Catalytic Asymmetric Synthesis of Axially Chiral Biaryls by Palladium-Catalyzed Enantioposition-Selective Cross-Coupling

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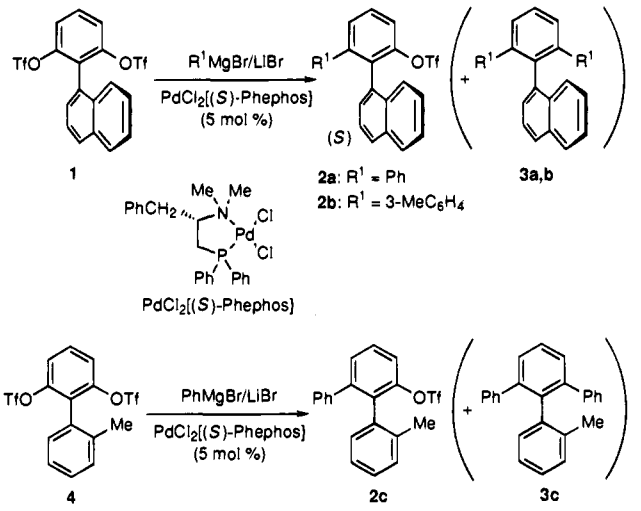
Optically active biaryls represented by 1,1′-binaphthyls have found extensive use in chiral auxiliaries for a variety of synthetic asymmetric reactions including catalytic ones,[1,2] and considerable attention has been paid to their preparation by asymmetric synthesis. In most of the asymmetric syntheses so far reported, the axial chirality of biaryls has been generated at the coupling of two aryl units.[3] Here we report a new catalytic method for their preparation which is realized by an enantioposition-selective substitution reaction of one of the two enantiotopic triflate groups on achiral biaryl ditriflates (Scheme 1).

For the cross-coupling of 1-[2,6-bis[[(trifluoromethyl)sulfonyl]oxy]phenyl]naphthalene (**1**) with phenymagnesium bromide, several chiral phosphine−palladium complexes were examined for their catalytic activity and enantioselectivity. The palladium complex $PdCl_2$[(*S*)-Phephos], where Phephos stands for 2-(dimethylamino)-1-(diphenylphosphino)-3-phenylpropane,[4] was found to be the best. Thus, the reaction of **1** with 2.1 equiv of phenylmagnesium bromide in ether/toluene in the presence of 5 mol % palladium catalyst and 1 equiv (to **1**) of lithium bromide[5] at −30 °C for 48 h gave 87% yield of axially chiral monophenylated biaryl (*S*)-**2a** in 93% ee and 13% yield of diphenylated biaryl **3a** (entry 1 in Table 1).[6] The biaryl **2a** is readily made enantiomerically pure with high recovery by simple recrystallization. Thus, recrystallization of a crude mixture of (*S*)-**2a** and **3a**, obtained in a separate run of the same asymmetric cross-coupling, from hexane gave 78% isolated yield of enantiomerically pure (*S*)-**2a**.[7] High enantioselectivity was also observed in the reaction of **1** with *m*-tolylmagnesium bromide and in the phenylation of 1,3-bis[[(trifluoromethyl)sulfonyl]oxy]-2-(2-methylphenyl)benzene (**4**) under similar conditions, which

Scheme 1



gave the corresponding monoalkylation products **2b** and **2c** in 90% ee and 84% ee, respectively, in high yields (entries 4 and 5).

It was found in the asymmetric cross-coupling of ditriflate **1** with PhMgBr that the enantiomeric purity of **2a** is dependent on the yield of diphenylation product **3a**. Thus, in entry 2, where **3a** was not formed at all, the enantiomeric purity of **2a** was 85% ee (*S*) (entry 2), significantly lower than that (93% ee (*S*)) of **2a** obtained in entry 1 where the reaction was accompanied by the formation of a considerable amount of **3a** (entry 1). A kinetic resolution at the second cross-coupling was demonstrated by a control experiment using racemic **2a**. At 20% conversion to diphenylation product **3a**, the recovered **2a** was an (*S*)-isomer with 17% ee, indicating that the (*R*)-isomer of **2a** undergoes the phenylation about 5 times faster than its (*S*)-isomer ($k(R)/k(S) = 5/1$). It follows that the minor enantiomer of **2a** formed at the first asymmetric cross-coupling is consumed preferentially at the second asymmetric cross-coupling, which causes an increase of enantiomeric purity of **2a** as the amount of diphenylation product **3a** increases (Scheme 2).[8]

The monoalkylated biaryls **2** obtained here are very useful as axially chiral building blocks because the remaining triflate group can be readily substituted with some other functional groups by transition-metal-catalyzed coupling-type reactions.[9]

(1) For reviews see: (a) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH Publishers New York, 1993. (b) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic Press: London, 1983−1985; Vols. 1−5. (c) Nógrádi, M. *Stereoselective Synthesis*; Weinheim: New York, 1987. (d) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(2) (a) 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP): Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345 and references cited therein. (b) 2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (MOP) and its derivatives: Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945. (c) 2,2′-Dihydroxy-1,1′-binaphthyl and its derivatives: Rosini, C.; Franzini, L.; Raffaelli, A.; Salvaori, P. *Synthesis* **1992**, 503.

(3) (a) Miyano, S.; Tobita, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3522. (b) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879. (c) Wilson, J. M.; Cram. D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881. (d) Yamamoto, K.; Fukushima, H.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1490. (e) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153 and references cited therein. (f) Osa, T.; Kashiwagi, Y.; Yanagisawa, Y.; Bobbitt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2535 and references cited therein.

(4) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195.

(5) The addition of lithium bromide is essential for the high enantioselectivity as well as for the high catalytic activity. See entry 3 in Table 1. Other metal salts such as lithium chloride, lithium iodide, and magnesium bromide were not as effective as lithium bromide.

(6) Palladium complexes coordinated with some other aminoalkylphosphines including (*S*)-Alaphos, (*S*)-Valphos, and (*R*,*S*)-PPFA, also catalyzed the reaction of **1** with PhMgBr under similar conditions, though the catalytic activity or enantioselectivity was lower. The chemical yields and enantiomeric purities of **2a** obtained for the reaction at 0 °C for 48 h are as follows: (*S*)-Phephos, 74%, 84% ee (*S*); (*S*)-Alaphos, 64%, 80% ee (*S*); (*S*)-Valphos, 48%, 58% ee (*S*); (*R*,*S*)-PPFA, 24%, 44% ee (*R*).

(7) A typical procedure is shown below: To a mixture of **1** (995 mg, 1.98 mmol), lithium bromide (174 mg, 2.00 mmol), $PdCl_2$[(*S*)-Phephos] (50 mg, 0.094 mmol) in toluene (2.6 mL) was added 2.4 mL of an ether solution of 1.8 M PhMgBr (4.3 mmol) at −30 °C, and the mixture was stirred at −30 °C for 48 h (monitoring by GLC). The mixture was hydrolyzed with 10% hydrochloric acid, and extracted with ether. The ether extracts were washed with water, dried over anhydrous sodium sulfate, and stripped of solvent in vacuo. Short silica gel column chromatography (hexane/ethyl acetate = 5/1) gave a mixture of **2a** (93% ee) and **3a** in a ratio of 85 to 15. Recrystallization of the crude mixture of **2a** and **3a** from hexane gave 666 mg (78%) of enantiomerically pure (*S*)-**2a** (mp 142 °C, $[\alpha]^{20}_D$ −145 (*c* 1.0, chloroform)). The enantiomeric purity of **2a** was determined by HPLC analysis (Sumichiral OA-4700, hexane/1,2-dichloroethane/ethanol = 250/20/1) of 1-[2-hydroxy-6-phenylphenyl]naphthalene obtained by alkaline hydrolysis of **2a**.

(8) Such a combination of selection of enantiotopic sites and kinetic resolution leading to enantiopurity enhancement has been reported: (a) Dokuzovic, Z.; Roberts, N. K.; Sawyer, J. F.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034. (b) Johnson, C. R.; Xu, Y.; Nicolaou, K. C.; Yang, Z.; Guy, R. K.; Dong, J. G.; Berova, N. *Tetrahedron Lett.* **1995**, *36*, 3291.

(9) For recent books and reviews see: (a) Hegedus, L. S. In *Organometallics in Synthesis;* Schlosser, M., Ed.; John Wiley and Sons: New York, 1994; p 383. (b) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994. (c) MacQuillin, F. J.; Parker, D. G.; Stephenson, G. R. *Transition Metal Organometallics for Organic Synthesis*; Cambridge University Press: Cambridge, 1991.

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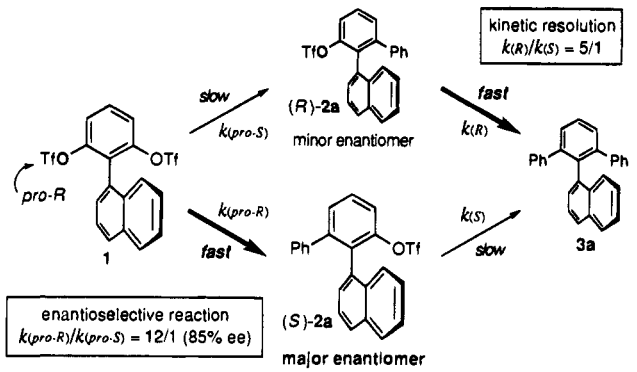
Table 1. Asymmetric Cross-Coupling of Ditriflate **1** or **4** with Grignard Reagents Catalyzed by $PdCl_2$[(*S*)-Phephos][a]

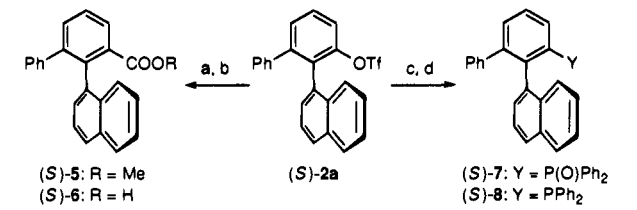
entry	ditriflate	Grignard reagent (equiv)	reaction temp (°C)	reaction time (h)	recovered ditriflate (%)[b]	yield of **2** (%)[b]	yield of **3** (%)[b]	% ee of **2**[c]
1	**1**	PhMgBr (2.1)	−30	48	0 (**1**)	87 (**2a**)	13 (**3a**)	93 (*S*)
2	**1**	PhMgBr (1.1)	−30	16	60 (**1**)	39 (**2a**)	0 (**3a**)	85 (*S*)
3[d]	**1**	PhMgBr (1.1)	−30	16	87 (**1**)	9 (**2a**)	0 (**3a**)	30 (*S*)
4	**1**	3-MeC_6H_4MgBr (2.1)	−20	48	6 (**1**)	83 (**2b**)	11 (**3b**)	90
5	**4**	PhMgBr (2.1)	−20	48	0 (**4**)	77 (**2c**)	23 (**3c**)	84

[a] The cross-coupling was carried out in ether/toluene (1/1) in the presence of 1 equiv of LiBr and 5 mol % $PdCl_2$[(*S*)-Phephos]. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenols obtained by alkaline hydrolysis of triflates **2**: for entries 1−4, Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1); for entry 5, Chiralcel OD-H (hexane/2-propanol = 95/5). [d] In the absence of LiBr.

Scheme 2



Scheme 3[a]



[a] Reagents and conditions: (a) CO (1 atm), $Pd(OAc)_2$/dppp/*i*-Pr_2NEt/DMSO, 80 °C, 15 h, 97% yield; (b) 50% KOH/MeOH, reflux 8 h and then 10% HCl, 94% yield; (c) $Ph_2P(O)H$/$Pd(OAc)_2$/dppb/*i*-Pr_2NEt/DMSO, 100 °C, 12 h, 99% yield; (d) $HSiCl_3$/Et_3N/toluene, 130 °C, 36 h, 73% yield.

For example, enantiomerically pure monotriflate (*S*)-**2a** was converted into methyl ester (*S*)-**5**[10] and carboxylic acid (*S*)-**6**[11] in high yields by palladium-catalyzed carbonylation[12] (Scheme 3). The carboxylic acid **6** is a useful alternative for Fukushi's biarenecarboxylic acid that has been successfully used for the determination of absolute configuration of secondary alkyl alcohols by NMR spectroscopy.[13,14] Another synthetic application is the preparation of a new chiral phosphine ligand. Thus, the triflate group in (*S*)-**2a** was replaced by the diphenylphosphino group by the palladium-catalyzed diphenylphosphinylation[15] followed by reduction of diphenylphosphine oxide in (*S*)-**7**[16] with trichlorosilane and triethylamine, which gave axially chiral triarylmonophosphine (*S*)-**8**.[17] This new monodentate chiral phosphine ligand (*S*)-**8** was found to be effective for the palladium-catalyzed asymmetric hydrosilylation of styrene with trichlorosilane[18] to give (*R*)-1-phenylethanol of 91% ee.[19,20] The enantioselectivity attained here is much higher than that reported with other chiral phosphine ligands including MeO-MOP[18,21] whose basic skeleton is analogous to that of the new ligand **8**.

The present catalytic asymmetric transformation based on the enantioposition-selective substitution is applicable to a wide range of axially chiral biaryl molecules, since a number of catalytic reactions have been reported which involve oxidative addition of aromatic halides or triflates.[9]

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Supporting Information Available: Text describing characterization data for compounds **2**−**8** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be down loaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) (*S*)-**5**: $[\alpha]^{20}_D$ −147 (*c* 1.0, chloroform).
(11) (*S*)-**6**: $[\alpha]^{20}_D$ −155 (*c* 0.5, chloroform).
(12) (a) Hotta, H.; Suzuki, T.; Miyano, S.; Inoue, Y. *J. Mol. Catal.* **1989**, *54*, L5. (b) Ohta, T.; Ito, M.; Inagaki, K.; Takaya, H. *Tetrahedron Lett.* **1993**, *34*, 1615.
(13) Fukushi, Y.; Yajima, C.; Mizutani, J. *Tetrahedron Lett.* **1994**, *35*, 599.
(14) The absolute configuration of **6** was tentatively assigned to be (*S*)-(−) by ^1H NMR studies of its diastereomeric esters of (*R*)-1-phenylethanol using Fukushi's rule (ref 12).
(15) Kurz, L.; Lee, G.; Morgans, D., Jr.; Waldyke, M. J.; Ward, T. *Tetrahedron Lett.* **1990**, *31*, 6321.
(16) (*S*)-**7**: $[\alpha]^{20}_D$ +49.2 (*c* 1.0, chloroform).
(17) (*S*)-**8**: $[\alpha]^{20}_D$ +15.3 (*c* 0.5, chloroform).
(18) Uozumi, Y.; Kitayama, K.; Hayashi, T. *Tetrahedron Asymm.* **1993**, *4*, 2419 and references cited therein.
(19) The hydrosilylation of styrene was carried out without solvent with 1.2 equiv of trichlorosilane in the presence of 0.1 mol % palladium catalyst generated from $[PdCl(\pi\text{-}C_3H_5)]_2$ and (*S*)-**8** (Pd/**8** = 1/2) at 0 °C for 24 h. For the oxidation of 1-(trichlorosilyl)-1-phenylethane into 1-phenylethanol, see ref 18.
(20) In the asymmetric hydroboration of styrene with catecholborane catalyzed by a rhodium−BINAP complex, 1-phenylethanol of 96% ee has been obtained: Hayashi, T.; Matsumoto Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426.
(21) MeO-MOP, which stands for 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (ref 2b), is an effective chiral ligand for the asymmetric hydrosilylation of alkyl-substituted terminal olefins and cyclic olefins such as norbornene, but it is not as effective for that of styrene derivatives: (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. (b) Hayashi, T.; Uozumi, Y. *Pure Appl. Chem.* **1992**, *64*, 1911. (c) Uozumi, Y.; Kitayama, K.; Hayashi, T.; Yanagi, Y.; Fukuyo, E. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 713 and references cited therein.