A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds

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Axially chiral biaryls are common structure motifs in natural products and are the core for many of the most effective chiral ligands.[1] The asymmetric synthesis of this class of compound has been effected by a number of useful methods, albeit mostly using stoichiometric chiral auxiliaries or chiral starting materials.[2] Pioneering work by Hayashi[3] has shown that axially chiral biaryls can be synthesized in high enantioselectivity by Ni- or Pd-catalyzed asymmetric Kumada couplings using chiral phosphine ligands.[4,5] Nicolaou recently reported an asymmetric Suzuki coupling to form chiral biaryls, whose *diastereoselectivity* was controlled by the chiral ligand used.[6] Diastereoselective Suzuki couplings of chiral aryl halide−chromium π-complexes were also reported by Uemura[2c] and Nelson.[2d]

Suzuki coupling of aryl halides or aryl triflates and aryl boronic acids is a powerful method for the synthesis of biaryl compounds.[7] To obtain configurationally stable chiral biaryls, at least three ortho substituents are usually necessary.[8] Such a requirement places stringent demands on the coupling efficiency, which generally is quite sterically sensitive. We have reported efficient and general protocols for Suzuki cross-couplings using bulky, electron-rich phosphine ligands that are based on a biphenyl backbone (**1**) (Figure 1).[9] In particular, the combination of sterically hindered substrates to give products with three ortho substituents can be accomplished using a catalyst system based on these ligands.[10] Here we report that binaphthyl ligands of type **2** can be used for the catalytic asymmetric Suzuki coupling to form highly enantiomerically enriched biaryls.[11] To our knowledge, this is the first example of a catalytic enantioselective cross-coupling procedure that allows for the preparation of *functionalized* biaryls.

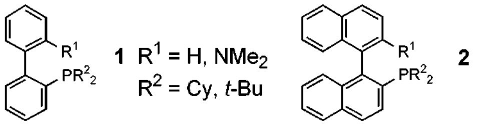
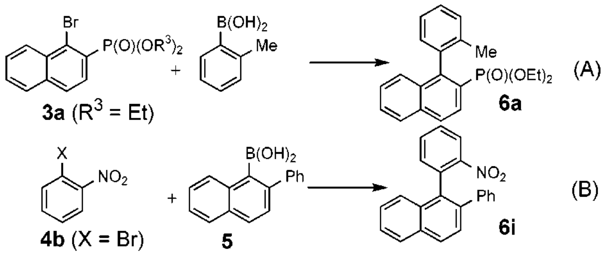


Figure 1.

To establish an efficient protocol for asymmetric Suzuki coupling, we first tested a number of binaphthyl-based phosphine ligands **2** in the reaction between bromide **3a** and *o*-tolylboronic acid (reaction A) and in that between 2-nitrobromobenzene (**4b**) and 2-phenyl-1-naphthylboronic acid (**5**) (reaction B) (Table 1).

Table 1. Ligand Screening[a]



entry	2	R^1	R^2	conv^b (%) (**A**)	ee^c (%) (**A**)	conv^b (%) (**B**)	ee^c (%) (**B**)
1	**2a**	Bu	Cy	100	54	100	32
2	**2b**	SiMe$_3$	Cy	100	23	60	62
3	**2c**	NMe$_2$	Cy	100	87^{d,e}	81	73^f
4	**2c**			100	87^{e,g}	72	68^g
5	**2d**	NMe$_2$	*i*-Pr	61	86	92	65
6	**2e**	NMe$_2$	Ph	76	75^h	67	38
7	**2f**	NMe$_2$	*t*-Bu	73	81^i		n.d.^{j}
8	**2g**	PPh$_2$	Ph	40	n.d.^{k}	46	22

[a] Conditions: 1.0 equiv of aryl bromide, 1.5 equiv of boronic acid, 1% $Pd_2(dba)_3$ (2% Pd), 2.4% of ligand **2**, 2 equiv of K_3PO_4, toluene, 70 °C, 13−22 h. [b] Determined by GC analysis. [c] Determined by HPLC with a Chiralcel OD column. [d] With 1% Pd. [e] With 3 equiv of K_3PO_4. [f] Reaction time was 92 h. [g] THF as solvent. [h] With 5% Pd. [i] Dehalogenated product was also observed in ca. 1/1 ratio to the coupling product. [j] No desired coupling product was detected. [k] Major dehalogenated product. Only traces of coupling product, whose ee was not determined.

Ligand **2c** was found to give the best ee values for both reactions (entry 3). While replacing the cyclohexyl by the isopropyl group (**2d**) had only a slight effect, for R^2 = phenyl or *tert*-butyl (**2e,f**), poorer levels of conversion and enantioselectivity of the resulting products were observed (entries 6 and 7). Replacing the dimethylamino group with an *n*-butyl or trimethylsilyl group (ligands **2a,b**) resulted in a significant decrease in enantioselectivity (entries 1 and 2). That the ee values of the products, while lower, ranged from 23 to 62% indicates that only one coordinating heteroatom is necessary for asymmetric induction to be realized. Use of the chelating bis-phosphine ligand BINAP provided only traces of the coupling product for reaction A and poor conversion to the coupling product with only 22% ee for reaction B (entry 8).

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(1) (a) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525−558 and references therein. (b) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; John Wiley and Sons: New York, 2000.

(2) For reviews, see: (a) Bringmann, G.; Walter, R.; Weirich, R. In *Methods of Organic Chemistry (Houben Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21a, p 567. (b) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977−991. For diastereroselective Suzuki couplings of chiral chromium-complexed aryl halides, see: (c) Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375−1384. (d) Nelson, S. G.; Hilfiker, M. A. *Org. Lett.* **1999**, *1*, 1379−1382. For other examples, see: (e) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879−881. (f) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943−8944. (g) Feldman, K. S.; Smith, R. S. *J. Org. Chem.* **1996**, *61*, 2606. (h) Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1842. (i) Lin, G.-Q.; Zhong, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1369. (j) Miyano, S.; Fukushima, H.; Handa, S.; Ito, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3249. (k) Tomioka, K.; Ishiguro, T.; Itaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303.

(3) For a review, see: Ogasawara, M.; Hayashi, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; John Wiley and Sons: New York, 2000; pp 651−674.

(4) (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153−8156. (b) Hayashi, T.; Hayashizaki, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 215−218. (c) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101−9102. (d) Kamikawa, T.; Hayashi, T. *Tetrahedron* **1999**, *55*, 3455−3466.

(5) During the completion of this manuscript, we became aware of a recent report by Cammidge in which two unfunctionalized chiral binaphthalenes[4a] were prepared by asymmetric Suzuki couplings: Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723−1724.

(6) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584−2601.

(7) (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(8) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 1142−1155.

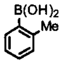
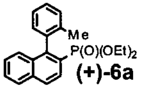
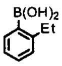
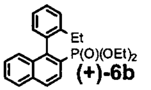
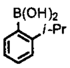
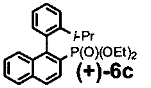
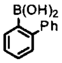
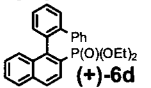
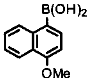
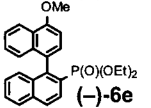
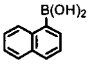
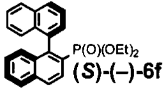
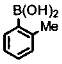
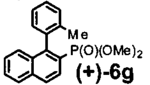
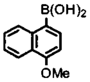
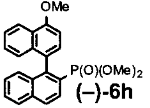
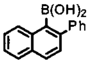
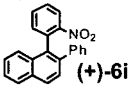
(9) (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9661. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413−2416.

(10) For the use of P(*t*-Bu)$_3$ for the Suzuki couplings of sterically hindered substrates, see: Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(11) For a report on the asymmetric Suzuki coupling of prochiral alkylboron compounds, see: Cho, S. Y.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3751−3754,

10.1021/ja005622z CCC: $19.00

Table 2. Asymmetric Suzuki Coupling[a]

Entry	ArX	ArB(OH)$_2$	Product	mol% Pd	temp (°C)	time (h)	yld (%)	ee (%)
1	**3a**		 **(+)-6a**	4	70	88	98	87^{b}
2				1	70	17	93	87^{c,d}
3			 **(+)-6b**	8	70	88	90	92
4				2	70	24	96	92^{c,d}
5				1	70	24	94	92^{c}
6			 **(+)-6c**	10	80	140	83	85^{b}
7				2	80	24	89	85^{c,d}
8			 **(+)-6d**	3	60	48	74	74
9			 **(−)-6e**	4	40	92	97	71^{b}
10			 **(*S*)-(−)-6f**	4	40	40	97	57^{e}
11	**3b**		 **(+)-6g**	2	70	24	91	84
12				0.3	60	24	95	86^{c,d}
13				0.2	60	24	95	86^{c,f}
14			 **(−)-6h**	2	40	48	80	73
15	**4a**		 **(+)-6i**	3	70	48	86	73
16	**4b**			10	70	48	82	72
17	**4c**			4	70	48	83	72

[a] Conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, **(*S*)-(+)-2c**/Pd$_2$(dba)$_3$ = 2.4 (L/Pd = 1.2), 2 equiv of K$_3$PO$_4$, toluene (4−6 mL/mmol of halide). Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and GC analysis or combustion analysis. The ee values were the averages of two runs as determined by HPLC on a Chiralcel OD or AD (for **6f**) column. [b] The catalyst was added in 2−3 portions; see Supporting Information for details. [c] 3 equiv of K$_3$PO$_4$ was used. [d] 3 equiv of NaI was added. [e] The absolute configuration was determined by comparing its optical rotation value with that in the literature.[13] [f] 99% ee and 63% overall yield after recrystallization from methylene chloride and hexanes.

A survey of reaction variables indicated that K$_3$PO$_4$ was a better base than KF, CsF, or KO*t*-Bu. Toluene was found to be superior to THF as a solvent; use of the latter sometimes gave slightly lower ee values and varying amounts of the dehalogenated starting material. It was also found that the enantioselectivity of reaction A was not effected by the concentration of the aryl bromide or the Pd/ligand ratio. One possible explanation for this is that the reaction proceeds via a 1:1 complex and that there is a high degree of ligand acceleration.[12]

Using **(*S*)-(+)-2c** as the ligand and the conditions noted in Table 2, Suzuki couplings between **3a**, **3b** (R^3 = Me), **4a** (X = I), **4b** (X = Br), or **4c** (X = Cl) and various boronic acids were carried out at 40−80 °C in good to excellent yields and with ee values up to 92% (Table 2). While most reactions utilized 1−4 mol % of Pd, levels as low as 0.2 mol % could be employed.

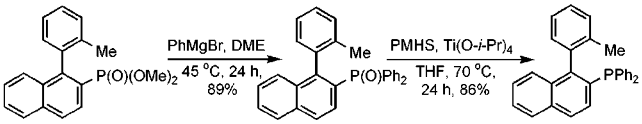
We have realized our best results using 1-halonaphthlenes with a (RO)$_2$P(O)− group at the 2-position. Reactions in which the boronic acid has an *o*-alkyl substituent proceed with high levels of enantioselectivity. The relationship between the size of the ortho substituent and the ee of the process remains unclear as can be seen from the preparation of **6a**−**d**.

It is important to note that the use of 3 equiv of K$_3$PO$_4$ as base gave much faster reactions than when the process was conducted with 2 equiv of K$_3$PO$_4$. For example, reactions that required 4−10 mol % Pd and 96−140 h (entries 1, 3, and 6) with 2 equiv of K$_3$PO$_4$ went to completion within 24 h with significantly less catalyst with 3 equiv of K$_3$PO$_4$ (entries 2, 5, and 7).[14] With 3 equiv of K$_3$PO$_4$, the reaction between **3b** and *o*-tolylboronic acid could be carried out with only 0.2% Pd and 0.24% chiral ligand **2c** to give **6g** in 95% yield and 86% ee (entry 13). After one recrystallization, **6g** was obtained in 63% yield and 99% ee.

In addition to bromides, an aryl iodide (**4a**, entry 15) and chloride (**4c**, entry 17) were demonstrated to be suitable substrates in the asymmetric Suzuki coupling. Interestingly, they both required much less catalyst than the corresponding bromide **4b** in the reaction with boronic acid **5** (entry 16).

The phosphonate moiety in **6a**−**h**[15] is suitable for further functionalizations. For example, heating **(+)-6g** (99% ee) with PhMgBr in DME[16] at 45 °C for 24 h[17] gave **7** in 89% yield and with no loss in ee (Scheme 1). Reduction of **7**[18] gave a new chiral phosphine ligand **(−)-8** in 86% yield and 99% ee.

Scheme 1



(+)-6g (99% ee) **(−)-7** (99% ee) **(−)-8** (99% ee)

In conclusion, a variety of chiral biaryl compounds have been synthesized in up to 92% ee via a catalytic asymmetric Suzuki coupling using a binaphthyl-based electron-rich phosphine ligand **2c**. Applications of this methodology as well as studies to enable a more general asymmetric Suzuki coupling procedure are underway in our laboratories.

Acknowledgment. We are very grateful to Dr. John P. Wolfe for his initial studies on asymmetric Suzuki coupling. We also thank Dr. Ken Kamikawa, Dr. André Chieffi, and Mr. Takayuki Hamada for providing samples of ligands **2a**,**b**,**d** and Dr. Joseph M. Fox for providing 1-naphthylboronic acid and 4-methoxy-1-naphthylboronic acid. We thank NIH GM46059 for support of this work. We are also grateful to Pfizer and Merck for additional unrestricted support.

Supporting Information Available: Experimental procedures and characterization data for compounds **2d**, **3**, and **5**−**8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA005622Z

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[12] Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.

[13] Kurz, L.; Lee, G.; Morgans, D., Jr.; Waldyke, M. J.; Ward, T. *Tetrahedron Lett.* **1990**, *31*, 6321−6324.

[14] Although 3 equiv of NaI was added in entries 2, 4, 7, and 12, this does not appear necessary as shown by comparing entries 4−5 and 12−13.

[15] Biphenyls **6** showed excellent thermal stability toward racemization. For example, **6a** and **6g** did not racemize when heated in THF at 100 °C over 18 h, and the ee of **6a** only decreased from 87% to 85% after 11 days at 120 °C. However, the ee of **6d** decreased from 73% to 0% after 80 h in THF at 100 °C. Product **6h** in 73% ee did not racemize at 70 °C, but the ee decreased to 66% after 22 h at 100 °C.

[16] Use of THF or ether as the solvent gave very poor yields.

[17] Although neither **6g** nor **7** racemized when heated at 70 °C in DME, **7** was only obtained in 85% ee and 86% yield when the reaction was run at 70 °C for 24 h. Even at 45 °C, **7** was obtained in 95% ee and 89% yield if the reaction time was 72 h. All these suggest the racemization of **7** under the reaction conditions.

[18] Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625−628.