α-acetamidocinnamic acid (99% ee, entry 1).[13] The reactivity of this catalyst is also notable. At a s/c ratio of 500, the hydrogenation proceeded to completion within 1 h. High turnover, up to 10 000 TON, was also achieved without compromising the enantioselectivity (entry 2). With Rh[(**3a**)(nbd)]BF_4 as the catalyst, an array of α-acetamidocinnamic acid esters were hydrogenated to provide chiral α-amino acid derivatives in almost perfect enantioselectivities at a very low catalyst loading (entries 4−10). An excellent ee (98%) was also achieved on a β-alkyl α-(acylamino)acrylate **4j** (entry 11).

Asymmetric hydrogenation of β-(acylamino)acrylic acid derivatives has become one of most efficient methods for the synthesis of chiral β-amino acid derivatives.[14] While a variety of effective chiral ligands have been developed for hydrogenation of (*E*)-β-(acylamino)acrylates, efficient ligands for hydrogenation of (*Z*)-β-(acylamino)acrylates are still limited. We have found that the POP ligands are efficient for both (*E*)- and (*Z*)-β-(acylamino)acrylates (Table 2). The

Table 2. Asymmetric Hydrogenation of β-(Acylamino)acrylic Acid Derivatives with the Rh-**3a** or Rh-**3b** Catalyst[a]



(*E*) or (*Z*)-**6a-e** **7a-e**

entry	L*	R, R' (geometry)	ee[b] (%)	config
1	**3a**	Me, Me ((*Z*)-**6a**)	99	*S*
2	**3a**	*n*Pr, Et ((*Z*)-**6b**)	98	*S*
3	**3a**	Me, *i*Pr ((*Z*)-**6c**)	99	*S*
4	**3a**	Et, Me ((*Z*)-**6d**)	98	*S*
5	**3a**	Ph, Me ((*Z*)-**6e**)	97	*R*
6	**3b**	Me, Me ((*E*)-**6a**)	95	*S*
7	**3b**	*n*Pr, Et ((*E*)-**6b**)	98	*S*
8	**3b**	Me, *i*Pr ((*E*)-**6c**)	98	*S*
9	**3b**	Et, Me ((*E*)-**6d**)	94	*S*
10	**3b**	Me, Me ((*E*)/(*Z*)-**6a** 1/1)	94	*S*

[a] Reactions were run at rt in MeOH under 100 psi H_2 for 12 h in the presence of 0.2 mol % Rh[(L*)(nbd)]BF_4. [b] Enantiomeric excesses were determined by chiral GC (betadex-225). See Supporting Information for chiral GC conditions. The absolute configuration was assigned by comparison of optical rotation with reported data.

hydrogenations were carried out at rt in methanol for 12 h under 100 psi of hydrogen at 0.2 mol % catalyst loading. Ligand **3a** was proven to be an excellent ligand for hydrogenation of (*Z*)-β-(acylamino)acrylates.[15] High enantioselectivities (97−99% ee's) were achieved on various (*Z*)-β-(acylamino)acrylates with different substituents (entries 1−5). Notably, a β-phenyl-β-(acylamino)acrylate substrate was hydrogenated with an excellent ee (97% ee, entry 5). Interestingly, for hydrogenation of (*E*)-methyl 3-acetamidobut-2-enoate (entry 6), ligand **3b** provided the highest ee[16] and up to 98% ee's were achieved on various (*E*)-β-(acylamino)acrylates. An *E*/*Z* mixture of **6a** was also hydrogenated with the Rh-**3b** catalyst to provide the chiral β-amino acid derivative in 94% ee (entry 13).

In summary, we have developed a series of structurally novel and operationally convenient chiral 2-phosphino-2,3-dihydrobenzo[*d*][1,3]oxaphosphole ligands (POPs) that

(12) Crystallographic data for compound Rh[(*ent*-**3a**)(nbd)]BF4 have been deposited at Cambridge Crystallographic Data Centre (deposition no. CCDC-760509). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

(13) Enantioselectivities on hydrogenation of 2-acetamido-3-phenylacrylic acid (**4a**) with the Rh catalysts of different ligands: 99% ee (**3a**), 87% ee (**3b**), 54% ee (**3c**), and 92% ee (**3d**).

(14) For a recent overview on asymmetric hydrogenation of β-(acylamino)acrylic acid derivatives, see: (a) Bruneau, C.; Renaud, J.-L.; Jerphagnon, T. *Coord. Chem. Rev.* **2008**, *252*, 532. For recent examples, see: (b) Magano, J.; Conway, B.; Bowles, D.; Nelson, J.; Nanninga, T. N.; Winkle, D. D.; Wu, H.; Chen, M. H. *Tetrahedron Lett.* **2009**, *50*, 6329. (c) Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Proc. Res. Dev.* **2003**, *7*, 355.

(15) Enantioselectivities on hydrogenation of (*Z*)-methyl 3-acetamidobut-2-enoate ((*Z*)-**6a**) with the Rh catalysts of different ligands: 99% ee (**3a**), 91% ee (**3b**), 94% ee (**3c**), and 75% ee (**3d**).

(16) Enantioselectivities on hydrogenation of (*E*)-methyl 3-acetamidobut-2-enoate ((*E*)-**6a**) with the Rh catalysts of different ligands: 80% ee (**3a**), 95% ee (**3b**), 46% ee (**3c**), and 88% ee (**3d**).

have shown excellent enantioselectivities and reactivities for rhodium-catalyzed hydrogenation of α-(acylamino)acrylates and β-(acylamino)arylates. Ligand **3a** is proven to be a very efficient and practical ligand for the synthesis of chiral α-amino acid derivatives by asymmetric hydrogenation. Ligands **3a** and **3b** have also demonstrated excellent applications toward the synthesis of chiral β-amino acid derivatives. Studies of these novel bisphosphorus ligands for other metal-catalyzed asymmetric transformations are currently ongoing, and results will be reported in due course.

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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