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Asymmetric Synthesis of Axially Chiral Biaryl Diphosphine Ligands by Rhodium-Catalyzed Enantioselective Intramolecular Double [2 + 2 + 2] Cycloaddition

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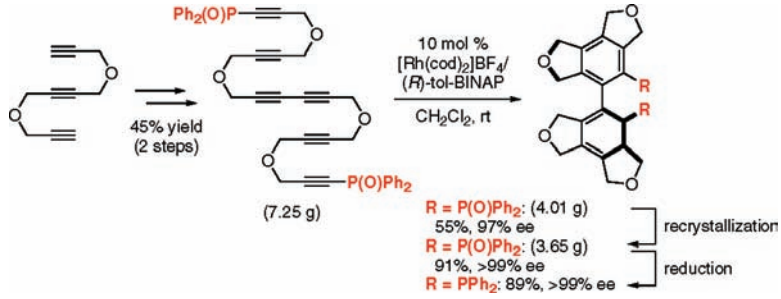
ABSTRACT



The concise synthesis of axially chiral biaryl diphosphine ligands by the rhodium-catalyzed intramolecular [2 + 2 + 2] cycloaddition of hexayne diphosphine oxides has been achieved. These new chiral diphosphine ligands could be employed as a ligand for the rhodium-catalyzed asymmetric catalyses.

C_2-Symmetric axially chiral biaryl diphosphines have been widely employed as ligands for various asymmetric catalyses.[1] Their conventional synthesis is based on the homocoupling reaction to construct C_2-symmetric biaryl skeletons followed by optical resolution and introduction of two diarylphosphinoyl groups.[1] Obviously, direct and enantioselective introduction of two bulky diarylphosphinoyl groups on biaryls is highly attractive.[2−4] For the enantioselective synthesis of biaryl phosphorus compounds, the enantioselective Suzuki−Miyaura cross-coupling reactions of phosphorus-containing aryl halides and aryl boronic acids were reported. However, this method is restricted to the synthesis of sterically less demanding biaryl monophosphonates or phosphine oxides.[4] On the other hand, Doherty and coworkers reported the cationic rhodium(I)/*rac*-BINAP complex-catalyzed double [2 + 2 + 2] cycloaddition[5−7] of a diphenylphosphinoyl-substituted 1,3-butadiyne with terminal 1,6-diynes leading to achiral biaryl diphosphine oxides (Scheme 1: R^1 = H, R^2 = Ph).[8] Our research group reported

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(1) For a review, see: Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

(2) For recent reviews of the atroposelective biaryl synthesis, see: (a) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (b) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223. (c) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197. (d) Ogasawara, M.; Watanabe, S. *Synthesis* **2009**, 1761. (e) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193. For a recent review involving the atroposelective biaryl phosphane synthesis, see: (f) Glueck, D. S. *Chem.—Eur. J.* **2008**, *14*, 7108.

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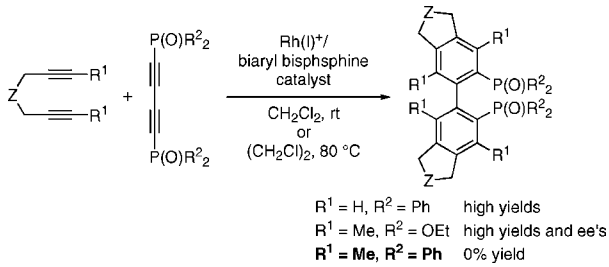
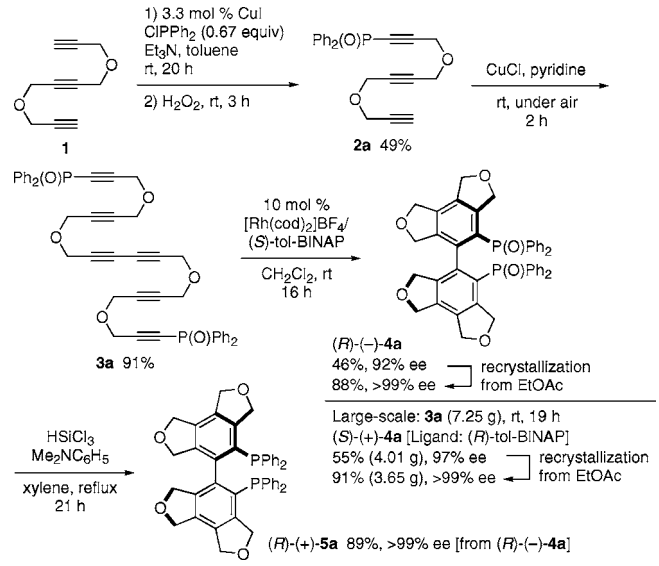
Scheme 1



the cationic rhodium(I)/Segphos complex-catalyzed enantioselective double [2 + 2 + 2] cycloaddition of a phosphonate-substituted 1,3-butadiyne with internal 1,6-diynes leading to C_2-symmetric axially chiral biaryl diphosphonates with excellent enantioselectivity (Scheme 1: R^1 = Me, R^2 = OEt).[9] Unfortunately, C_2-symmetric axially chiral biaryls with two bulky diphenylphosphinoyl groups could not be obtained by the cationic rhodium(I) complex-catalyzed intermolecular double [2 + 2 + 2] cycloaddition (Scheme 1: R^1 = Me, R^2 = Ph).[10]

To overcome this limitation, an enantioselective intramolecular [2 + 2 + 2] cycloaddition of hexayne **3a**,[11] bearing two diphenylphosphinoyl groups at alkyne termini, leading to C_2-symmetric axially chiral biaryl diphosphine oxide **4a** was examined as shown in Scheme 2. Hexayne **3a** was readily prepared via the copper(I)-catalyzed monodiphenylphosphination[12,13] of known triyne **1**[14] followed by oxidation of phosphine to generate phosphine oxide **2a** and oxidative homocoupling of **2a**. The [2 + 2 + 2] cycloaddition of hexayne **3a** in the presence of cationic rhodium(I)/axially chiral biaryl diphosphine (Figure 1) complexes was then examined (Table 1). We were pleased to find that the reaction of **3a** leading to biaryl **4a** proceeded at room temperature by using H_8-BINAP as a ligand (entry 1). Interestingly, the yield of **4a** is dependent on the dihedral angle of the biaryl diphosphine ligands [dihedral angle:[15] H_8-BINAP (entry 1) > BINAP (entry 2) > Segphos (entry 3); yield of **4a**: entry 1 > entry 2 > entry 3]. As the highest enantioselectivity was obtained by using BINAP, the effect of the steric bulk of the aryl group on the phosphorus of BINAP was examined (entries 4 and 5). The study revealed that the use of tol-BINAP increased both yield and enantioselectivity (entry 4), while that of xyl-BINAP failed to furnish **4a** (entry 5).

Scheme 2



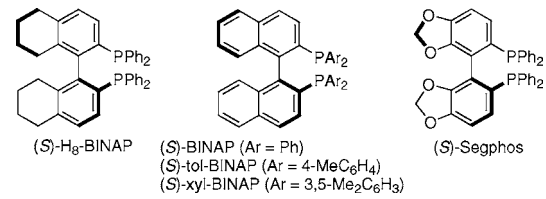


Figure 1. Structures of axially chiral biaryl diphosphine ligands.

(3) For enantioselective synthesis of axially chiral biaryl monophosphonates and monophosphine oxides by the rhodium-catalyzed [2 + 2 + 2] cycloaddition, see: (a) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3951. For an example of enantioselective synthesis of a biaryl monophosphine sulfide, see: (b) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 6996. By using chiral cobalt(I) catalysts, see: (c) Heller, B.; Gutnov, A.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Redkin, D.; Sundermann, C.; Sundermann, B. *Chem.—Eur. J.* **2007**, *13*, 1117. For enantioselective synthesis of *P*-stereogenic phosphine oxides, see: (d) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3410.

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(5) For a review of atroposelective biaryl synthesis by the transition metal-catalyzed [2 + 2 + 2] cycloaddition, see: Tanaka, K. *Chem. Asian J.* **2009**, *4*, 508.

(6) For our first discovery of the cationic rhodium(I)/biaryl diphosphine complex-catalyzed [2 + 2 + 2] cycloaddition, see: (a) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697. For our account, see: (b) Tanaka, K. *Synlett* **2007**, 1977.

(7) For enantioselective synthesis of axially chiral biarylcarboxylates by the rhodium-catalyzed double [2 + 2 + 2] cycloaddition, see: Nishida, G.; Suzuki, N.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2006**, *8*, 3489.

(8) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Org. Lett.* **2007**, *9*, 4925.

(9) Nishida, G.; Ogaki, S.; Yusa, Y.; Yokozawa, T.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2849.

(10) Enantioselective synthesis of tri-ortho-substituted axially chiral biaryl diphosphine oxides via the stepwise double [2 + 2 + 2] cycloaddition was reported. See: Doherty, S.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2008**, *27*, 4837.

(11) For atroposelective biaryl synthesis by the iridium-catalyzed intramolecular double [2 + 2 + 2] cycloaddition of hexaynes, see: (a) Shibata, T.; Yoshida, S.; Arai, Y.; Otsuka, M.; Endo, K. *Tetrahedron* **2008**, *64*, 821. For racemic biaryl synthesis by the iron-catalyzed intramolecular double [2 + 2 + 2] cycloaddition of a hexayne, see: (b) Saino, N.; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065. (c) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organomet. Chem.* **2006**, *691*, 3129.

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Table 1. Rh-Catalyzed Enantioselective Intramolecular Double [2 + 2 + 2] Cycloaddition of Hexayne **3a** Leading to Biaryl **4a**[a]

entry	ligand	yield (%)[b]	ee (%)
1	(*S*)-H_8-BINAP	44	58 (*R*)
2	(*S*)-BINAP	30	82 (*R*)
3	(*S*)-Segphos	8	78 (*R*)
4	(*S*)-tol-BINAP	46	92 (*R*)
5	(*S*)-xyl-BINAP	0	

[a] $[Rh(cod)_2]BF_4$ (0.0050 mmol), ligand (0.0050 mmol), **3a** (0.050 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Isolated yield.

Enantiopure diphosphine oxide (−)-**4a** could be readily obtained by a single recrystallization from EtOAc in high yield. Subsequent reduction with $HSiCl_3/Me_2NC_6H_5$ furnished enantiopure (+)-**5a** in high yield without racemization. The scale-up of the present enantioselective intramolecular double [2 + 2 + 2] cycloaddition was successfully accomplished. The reaction of hexayne **3a** (7.25 g) in the presence of the cationic rhodium(I)/(*R*)-tol-BINAP complex (10 mol %) at room temperature furnished diphosphine oxide (+)-**4a** (4.01 g) with higher yield and ee value than those of the small scale reaction. A subsequent recrystallization from EtOAc furnished enantiopure (+)-**4a** (3.65 g) in high yield.

The absolute configurations of axially chiral biaryl diphosphine oxide (−)-**4a** and diphosphine (+)-**5a** were unambiguously determined to be *R* by the anomalous dispersion method (Figure 2).

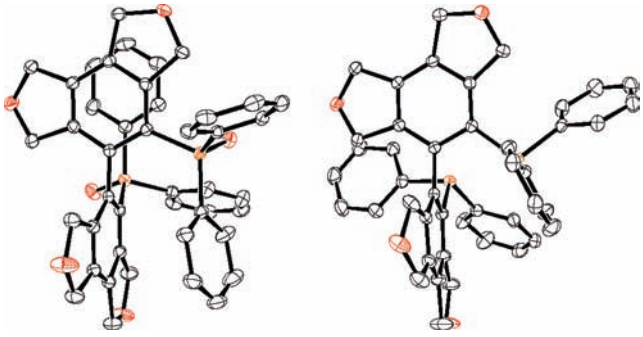
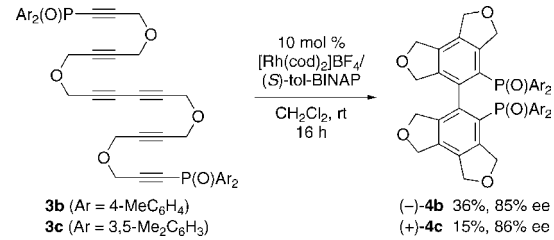


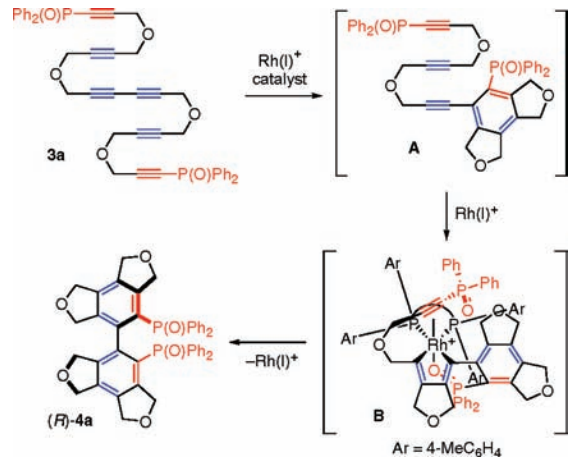
Figure 2. ORTEP diagrams of diphosphine oxide (*R*)-(−)-**4a** (left) and diphosphine (*R*)-(+)-**5a** (right) with ellipsoids at 30% probabilities. All hydrogen atoms were omitted for simplicity.

Enantioselective synthesis of sterically more demanding C_2-symmetric axially chiral biaryl diphosphine oxides **4b** and **4c** was also examined as shown in Scheme 3. Although the enantioselective intramolecular [2 + 2 + 2] cycloadditions of hexayne di(*p*-tolyl)phosphine oxide **3b** and hexayne di(3,5-xylyl)phosphinoyl oxide **3c** proceeded to give the corresponding biaryls **4b** and **4c**, respectively, under the same

Scheme 3



Scheme 4



reaction conditions shown in Scheme 2, the yields and ee values were lower than those of biaryl **4a**.[16]

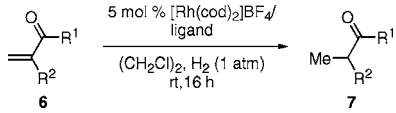
Scheme 4 depicts a possible mechanism for the selective formation of diphosphine oxide (*R*)-**4a** by using (*S*)-tol-BINAP as a ligand. The first intramolecular [2 + 2 + 2] cycloaddition of hexayne **3a** proceeds to give triyne **A**. The second [2 + 2 + 2] cycloaddition through intermediate **B**, as a result of the coordination of triarylphosphine oxide moiety of **A** to rhodium and the avoidance of steric repulsion between the alkynylphosphine oxide moiety of **A** and the axial phenyl group of (*S*)-tol-BINAP, would furnish (*R*)-**4a**.

It was already reported that axially chiral 3,3′-disubstituted biaryl diphosphines are superior ligands than BINAP in the rhodium-catalyzed asymmetric hydrogenation of disubstituted alkenes, such as 2-acetamidoacrylic acid derivatives **6a** and **6b**.[17,18] Therefore application of ligand (*R*)-(+)-**5a** in the

(16) In the reaction of **3b**, a pure mono-annulation product was isolated in 23% yield as a byproduct. In the reaction of **3c**, an unidentified mixture of byproducts was generated.

(17) (a) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett.* **2002**, *4*, 1695. (b) Shibata, T.; Tsuruta, H.; Danjo, H.; Imamoto, T. *J. Mol. Catal. A: Chem.* **2003**, *196*, 117. (c) Wu, S.; He, M.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2177. (d) Hopkins, J. M.; Dalrymple, S. A.; Parvez, M.; Keay, B. A. *Org. Lett.* **2005**, *7*, 3765. (e) Rankic, D. A.; Hopkins, J. M.; Parvez, M.; Keay, B. A. *Synlett* **2009**, 2513. For applications in palladium-catalyzed asymmetric reactions, see: (f) Gorobets, E.; Sun, G.-R.; Wheatley, B. M. M.; Parvez, M.; Keay, B. A. *Tetrahedron Lett.* **2004**, *45*, 3597. (g) Gorobets, E.; Sun, G.-R.; Wheatley, B. M. M.; Parvez, M.; Keay, B. A. *Tetrahedron Lett.* **2004**, *45*, 3597. (h) Hopkins, J. M.; Gorobets, E.; Wheatley, B. M. M.; Parvez, M.; Keay, B. A. *Synlett* **2006**, 3120. (i) Rankic, D. A.; Lucciola, D.; Keay, B. A. *Tetrahedron Lett.* **2010**, *51*, 5724.

Table 2. Comparison of Enantioselectivity between (*R*)-(+)-**5a**, (+)-**5b**, (+)-**5c**, and (*S*)-BINAP in Rh-Catalyzed Asymmetric Hydrogenation of Disubstituted Alkenes **6a**−**d**[a]



6 **7**

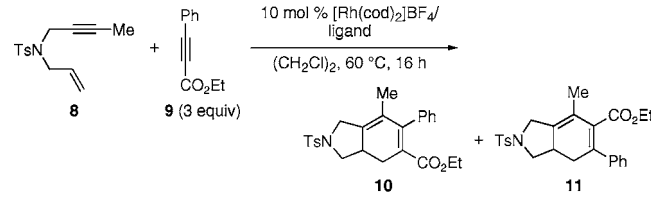
entry	**6**	R_1	R_2	ligand	**7**	ee (%)
1	**6a**	OMe	NHAc	(*R*)-(+)-**5a**	(*R*)-**7a**	98
2	**6a**	OMe	NHAc	(*S*)-BINAP	(*R*)-**7a**	25
3	**6b**	OH	NHAc	(*R*)-(+)-**5a**	(*R*)-**7b**	96
4	**6b**	OH	NHAc	(*S*)-BINAP	(*R*)-**7b**	23
5	**6c**	OMe	CH_2CO_2Me	(*R*)-(+)-**5a**	(*S*)-**7c**	78
6	**6c**	OMe	CH_2CO_2Me	(*S*)-BINAP	(*S*)-**7c**	76
7	**6d**	NPh_2	Ph	(*R*)-(+)-**5a**	(+)-**7d**	48
8	**6d**	NPh_2	Ph	(*S*)-BINAP	(−)-**7d**	18

[a] All reactions were completed under the conditions.

rhodium-catalyzed asymmetric hydrogenation of disubstituted alkenes including **6a** and **6b** was briefly examined, and the observed enantioselectivities were compared to those with (*S*)-BINAP under the same reaction conditions (Table 2). Significantly higher enantioselectivities were observed with (*R*)-(+)-**5a** than those with (*S*)-BINAP in the hydrogenation of **6a** and **6b** (entries 1 and 3 vs entries 2 and 4). In the hydrogenation of itaconic acid dimethyl ester (**6c**), good enantioselectivities were observed by using both (*R*)-(+)-**5a** and (*S*)-BINAP (entries 5 and 6). Interestingly, the same facial enantioselections were observed between (*R*)-(+)-**5a** and (*S*)-BINAP in the hydrogenation of **6a**−**c** (entries 1−6). The hydrogenation of acrylamide derivative **6d** with (*R*)-(+)-**5a** showed higher enantioselectivity than that with (*S*)-BINAP (entry 7 vs entry 8), although the ee value was moderate.

Application of ligand (*R*)-(+)-**5a** in the rhodium-catalyzed asymmetric C−C bond forming reaction was also examined briefly. Interestingly, the rhodium-catalyzed asymmetric [2 + 2 + 2] cycloaddition of 1,6-enyne **8** with ethyl phenylpropiolate (**9**) using (*R*)-(+)-**5a** as a ligand furnished a pair of two regioisomeric products **10** and **11** with 72:28 regioselectivity and good ee values; this regioselectivity is contrary to that using (*S*)-BINAP (**10**/**11** = 29:71) (Scheme 5).[19] With regard to enantioselectivity, the opposite facial enantioselections were observed between (*R*)-(+)-**5a** and (*S*)-BINAP.

Scheme 5



ligand	% yield (**10**/**11**)	**10** / % ee	**11** / % ee
(*R*)-(+)-**5a**	65 (72:28)	82	86
(*S*)-BINAP	86 (29:71)	69	93

In conclusion, we have achieved the concise asymmetric synthesis of axially chiral biaryl diphosphine ligands by the rhodium-catalyzed intramolecular [2 + 2 + 2] cycloaddition of hexayne diphosphine oxides. These new chiral diphosphine ligands could be employed as a ligand for the rhodium-catalyzed asymmetric catalyses. Future work will focus on further optimization of the large-scale synthesis of these new chiral biaryl diphosphine ligands and their application in various asymmetric catalyses.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For a review of new chiral phosphorus ligands for enantioselective hydrogenation, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278.

(19) For the cationic rhodium(I)/axially chiral biaryl diphosphine complex-catalyzed regio- and enantioselective [2 + 2 + 2] cycloaddition of 1,6-enynes with alkynes, see: (a) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 12466. (b) Shibata, T.; Arai, Y.; Tahara, Y. *Org. Lett.* **2005**, *7*, 4955. During the preparation of this manuscript, the regiodivergent ligand (xyl-BINAP vs PPh_3)-controlled rhodium-catalyzed [2 + 2 + 2] cycloaddition of 1,6-enynes with alkyl-substituted methyl propiolates was reported. See: (c) Evans, P. A.; Sawyer, J. R.; Inglesby, P. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 5746.