ORGANIC LETTERS

2004
Vol. 6, No. 19
3357−3359

Preparation of an Amphiphilic Resin-Supported BINAP Ligand and Its Use for Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid in Water

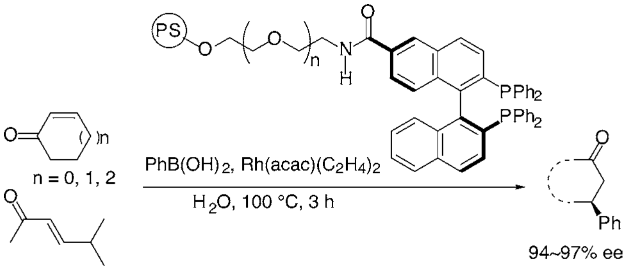
Yusuke Otomaru, Taichi Senda, and Tamio Hayashi*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

thayashi@kuchem.kyoto-u.ac.jp

Received July 8, 2004

ABSTRACT



The axially chiral bisphosphine ligand, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap), was supported on a polystyrene–poly(ethylene glycol) copolymer (PS–PEG) resin and was used successfully for the rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acid to α,*β*-unsaturated ketones in water.

The axially chiral bisphosphine ligand, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap),[1] is known to be one of the most effective chiral ligands for asymmetric reactions catalyzed by late transition metals.[2] It has been used successfully for a various kinds of asymmetric reactions represented by rhodium- and ruthenium-catalyzed asymmetric hydrogenation of olefins and ketones giving the corresponding reduction products with high, usually over 90%, enantioselectivity.[3] Recently, heterogenization of the binap ligand has attracted considerable attention,[4] which may provide a solution to the problem of separation and recycling of this precious chiral ligand. Typical examples are its immobilization on polystyrene[5] and a silica gel,[6] preparation of polymers[7] and dendrimers[8] containing the binap unit inside, and introduction of water-soluble functional groups onto the binap.[9] On the other hand, we have been using binap ligand for rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids to electron-deficient olefins,[10−12] which is usually carried out in a solvent system containing a certain

---

[1] (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

[2] For reviews: (a) Ojima, I. *Catalytic Asymmetric Synthesis II*; Wiley-VCH: New York, 2000. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. 1−3. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

[3] Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

[4] For a review: Saluzzo, C.; Lemaire, M. *Adv. Synth. Catal.* **2002**, *344*, 915.

[5] (a) Vankelecom, I. F. J.; Tas, D.; Parton, R. F.; Van de Vyver, V.; Jacobs, P. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1346. (b) Bayston, D. J.; Fraser, J. L.; Ashton, M. R.; Baxter, A. D.; Polywka, M. E. C.; Moses, E. *J. Org. Chem.* **1998**, *63*, 3137.

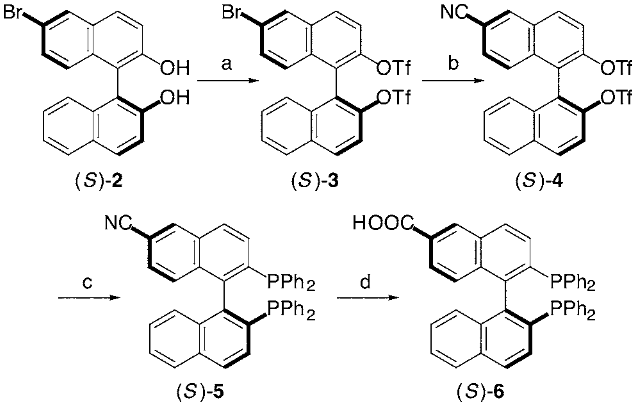
[6] Shimada, T.; Aoki, K.; Shinoda, Y.; Nakamura, T.; Tokunaga, N.; Inagaki, S.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 4688.

10.1021/ol048695m CCC: $27.50

amount of water. For the separation and recycling of the rhodium/binap catalyst in the rhodium-catalyzed asymmetric 1,4-addition, we chose a polystyrene−poly(ethylene glycol) copolymer (PS−PEG) resin as an immobilization partner because of its amphiphilic character suitable to the reactions in an aqueous solvent.[13] The use of an achiral phosphine ligand supported on PS−PEG resin for rhodium-catalyzed reactions, including the 1,4-addition, has been recently reported by Uozumi.[14] Here we report the preparation of PS−PEG resin-supported binap ligand **1** and its successful use for the rhodium-catalyzed asymmetric 1,4-addition of an organoboronic acid to α,β-unsaturated ketones in water.[15]

For connection of the axially chiral 1,1′-binaphthyl bisphosphine (binap) unit with the PS−PEG resin having an amino group (PS−PEG−NH$_2$) by amide bond formation, binap-carboxylic acid (*S*)-**6**, which contains a carboxyl group at the 6-position, was prepared (Scheme 1). The preparation starts with (*S*)-6-bromo-2,2′-dihydroxy-1,1′-binaphthyl (**2**) whose preparation from (*S*)-2,2′-dihydroxy-1,1′-binaphthyl has been reported by Cai.[16] Thus, treatment of (*S*)-**2** with triflic anhydride and pyridine[17] followed by cyanation of the resulting (*S*)-6-bromoditriflate **3** with cuprous cyanide according to the reported procedures[18] gave (*S*)-6-cyanoditriflate **4**. Introduction of two diphenylphosphino groups by the nickel-catalyzed phosphination of ditriflate **4** with diphenylphosphine[19] gave (*S*)-6-cyano-binap **5**. Alkaline hydrolysis of the cyano group in **5** gave the binap-carboxylic acid (*S*)-**6** in a high yield.

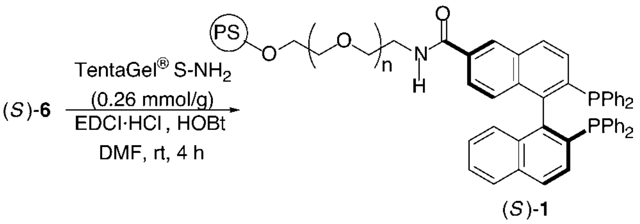
Scheme 1[a]



[a] Reagents and conditions: (a) Tf$_2$O, pyridine, CH$_2$Cl$_2$, 0 °C, 8 h, 78%; (b) CuCN, NMP, 180 °C, 4 h, 73%; (c) NiCl$_2$(dppe), HPPh$_2$, DABCO, DMF, 100 °C, 3 d, 73%; (d) KOH, dioxane/MeOH/H$_2$O, reflux, 24 h, 85%.

Treatment of the carboxylic acid (*S*)-**6** with the PS−PEG amino resin (TentaGel S-NH$_2$, 0.26 mmol/g NH$_2$) under the standard conditions for solid-phase amide condensation by use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBt) in DMF gave PS−PEG resin-supported (*S*)-binap **1** (Scheme 2). The content of the binap unit in the resin **1** was determined to be 0.17 mmol/g by elemental analysis. The

Scheme 2



---

(7) (a) Fan, Q.-H.; Deng, G.-J.; Lin, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1999**, *121*, 7407. (b) Fan, Q.-H.; Ren, C.-Y.; Yeung, C.-H.; Hu, W.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1241. (c) Yu, H.-B.; Hu, Q.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 1681. (d) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500. (e) Saluzzo, C.; ter Halle, R.; Touchard, F.; Fache, F.; Schulz, E.; Lemaire, M. *J. Organomet. Chem.* **2000**, *603*, 30. (f) Saluzzo, C.; Lamouille, T.; Hérault, D.; Lemaire, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1841.

(8) Fan, Q.-H.; Chen, Y.-M.; Chen, X.-M.; Jiang, D.-Z.; Xi, F.; Chan, A. S. C. *Chem. Commun.* **2000**, 789.

(9) (a) Wan, K. T.; Davies, M. E.; *J. Catalysis* **1994**, *148*, 1. (b) Fan, Q.-H.; Deng, G.-J.; Chen, X.-M.; Jiang, D.-Z.; Liu, D.-S.; Chan, A. S. C. *J. Mol. Catal. A: Chem.* **2000**, *159*, 37. (c) Lamouille, T.; Saluzzo, C.; ter Halle, R.; Le Guyader, F.; Lemaire, M. *Tetrahedron Lett.* **2001**, *42*, 663. (d) Guerreiro, P.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Dellis, P. *Tetrahedron Lett.* **2001**, *42*, 3423.

(10) For reviews: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(11) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (c) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957. (d) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. (e) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716. (f) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852. (g) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(12) Other examples of the use of binap or its derivatives for the rhodium-catalyzed asymmetric 1,4-addition: (a) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. (b) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944. (c) Amengual, R.; Michelet, V.; Genêt, J.-P. *Synlett* **2002**, 1791. (d) Pucheault, M.; Darses, S.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 6155. (e) Pucheault, M.; Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2002**, 3552.

(13) Some phosphine ligands supported on the PS−PEG resin have been used for palladium-catalyzed cross-coupling and allylic substitution reactions in water: (a) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 3557. (b) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8303. (c) Danjo, H.; Tanaka, D.; Hayashi, T.; Uozumi, Y. *Tetrahedron* **1999**, *55*, 14341. (d) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384. (e) Uozumi, Y.; Watanabe, T. *J. Org. Chem.* **1999**, *64*, 6921. (f) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919. (g) Shibatomi, K.; Uozumi, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1769. (h) Uozumi, Y.; Nakai, Y. *Org. Lett.* **2002**, *4*, 2997. (i) Uozumi, Y.; Kimura, T. *Synlett* **2002**, 2045. (j) Hocke, H.; Uozumi, Y. *Synlett* **2002**, 2049. (k) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71. (l) Uozumi, Y.; Tanaka, H.; Shibatomi, K. *Org. Lett.* **2004**, *6*, 281.

(14) Uozumi, Y.; Nakazono, M. *Adv. Synth. Catal.* **2002**, *344*, 274.

(15) For reviews on organic reactions in water: (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley-VCH: New York, 1997. (c) Grieco, P. A. *Organic Synthesis in Water*; Kluwer Academic Publishers: Dordrecht, 1997. (d) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524.

(16) Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4055. See also, Hocke H.; Uozumi, Y. *Tetrahedron* **2003**, *59*, 619.

(17) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945.

(18) (a) ter Halle, R.; Colasson, B.; Schulz, E.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* **2000**, *41*, 643. (b) Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522. (c) Newman, M. S.; Boden, H. *J. Org. Chem.* **1961**, *26*, 2525. (d) Vondenhof, M.; Mattay, J. *Tetrahedron Lett.* **1990**, *31*, 985.

(19) Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180.

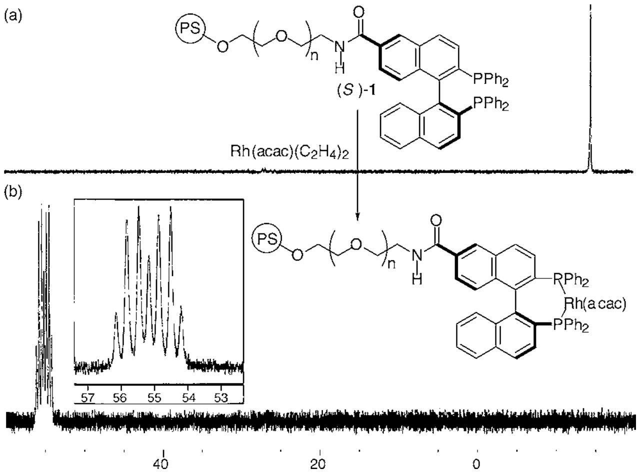
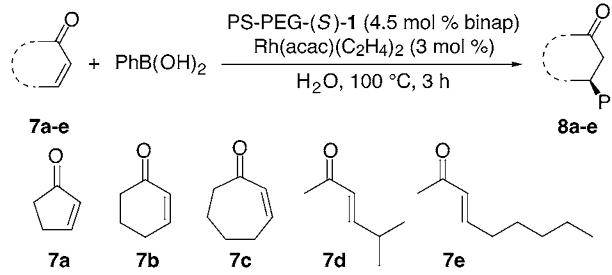


Figure 1. Comparison of the ^{31}P NMR spectra (at 202 MHz in THF) of PS−PEG−(*S*)-binap **1** and its rhodium complex. (a) PS−PEG−(*S*)-binap **1**: δ −14.5 ppm (broad s). (b) Addition of Rh(acac)(C_2H_4)$_2$ to (*S*)-**1** giving its rhodium complex: δ 55.0 ppm (dd, J_{Rh-P} = 194 Hz, J_{P-P} = 64 Hz), 55.3 ppm (dd, J_{Rh-P} = 193 Hz, J_{P-P} = 64 Hz).

Table 1. Asymmetric 1,4-Addition of Phenylboronic Acid to α,β-Unsaturated Ketones **7** Catalyzed by PS−PEG−(*S*)-Binap (**1**)/Rh in Water[a]



entry		enone **7**	yield[b] (%) of **8**	% ee[c]
1		**7a**	95 (**8a**)	94 (*S*)
2		**7b**	83 (**8b**)	97 (*S*)
3		**7c**	86 (**8c**)	95 (*S*)
4		**7d**	71 (**8d**)	96 (*S*)
5		**7e**	80 (**8e**)	91 (*R*)
	recycle			
6	first[d]	**7a**	85 (**8a**)	94 (*S*)
7	second[d]	**7a**	94 (**8a**)	93 (*S*)
8	third[d]	**7a**	94 (**8a**)	94 (*S*)
9	fourth[e]	**7a**	99 (**8a**)	94 (*S*)

[a] Reaction was carried out with enone **7** (0.20 mmol), phenylboronic acid (1.0 mmol), Rh(acac)(C_2H_4)$_2$ (3 mol % Rh), and PS−PEG−(*S*)-binap **1** (**1**/Rh = 1.5/1.0) in H_2O (1.0 mL). [b] Isolated yield after silica gel chromatography. [c] Determined by HPLC analysis with chiral stationary phase columns: Chiralcel OB-H for **8a**; OD-H for **8b**−**e**. [d] Reaction mixture was extracted once with diethyl ether. To the water layer was added enone **7a** and phenylboronic acid, and the next run was carried out under the same conditions. [e] Reaction mixture was filtered, and the resin was washed several times with diethyl ether.

gel-phase ^{31}P NMR studies[20] showed that the resin-supported (*S*)-binap **1** coordinates to a rhodium-forming chelating bisphosphine complex (Figure 1). Two nonequivalent phosphorus atoms in **1** appear as a broad singlet at −14.5 ppm in THF. On addition of Rh(acac)(C_2H_4)$_2$ to **1**, new signals appeared at a lower field as two double doublets (55.0 ppm (dd J_{Rh-P} = 194 Hz, J_{P-P} = 64 Hz) and 55.3 ppm (dd J_{Rh-P} = 193 Hz, J_{P-P} = 64 Hz)). The chemical shifts and coupling constants are quite similar to those of Rh(acac)(binap) complex (55.3 ppm (d, J_{Rh-P} = 193 Hz)),[11a] supporting that the PS−PEG resin-supported binap **1** forms a stable chelating complex with rhodium.

The rhodium complex of PS−PEG resin-supported binap **1** showed high catalytic activity and high enantioselectivity in water for the asymmetric 1,4-addition of phenylboronic acid to α,β-unsaturated ketones (Table 1). Thus, a mixture of Rh(acac)(C_2H_4)$_2$ (6.0 μmol) and **1** (9.0 μmol binap), as well as phenylboronic acid (1.0 mmol) in THF (0.5 mL), was stirred at room temperature for 3 min. Removal of the solvent under reduced pressure was followed by addition of enone **7** (0.20 mmol) and water (1 mL). The mixture was heated at 100 °C for 3 h. Removal of the catalyst by filtration and extraction with diethyl ether gave a high yield of 1,4-addition product **8**. As shown in Table 1, the 1,4-addition proceeded in water with high enantioselectivity for both cyclic enones **7a**−**c** and acyclic enones **7d**,**e** (entries 1−5). The enantioselectivities (91∼97% ee) observed here are comparable to those reported for the reaction carried out with homogeneous (*S*)-binap in dioxane/H_2O (10/1).[11a]

The recycle experiments were examined for the reaction of 2-cyclopentenone (**7a**). Although separation of the PS−PEG resin-supported catalyst by filtration sometimes caused the loss of its catalytic activity,[21] separation of the organic product by extraction with diethyl ether always kept the reusable active catalyst in the water layer. The second run was carried out by addition of enone **7a** and phenylboronic acid to the catalyst in water and heating the mixture at 100 °C for 3 h. The catalyst was recycled four times during which the yield and enantioselectivity were kept high (entries 6−9).

To summarize, the binap ligand supported on PS−PEG resin was prepared and used successfully for the rhodium-catalyzed asymmetric 1,4-addition in water. This amphiphilic resin-supported binap will find application in many transition metal-catalyzed asymmetric reactions which can be performed in an aqueous solvent.

Acknowledgment. We thank the Ministry of Education, Culture, Sports, Science, and Technology, Japan, for a Grant-in-Aid for Scientific Research for partial financial support of this work.

Supporting Information Available: Experimental procedures for the preparation of **1** and rhodium-catalyzed asymmetric 1,4-addition. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048695M

---

(20) Johnson, C. R.; Zhang, B. *Tetrahedron Lett.* **1995**, *36*, 9253.

(21) Water phase, which is colorless, did not show any catalytic activity, indicating that no leaching of the rhodium catalyst to water. The loss of catalytic activity observed for the resin recovered by filtration is due probably to a technical problem such as exposure to air.