

# Tris(2-methoxyphenyl)phosphine as a Highly Active Ligand for the Synthesis of Biaryls by Suzuki Coupling Reaction

Pill-Seong Kang,<sup>†</sup> Sung Bo Ko,<sup>‡</sup> Jang Myoun Ko, and Jeong Ho Park<sup>\*</sup>

Division of Applied Chemistry and Biotechnology, Hanbat National University, Daejeon 305-719, Korea

<sup>\*</sup>E-mail: jhpark@hanbat.ac.kr

<sup>†</sup>Medigen Inc., Daejeon 305-811, Korea

Received July 31, 2009, Accepted September 30, 2009

A Pd(OAc)<sub>2</sub>/(*o*-MeOPh)<sub>3</sub>P system has been developed for the catalytic Suzuki coupling of aryl bromides with arylboronic acids. Our catalyst system covers a broad spectrum of commonly available arylboronic acids and aryl bromides to provide biaryls in very good yields. The catalyst system works very well in the synthesis of sterically hindered biaryls.

**Key Words:** Tris(2-methoxyphenyl)phosphine, Suzuki coupling reaction

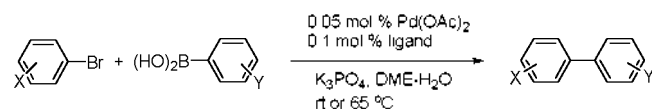
## Introduction

The palladium catalyzed Suzuki cross-coupling of aryl halides with arylboronic acids results in biaryl compounds (Scheme 1) and has emerged as an extremely powerful tool in organic synthesis.<sup>1</sup> The biaryls are one of the important classes of organic compounds because various types of compounds such as natural products, electronic materials, liquid crystals and pharmaceuticals include the biaryl units.

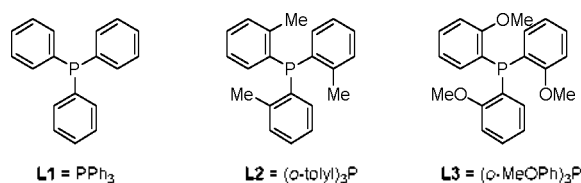
Therefore intensive studies in regard to the biaryl synthesis have been carried out<sup>2</sup> and several kinds of phosphine ligands are commonly employed in Suzuki coupling.<sup>3</sup> Often these ligands are sensitive to air oxidation and need several steps for the synthesis. We now wish to report the results of a simple and efficient combination of Pd(OAc)<sub>2</sub>/(*o*-MeOPh)<sub>3</sub>P as a catalytic system in Suzuki coupling reactions.

## Results and Discussion

Tris(2-methoxyphenyl)phosphine<sup>4</sup> (Fig. 1, **L3**) is readily available from anisole and very stable to air oxidation (see experimental section for the preparation of the ligand **L3**). Also the ligand is expected to satisfy the demands of bulkiness



**Scheme 1.** General synthesis of biaryls through Suzuki coupling reaction.



**Figure 1.** Structure of organophosphine ligands.

and basicity which are often required for the catalytic activity in Suzuki coupling. In this paper we described the ligand effect of (*o*-MeOPh)<sub>3</sub>P in several Suzuki coupling reactions between aryl halides and arylboronic acids. **L3** has been shown to be superior to triphenylphosphine in many palladium-catalyzed coupling reactions.


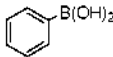
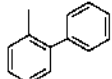

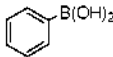
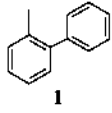

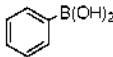
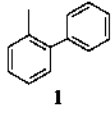

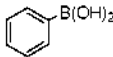
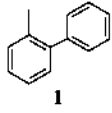

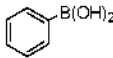
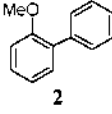

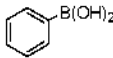
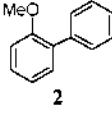

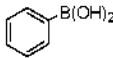
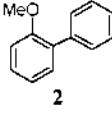

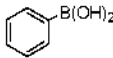
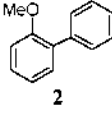

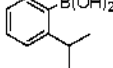
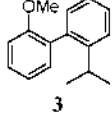

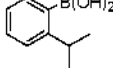
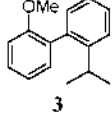

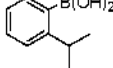
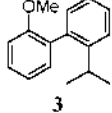

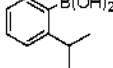
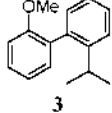
Preliminary Suzuki coupling reactions between *ortho*-substituted aryl halides and aryl boronic acids using different ligands such as PPh<sub>3</sub>, (*o*-tolyl)<sub>3</sub>P and (*o*-MeOPh)<sub>3</sub>P were carried out with usual condition for Suzuki coupling, *i.e.* Pd(OAc)<sub>2</sub> as a palladium source and K<sub>3</sub>PO<sub>4</sub> as base in DME/H<sub>2</sub>O (4:1) at 65 °C (Table 1). *Ortho*-substituted aryl halides with methyl or methoxy group gave both electron donating effect and steric hindrance. We observed that the ligand **L3** dramatically improved the isolation yield from 64 ~ 69% to 96% with *ortho*-methyl aryl halides compared to other ligands [**L1** and **L2**] (Table 1, entries 2, 3 and 4).

The steric factor of the coupling site on aryl boronic acid did give a great influence on the coupling yield. The introduction of isopropyl group on the *ortho* position of aryl boronic acid reduced the coupling yield to 54 ~ 69% at the coupling reaction using **L1** or **L2** (Table 1, entries 10 and 11). In contrast, **L3** resulted in 2'-isopropyl-2-methoxybiphenyl (**3**) in very high yield regardless of the presence of isopropyl group on the *ortho* position of arylboronic acid (Table 1, entry 12). Therefore, (*o*-MeOPh)<sub>3</sub>P proved to be excellent ligand for the coupling reaction between sterically hindered arylboronic acids and aryl bromides.<sup>5</sup>

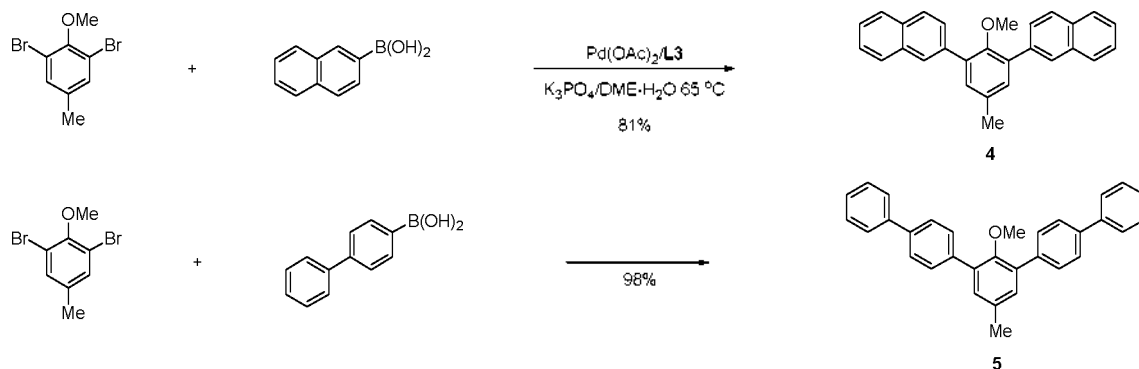
Encouraged by these results, we carried out the construction of polyaryl frameworks from 2,6-dibromo-4-methylanisole and arylboronic acids with our catalyst system. The corresponding polyaryls **4** and **5** were obtained with satisfactory yield (Scheme 2).

Even though excellent results have been achieved between the coupling of wide range of aryl bromides and boronic acids, coupling reactions between *ortho*-substituted aryl bromides and di-*ortho*-substituted arylboronic acids are challenging reactions because of forming highly hindered biaryls. We examined the tolerance of *ortho*-substitution in both the aryl

**Table 1.** Ligand effect on Suzuki coupling reaction.<sup>a</sup>

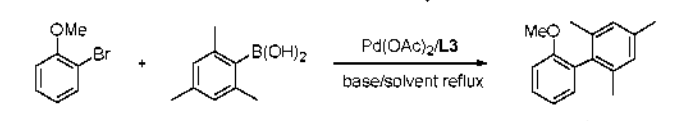
entry	arylbromide	boronic acid	product	ligand	yield (%)
1				none	54
2				PPh <sub>3</sub>	64
3				( <i>o</i> -tolyl) <sub>3</sub> P	69
4				( <i>o</i> -MeOPh) <sub>3</sub> P	96
5				none	87
6				PPh <sub>3</sub>	90
7				( <i>o</i> -tolyl) <sub>3</sub> P	91
8				( <i>o</i> -MeOPh) <sub>3</sub> P	> 99
9				none	50
10				PPh <sub>3</sub>	54
11				( <i>o</i> -tolyl) <sub>3</sub> P	69
12				( <i>o</i> -MeOPh) <sub>3</sub> P	> 99

<sup>a</sup>The Suzuki coupling reaction was carried out on the condition (0.05 mol% Pd(OAc)<sub>2</sub>, 0.1 mol% ligand, 3.5 equiv K<sub>3</sub>PO<sub>4</sub> in DME-H<sub>2</sub>O at 65 °C).

**Scheme 2.** Synthesis of polyaryls **4** and **5**.

halides and the arylboronic acids. Unfortunately, our standard reaction condition was not suitable for the synthesis of more sterically hindered biaryls when the boronic acid has di-*ortho*-substitution group. For example, coupling reaction between 2-bromoanisole and 2,4,6-trimethylboronic acid was carried out to give 2'-methoxy-2,4,6-trimethylbiphenyl (**6**) (Table 2, entry 1) in only 36% yield. To improve yield the base K<sub>3</sub>PO<sub>4</sub> was replaced by Ba(OH)<sub>2</sub>, and the isolation yield moderately improved to 65% (Table 2, entry 2).

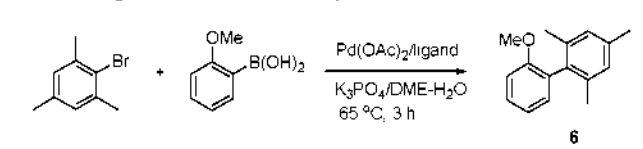
Striking ligand effect was observed when substitution on aryl boronic acid and aryl halide was switched each other.

**Table 2.** Screening of base effect in sterically hindered coupling reaction with 2-bromoanisole and 2,4,6-trimethylboronic acid


entry	base	solvent	time (h)	yield (%)
1	K <sub>3</sub> PO <sub>4</sub>	Toluene	12	36
2	Ba(OH) <sub>2</sub>	DME-H <sub>2</sub> O	16	65

With (*o*-tolyl)<sub>3</sub>P, Suzuki coupling reaction of 2,4,6-trimethylbromobenzene and 2-methoxyphenylboronic acid gave a trace amount of biaryl **6** even at the elevated temperature (90 °C). On the contrary, (*o*-MeOPh)<sub>3</sub>P provided the desired product in 90% yield at mild condition (Table 3, entry 2).

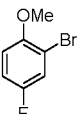
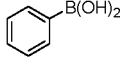

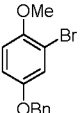
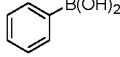
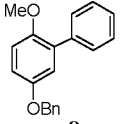
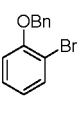
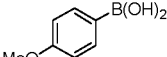
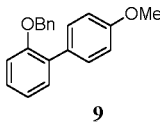
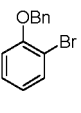
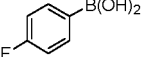
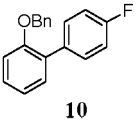
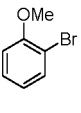
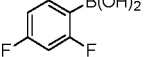
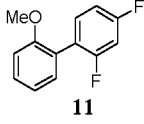
Finally, the effect of electronic variation on aryl halides was tested by using phenylboronic acid. Regardless of the electron-donating or electron-withdrawing substitution, Suzuki coupling reaction progressed smoothly and resulted in desired product in very high yield (Table 4).

**Table 3.** Ligand effect on sterically hindered substrate<sup>a</sup>


entry	ligand	mol% ("Pd"/L)	yield (%)
1	( <i>o</i> -tolyl) <sub>3</sub> P	0.05/0.1	trace
2	( <i>o</i> -MeOPh) <sub>3</sub> P	0.05/0.1	90

<sup>a</sup>The Suzuki coupling reaction was carried out on the condition (0.05 mol% Pd(OAc)<sub>2</sub>, 0.1 mol% ligand, 3.5 eq. K<sub>3</sub>PO<sub>4</sub> in DME-H<sub>2</sub>O at 65 °C).

**Table 4.** Synthesis of biaryls with electronic variations on arylbromides and arylboronic acids.<sup>a</sup>

entry	aryl halide	boronic acid	product	yield (%)
1				> 99
2				> 99
3				98
4				98
5				98

<sup>a</sup>The Suzuki coupling reaction was carried out on the condition (0.05 mol% Pd(OAc)<sub>2</sub>, 0.1 mol% (*o*-MeOPh)<sub>3</sub>P, 3.5 eq. K<sub>3</sub>PO<sub>4</sub> in DME-H<sub>2</sub>O at 65 °C).

## Conclusions

In summary, a general and highly efficient synthesis of biaryls based on Pd(OAc)<sub>2</sub>/*o*-MeOPh)<sub>3</sub>P system has been developed. The use of (*o*-MeOPh)<sub>3</sub>P, which is very stable to air oxidation and easy to prepare, represents an alternative to existing catalytic systems based on the use of phosphine ligands. Further investigation will be carried out to apply the use of (*o*-MeOPh)<sub>3</sub>P ligand toward the Suzuki reaction of aryl chloride and more hindered substrates as well as Pd-catalyzed amination reactions.

## Experimental Section

**Preparation of tris(2-methoxyphenyl)phosphine (L3).**<sup>6</sup> *n*-BuLi (210 mL of 1.6 M in hexane or 130 mL of 2.5 M in hexane, 0.32 mol) was placed into 1 L three neck round bottom flask equipped with dropping funnel under N<sub>2</sub> atmosphere. Tetramethylethylenediamine (TMEDA, 48.3 mL, 0.32 mol) was dropwise added to the reaction flask at room temperature and then anisole (43.5 mL, 0.4 mol) was slowly added to the flask. Exothermic reaction took place and the reaction mixture was stirred for 30 min at 45 ~ 50 °C. The reaction mixture was cooled down to -70 °C and then dry THF (100 mL) was added. The flash distilled PCl<sub>3</sub> (8.8 mL, 0.1 mol) was slowly added to

the mixture during maintaining reaction temperature at -70 °C for 10 min. The cooling bath was removed and the temperature was raised to -10 °C. The reaction was quenched by adding 2 M HCl (500 mL) to the reaction mixture. The white solid appeared and the solution was filtered to separate the white solid (22 g, 63%). No recrystallization was necessary: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): 7.32 (t, 3H), 6.83 (m, 6H), 6.69 (m, 3H), 3.73 (s, 9H); Mass [M+H]: 353.1.

### General Procedure for Suzuki Coupling Reactions.

**Preparation of *o*-phenylanisole (2).** A mixture of *o*-bromoanisole (1.0 g, 5.35 mmol), phenylboronic acid (0.72 g, 5.88 mmol), Pd(OAc)<sub>2</sub> (60 mg, 0.27 mmol, 0.05 mol%), (*o*-MeOPh)<sub>3</sub>P (100 mg, 0.54 mmol, 0.1 mol%), and K<sub>3</sub>PO<sub>4</sub> (33.97 g, 18.7 mmol) in DME-H<sub>2</sub>O (10 mL, 4 : 1) was heated to 60 ~ 65 °C and stirred for 4 h. The reaction was monitored by TLC. When the reaction was complete, it was diluted with ether. The aqueous layer was extracted two times with ether, the combined organic extracts were applied directly to celite to remove the palladium catalyst and the eluent was dried (Na<sub>2</sub>SO<sub>4</sub>). After evaporation of the organic layer, the resulting residue was purified by flash column chromatography (silica gel, hexanes) to give the product as colorless oil (0.98 g, 5.32 mmol) in 99% yield.

**2-Methylbiphenyl (1):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 2.26 (s, 3H), 7.22 (m, 2H), 7.32 (m, 3H), 7.37 (m, 2H), 7.61 (d, *J* = 1.6 Hz, 2H).

**2-Methoxybiphenyl (2):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 3.80 (s, 3H), 6.99 (m, 2H), 7.30 (m, 3H), 7.40 (dd, *J* = 1.6 Hz, 2H), 7.52 (d, *J* = 1.6 Hz, 2H).

**2'-Isopropyl-2-methoxybiphenyl (3):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 1.04 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 2.77 (m, 1H), 3.74 (s, 3H), 6.97 (q, 2H), 7.14 (m, 3H), 7.35 (m, 3H).

**2'-Methoxy-5'-methyl-[1,4';1',1'';3',1''';4'',1''']quinquephenyl (5):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 2.42 (s, 3H), 3.24 (s, 3H), 7.18 (s, 2H), 7.36 (t, 2H), 7.45 (t, 2H), 7.71 (m, 10H).

**2'-Methoxy-2,4,6-trimethylbiphenyl (6):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 1.98 (s, 6H), 2.33 (d, *J* = 6.8 Hz, 3H), 3.74 (s, 3H), 6.94 (q, 2H), 7.02 (m, 3H), 7.35 (m, 1H).

**5-Fluoro-2-methoxybiphenyl (7):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 3.77 (s, 3H), 6.89 (q, 1H), 6.97 (t, 1H), 7.04 (dd, 1H), 7.35 (t, 1H), 7.41 (t, 2H), 7.51 (d, 2H).

**5-Benzyloxy-2-methoxybiphenyl (8):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 3.79 (s, 3H), 4.95 (s, 2H), 6.81 (d, 1H), 6.92 (t, 2H), 7.35 (m, 8H), 7.57 (d, 2H).

**Acknowledgments.** This work was financially supported by the World Class University Program from Ministry of Education, Science and Technology, Korea.

## References

- (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Suzuki, A. *J. Organometal. Chem.* **1999**, *576*, 147. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.
- (a) Thimmaiah, M.; Fang, S. *Tetrahedron* **2007**, *63*, 6879. (b) Nishimura, M.; Ueda, M.; Miyaura, N. *Tetrahedron* **2002**, *58*, 5779. (c) Shi, J.-C.; Yang, P.-Y.; Tong, Q.; Wu, Y.; Peng, Y. *J. Mol. Cat.* **2006**, *259*, 7.
- (a) Kevin, H. S.; Rebecca, S. B. *Org. Lett.* **2001**, *3*, 2757. (b)

- Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (c) Hoshi, T.; Nakazawa, T.; Saitoh, I.; Mori, A.; Suzuki, T.; Sakai, J.; Hagiwara, H. *Org. Lett.* **2008**, *10*, 2063. (d) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. (e) Moore, L. R.; Western, E. C.; Craciun, R.; Spruell, J. M.; Dixon, D. A.; O'Halloran, K. P.; Shaughnessy, K. H. *Organometallics* **2008**, *27*, 576.
4. For some examples of the use of the ligand, see: (a) Hagio, H.; Sugiura, M.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 375. (b) Okamoto, K.; Akiyama, R.; Kobayashi, S. *Org. Lett.* **2004**, *6*, 1987. (c) Cai, C.; Shung, J. Y. L.; McWilliams, J. C.; Sun, Y.; Schultz, C. S.; Paluck, M. *Organic Process Res. Dev.* **2007**, *11*, 328.
5. (a) Singh, R.; Viciu, M. S.; Kramareva, N.; Navarro, O.; Nolan, S. P. *Org. Lett.* **2005**, *7*, 1829. (b) Baillie, C.; Zhang, L.; Xiao, J. *J. Org. Chem.* **2004**, *69*, 7779.
6. For the preparation of the ligand **L3**, see: Brandsma, L.; Verkruijsse, H. D. *Synth. Commun.* **1990**, *20*, 2273.
-