



## Application of a readily available and air stable monophosphine HBF<sub>4</sub> salt for the Suzuki coupling reaction of aryl or 1-alkenyl chlorides

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### ABSTRACT

In this Letter, a readily available monophosphine HBF<sub>4</sub> salt was applied for the Suzuki coupling reactions of organoboronic acids to afford the cross-coupling products in high to excellent yields. Both aryl or 1-alkenyl boronic acids and chlorides may be used. It is also suitable for sterically hindered cases.

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During the last 10 years much attention has been paid to the reaction of C–Cl bond<sup>1</sup> due to the easily available and cost-effective nature of organic chlorides and the atom economy caused by the low atomic weight of chlorine atom as compared to reactions of the corresponding bromides or iodides.<sup>2</sup> Mainly electron-rich and sterically bulky phosphines have been developed for different types of coupling reactions involving C–Cl bonds. In this area, some of the most notable ligands are listed in Figure 1.

After some screening, we have recently designed and prepared a new ligand, dicyclohexyl 2,4,6-trimethoxyphenyl phosphine, in which the two cyclohexyl groups and one 2,4,6-trimethoxyphenyl group may provide the required electron density, steric bulk, and ease of handling. The methoxy groups may not only play a role for the coordination to stabilize Pd complex as pointed by Buchwald et al.<sup>3e</sup> but also facilitate the lithiation to dramatically shorten the synthetic route of the ligand. In fact, *S*-trimethoxybenzene was treated with *n*-BuLi in THF to generate 2,4,6-trimethoxyphenyl lithium, which was reacted with Cy<sub>2</sub>PCl in situ generated from the reaction of cyclohexyl magnesium chloride with PCl<sub>3</sub> to afford dicyclohexyl 2,4,6-trimethoxyphenyl phosphine **1**. This compound may further be purified by its reaction with HBF<sub>4</sub> to afford the air stable solid salt **2** as Fu and Netherton did<sup>5</sup> for further study (Scheme 1).

We chose the Pd(OAc)<sub>2</sub>-catalyzed Suzuki coupling of PhB(OH)<sub>2</sub> with *p*-methoxyphenyl chloride to optimize the reaction conditions. The yield of **5aa** with K<sub>3</sub>PO<sub>4</sub>·3H<sub>2</sub>O is higher than that with K<sub>3</sub>PO<sub>4</sub> (Table 1, entries 1 and 2). Thus, we reasoned that the amount of water may have something to do with the coupling reactions: with 3.0 equiv of water using 3.5 equiv of K<sub>3</sub>PO<sub>4</sub> as the base, **5aa** could be afforded in 100% NMR yield (Table 1, entry 4); less or more amount of water would lead to a lower yield of **5aa** (Table 1, entries 3 and 5); decreasing the amounts of **4a**, Pd(OAc)<sub>2</sub>/**2** and K<sub>3</sub>PO<sub>4</sub> would also lead to lower yields (Table 1, en-

tries 6–8). Finally, 3 mol % of Pd(OAc)<sub>2</sub> and 6 mol % of **2** as the ligand were defined as the standard catalytic system (Table 1, entry 9).

With the optimized reaction conditions in hand, differently substituted electron-rich aryl chlorides and aryl boronic acids were cross-coupled readily to afford the biaryls in 81–97% isolated yields; even the hindered aryl chlorides and/or the aryl boronic acids may be used<sup>3a,e,h,k,l</sup> (Table 2, entries 5 and 7–10). This reaction could also be extended to electron-deficient aryl chlorides to give the corresponding Suzuki coupling products in good yields within relatively shorter reaction time as expected (Table 2, entries 11 and 12).

The optimized conditions could also be extended to the Suzuki coupling reactions with 1-alkenyl boronic acids: 3,5-dimethoxyphenyl chloride **3e** could react with styryl boronic acid **4f** to form the Suzuki coupling product **5ef** with 81% yield (Scheme 2). For a more complex substrate **3i**,<sup>6</sup> the Suzuki coupling could also occur with the C–Cl bond exclusively over the C–O bond to give the cor-

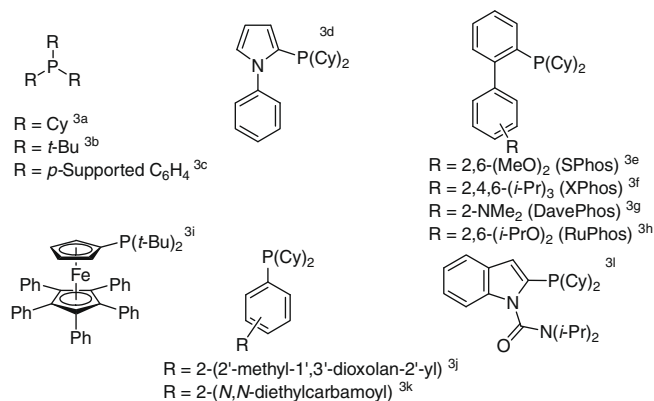
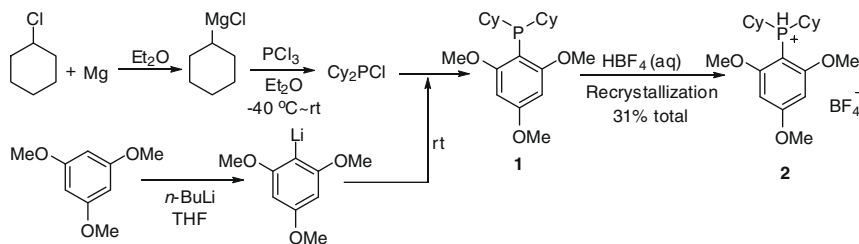


Figure 1. Typical examples of phosphine ligands for the Suzuki coupling reaction of C–Cl bonds.

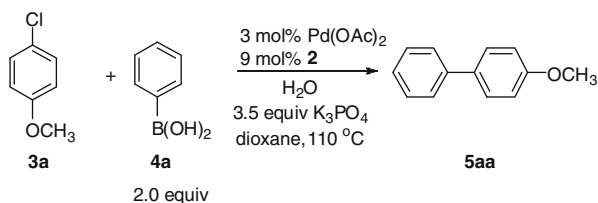
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Scheme 1. See Ref. 4.

**Table 1**  
Suzuki coupling reactions of **3a** with **4a** under different conditions



Entry	H <sub>2</sub> O (equiv)	Time (h)	NMR yield <sup>a</sup> (%)	Recovery of <b>3a</b> (%)
1	—	11	62	23
2 <sup>b</sup>	—	15.5	79	16
3	1.0	12	92	3
4	3.0	15.5	100	—
5	5.0	15.5	65	35
6 <sup>c</sup>	3.0	11.5	77	17
7 <sup>d</sup>	3.0	11.3	77	20
8 <sup>e</sup>	3.0	21	60	40
9 <sup>f</sup>	3.0	11	100	—

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis using methylene bromide as an internal standard.

<sup>b</sup> K<sub>3</sub>PO<sub>4</sub>·3H<sub>2</sub>O was used.

<sup>c</sup> K<sub>3</sub>PO<sub>4</sub> (3.0 equiv) was used.

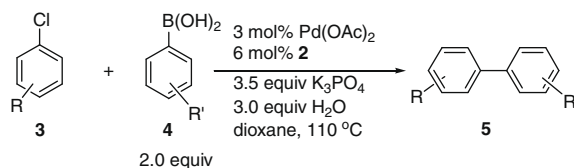
<sup>d</sup> PhB(OH)<sub>2</sub> (1.5 equiv) was used.

<sup>e</sup> Pd(OAc)<sub>2</sub> (1 mol %) and **2** (3 mol %) were used.

<sup>f</sup> Compound **2** (6 mol %) was used.

responding product **5ie** in 88% yield (Scheme 2). This coupling was also suitable for 1-cyclooctenyl chloride **3j** to form the corresponding Suzuki coupling product **5jb** with 63% yield (Scheme 2).

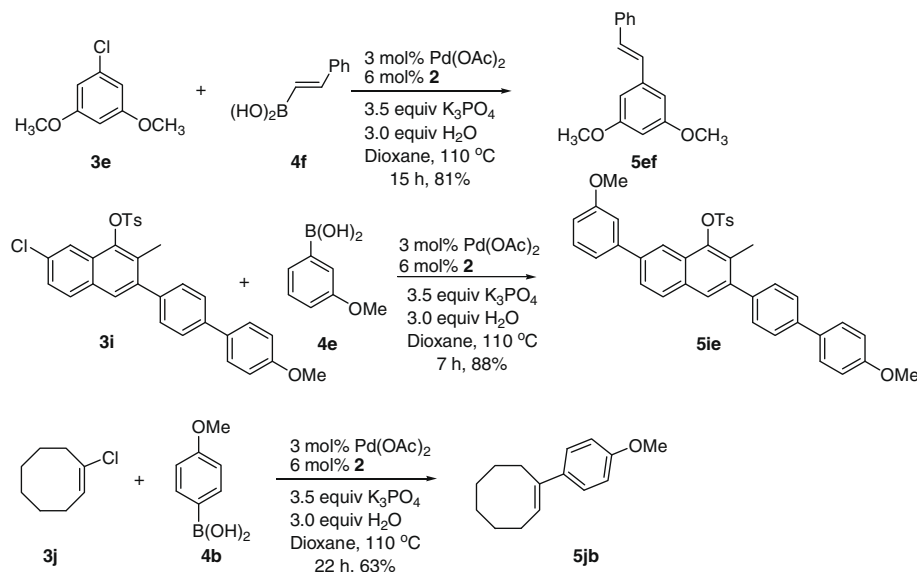
**Table 2**  
Suzuki coupling reactions of various **3** and **4** using **2** as the ligand



Entry	R	R'	Time (h)	Isolated yield of <b>5</b> (%)
1	4-MeO ( <b>3a</b> )	H ( <b>4a</b> )	11	90 ( <b>5aa</b> )
2	4-Me ( <b>3b</b> )	4-MeO ( <b>4b</b> )	16	83 ( <b>5bb</b> )
3	4-MeO ( <b>3a</b> )	4-Me ( <b>4c</b> )	9.5	97 ( <b>5bb</b> )
4	H ( <b>3c</b> )	4-MeO ( <b>4b</b> )	11.5	88 ( <b>5aa</b> )
5	2,6-(Me) <sub>2</sub> ( <b>3d</b> )	H ( <b>4a</b> )	13	91 <sup>a</sup> ( <b>5da</b> )
6	3,5-(MeO) <sub>2</sub> ( <b>3e</b> )	H ( <b>4a</b> )	13	94 ( <b>5ea</b> )
7	2,6-(Me) <sub>2</sub> ( <b>3d</b> )	4-MeO ( <b>4b</b> )	22	81 ( <b>5db</b> )
8	3,5-(MeO) <sub>2</sub> ( <b>3e</b> )	2,6-(Me) <sub>2</sub> ( <b>4d</b> )	13	94 ( <b>5ed</b> )
9	2,6-(Me) <sub>2</sub> ( <b>3d</b> )	3-MeO ( <b>4e</b> )	12.5	97 ( <b>5de</b> )
10	2-MeO ( <b>3f</b> )	2,6-(Me) <sub>2</sub> ( <b>4d</b> )	22	82 ( <b>5fd</b> )
11	2-NO <sub>2</sub> ( <b>3g</b> )	H ( <b>4a</b> )	1	90 ( <b>5ga</b> )
12	4-CHO ( <b>3h</b> )	H ( <b>4a</b> )	0.6	91 ( <b>5ha</b> )

<sup>a</sup> Biphenyl (5.7%) was formed, which cannot be separated from **5da**.

In conclusion, we have applied the HBF<sub>4</sub> salt of a monophosphine ligand, that is, dicyclohexyl 2,4,6-trimethoxyphenyl phosphine, recently prepared in this group, for the Suzuki coupling reaction of aryl or 1-alkenyl chlorides with different organoboronic acids in high to excellent yields. The HBF<sub>4</sub> salt of this ligand is easy



Scheme 2.

to prepare and air-stable.<sup>4</sup> Although the reaction temperature is still high at this moment, further optimization and new applications of this type of ligands are being conducted in our laboratory.

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### Supplementary data

Supplementary data (typical experimental procedures and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of all the products) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.12.143](https://doi.org/10.1016/j.tetlet.2009.12.143).

### References and notes

1. For recent reviews on coupling reactions of C–Cl bonds, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176; (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275; (c) Weng, Z.; Teo, S.; Hor, T. S. A. *Acc. Chem. Res.* **2007**, *40*, 676; (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461; (e) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013; (f) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.
2. Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.
3. (a) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575; (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387; (c) Lemo, J.; Heuzé, K.; Astruc, D. *Chem. Commun.* **2007**, 4351; (d) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983; (e) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871; (f) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653; (g) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722; (h) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028; (i) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553; (j) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797; (k) Kwong, F. Y.; Lam, W. H.; Yeung, C. H.; Chan, K. S.; Chan, A. S. C. *Chem. Commun.* **2004**, 1922; (l) So, C. M.; Yeung, C. C.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7803.
4. China Patent Application No. 200910154029.4.
5. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.
6. Chai, G.; Lu, Z.; Fu, C.; Ma, S. *Chem. Eur. J.* **2009**, *15*, 11083.