



## A functionalized phosphine ligand with a pentaarylbenzene moiety in palladium-catalyzed Suzuki–Miyaura coupling of aryl chlorides

Tetsuo Iwasawa\*, Toshinori Kamei, Satoshi Watanabe, Masaki Nishiuchi, Yasuhiko Kawamura\*

Institute of Technology and Science, Graduate School of The University of Tokushima, Minami-josanjima-cho, Tokushima 770-8506, Japan

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### ABSTRACT

A functionalized phosphine with a pentaarylbenzene moiety was found to facilitate the palladium-catalyzed Suzuki–Miyaura coupling of aryl chlorides. The new ligand achieved high turnover numbers (up to TON 5000).

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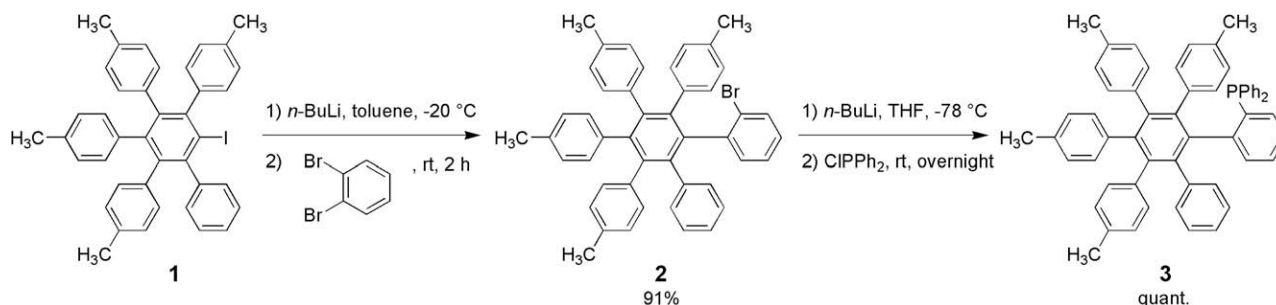
The need for a functionalized pentaarylbenzene<sup>1</sup> has been growing in several application materials such as luminescent materials,<sup>2</sup> optical devices,<sup>3</sup> supramolecular electronics,<sup>4</sup> and catalyst materials.<sup>5</sup> The well-defined array of aromatic rings<sup>6</sup> enhances the properties inherent in functional groups and useful materials.<sup>7</sup> Thus, these applications imply that it could be of interest to prepare a novel pentaarylbenzene derivative endowed with functional moieties.

On the other hand, we recently reported a simple method for functionalizing a 1-iodo-2,3,4,5,6-pentaarylbenzene **1**.<sup>8</sup> The synthetic approach employs iodide **1** and *n*-BuLi in toluene at  $-20\text{ }^{\circ}\text{C}$  to quickly conduct lithium–halogen exchange, followed by smooth reactions with various electrophiles. The key to success was increasing the solubility of **1** by installing four methyl groups onto the phenyl rings. The reaction with 1,2-dibromobenzene as an electrophile,<sup>9</sup> for example, produced a bromide **2** in 91% yield (Scheme 1).

In this Letter, we describe a novel pentaarylbenzene derivative that works well as a catalyst material. First, the new phosphorous

molecule **3** was synthesized through the lithiation of **2**, which is outlined in Scheme 1. Then, the phosphine **3** was found to promote the palladium-catalyzed Suzuki–Miyaura coupling of aryl chlorides<sup>10</sup> with high turnover numbers.<sup>11</sup> Besides, a survey on the structural features of **3** revealed that it is indispensable for the catalytic activity to have the peripheral five aromatic rings in the pentaarylbenzene covalently bonded to a triphenylphosphine moiety.

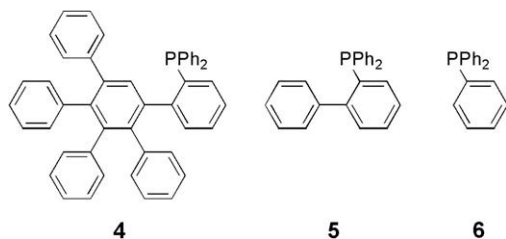
The phosphine **3** was synthesized through the activation of **2**, which was derived from **1** according to our previous work (Scheme 1).<sup>8</sup> The lithiation of **2** smoothly occurred in THF at  $-78\text{ }^{\circ}\text{C}$ , and it was followed by the clean reaction with chlorodiphenylphosphine.<sup>12</sup> The crude was purified by silica gel column chromatography to give **3** quantitatively. The stable solid material **3** was very easy to handle, and well dissolved into  $\text{CHCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ , and THF. Note that any corresponding phosphine oxide was not observed in <sup>31</sup>P NMR after usual workup and purification with column chromatography. This indicates that phosphine **3** was basically robust: the large pentaarylbenzene moiety would prevent the phosphorous lone-pair from being oxidized.<sup>13</sup>



Scheme 1. Synthesis of phosphine **3**, and bromide **2** from the starting pentaarylbenzene **1**.

\* Corresponding authors. Tel.: +81 88 656 7405; fax: +81 655 7025 (T.I.).

E-mail addresses: [iwasawa@chem.tokushima-u.ac.jp](mailto:iwasawa@chem.tokushima-u.ac.jp) (T. Iwasawa), [kawamura@chem.tokushima-u.ac.jp](mailto:kawamura@chem.tokushima-u.ac.jp) (Y. Kawamura).

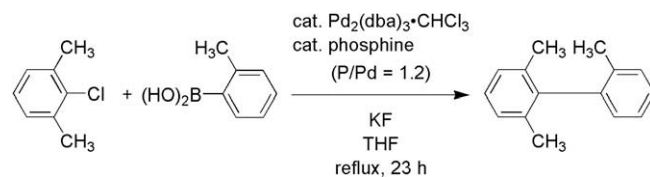
Figure 1. Phosphines **4**, **5**, and **6**.

The readily availability of phosphine **3** led us to investigate the performance as a supporting ligand in palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl chlorides.<sup>10,14</sup> The phosphines **4**,<sup>5b</sup> **5**<sup>15</sup> and **6**, which are structurally similar to **3**, were also examined (Fig. 1).

In preliminary experiments, the reactions were carried out with *o*-tolylboronic acid and 2-chloro-1,3-dimethylbenzene in the presence of [Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>] (dba = dibenzylideneacetone), phosphine, KF, and refluxing THF (Table 1).<sup>16</sup> The P/Pd ratio was

Table 1

Effect of phosphines **3–6** on the coupling of 2-chloro-1,3-dimethylbenzene with *ortho*-tolylboronic acid<sup>a</sup>



Entry	S/C <sup>b</sup>	Phosphines	Yield <sup>c</sup> (%)
1	1000	<b>3</b>	92
2	2000	<b>3</b>	>99
3	2000	<b>4</b>	81
4	2000	<b>5</b>	Trace
5	2000	<b>6</b>	Trace
6	2000	None	0
7	4000	<b>3</b>	>99
8	4000	<b>4</b>	42

<sup>a</sup> All reactions were performed in accordance with the representative procedure in Ref. 16, unless otherwise noted.

<sup>b</sup> Substrate to catalyst molar ratio.

<sup>c</sup> Isolated yields.

Table 2

Evaluation of [Pd<sub>2</sub>(dba)<sub>3</sub>]/phosphine **3**-catalyzed Suzuki–Miyaura coupling of aryl chlorides<sup>a</sup>

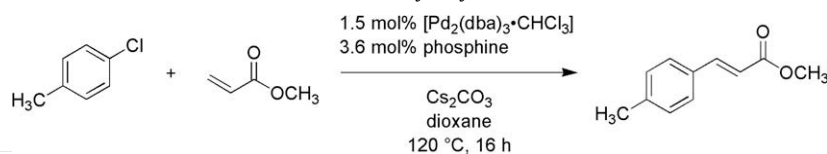
Entry	Aryl chlorides	Arylboronic acids	S/C <sup>b</sup>	Products	Time (h)	Yield <sup>c</sup> (%)
1			5000		14	92
2			5000		14	99
3			5000		23	84
4			50		18	0
5			500		13	99
6			500		2	>99
7			1000		13	>99
8			500		51	18

<sup>a</sup> All reactions were performed in accordance with the representative procedure in Ref. 18, unless otherwise noted.

<sup>b</sup> Substrate to catalyst molar ratio.

<sup>c</sup> Isolated yields.

**Table 3**  
Effect of phosphines **3–6** on the Mizoroki–Heck reaction of 4-chlorotoluene with methyl acrylate<sup>a,b</sup>



Entry	Phosphines	Yield <sup>c,d</sup>
1	<b>3</b>	50 (57)
2	<b>4</b>	1
3	<b>5</b>	Trace
4	<b>6</b>	Trace
5	None	0

<sup>a</sup> All reactions were performed in accordance with the representative procedure in Ref. 21, unless otherwise noted.

<sup>b</sup> Bath temperature was at 120 °C.

<sup>c</sup> Isolated yields.

<sup>d</sup> Isolated yield for the reaction time of 40 h is shown in parentheses.

maintained as 1.2,<sup>17</sup> and efficiency of the supporting ligand **3** was studied by raising the substrate to catalyst molar ratio (S/C). In entry 1, the reaction with S/C = 1000 yielded 2,2',6-trimethylbiphenyl in 92%. In entry 2, the **3**/Pd catalyst system was tolerable in high S/C of 2000, and desired construction of the biaryl was achieved with >99% yield. Then, the structurally related phosphines **4**, **5**, and **6** were also surveyed under the same conditions with S/C = 2000 (entries 3–5). In entry 3, phosphine **4**, which has a tetraphenylbenzene covalently bonded to a triphenylphosphine moiety, gave the desired biaryl in 81% yield. On the other hand, little amounts of coupling adducts were observed with use of **5** and **6** (entries 4 and 5), and no cross-coupling proceeded in the absence of phosphine (entry 6). Thus, S/C ratio was further increased to 4000 to compare the catalytic activity between ligands **3** and **4** (entries 7 and 8). Surprisingly, the reaction with **3** was smoothly catalyzed, providing the target biaryl quantitatively (entry 7). However, in the case of ligand **4**, the yield was significantly reduced to 42% along with the observation of palladium black formations. Hence, the complete reaction with **3** was attributed to the peripheral one more aryl group as compared with **4**.

To examine the potential of **3** in other coupling partners, scope and limitations of [Pd<sub>2</sub>(dba)<sub>3</sub>]/**3**-catalyzed Suzuki–Miyaura coupling of aryl chlorides were attempted with P/Pd = 1.2. The results are summarized in Table 2.<sup>18</sup> In entries 1 and 2, the aryl chlorides endowed with electron-deficient groups at *ortho*-position smoothly reacted with *p*-tolylboronic acid under the condition of S/C = 5000 to give 92% and 99% yields, respectively. In entry 3, 2-chloroanisole bearing electron-rich group was also ensured to yield the biaryl product in 84% with S/C = 5000.

The catalyst system was challenged to make the tetra-*ortho*-substituted biaryl in entry 4; however, no reaction occurred even in S/C = 50. On the other hand, di-*ortho*-substituted biaryls were smoothly formed (entries 5 and 6), and the sterically hindered biaryl with unsymmetrical tri-*ortho*-substitution was quantitatively furnished with S/C = 1000 (entry 7). The formation of tri-*ortho*-substituted biaryl with mesitylboronic acid in entry 8 was laborious: the reaction resulted in 18% yield even in prolonged reaction time for 51 h.

To further investigate the efficacy of [Pd<sub>2</sub>(dba)<sub>3</sub>]/**3** system, Mizoroki–Heck reaction<sup>19,20</sup> was carried out,<sup>5a</sup> as shown in Table 3.<sup>21</sup> The palladium-catalyzed reaction of 4-chlorotoluene and methyl acrylate was conducted with phosphines **3–6** under the condition of P/Pd = 1.2, giving the target molecule of methyl (*E*)-*p*-methylcinnamate. The ligand **3** afforded 50% yield (entry 1),<sup>22</sup> while in the absence of phosphine and in the presence of phosphine **4**, **5**, and **6** the reactions proceeded with significantly diminished efficiency (entries 2–5). Thus, the one more aryl ring

attached to **3** as compared with **4** contributes toward catalyzing the reaction, in a similar vein of the cross-coupling in Table 1. The increased rigidity in **3** would give emphasis to the stability of catalyst, and it could endow the catalyst with the durable nature to give high yields of products.

In summary, the pentaarylbenzene endowed with triphenylphosphine was found to work well in palladium-catalyzed transformation of aryl chlorides. One more aryl group of **3** as compared with **4** was ensured to play a quintessential role in the catalyst system, and accomplished the reactions with large turnover numbers, up to TON 5000. Work is now in progress to obtain the single crystal of **3** and to amplify the property of pentaarylbenzene moiety as an attractive catalyst material.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.071.

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12. *Synthetic procedure for the phosphine 3*: To a solution of **2** (668 mg, 1 mmol) in THF (12 mL) at  $-78^{\circ}\text{C}$  was added *n*-BuLi (1.2 mmol, 1.6 M in hexane) dropwise over 5 min, and the mixture was stirred for 2 h. ClPPH<sub>2</sub> (0.22 mL, 1.2 mmol) was slowly added, and the reaction mixture was allowed to warm to room temperature. After stirring for 18 h, the solvent was evaporated, and the residue was dissolved in CHCl<sub>3</sub>, washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by silica gel column chromatography (hexane/CHCl<sub>3</sub> = 4:1) quantitatively afforded **3** (787 mg) as white solid materials. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.16 (m, 6H), 7.13–7.10 (m, 1H), 7.01–6.90 (m, 5H), 6.85–6.79 (m, 5H), 6.75–6.58 (m, 14H), 6.42 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H), 6.33 (d, *J* = 7.8 Hz, 1H), 6.24 (dd, *J* = 7.8 Hz, 15.1 Hz, 2H), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (br s, 3H  $\times$  2). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  148.2, 147.9, 141.0, 140.9, 140.6, 140.44, 140.37, 139.23, 139.18, 138.8, 138.7, 138.6, 138.4, 138.23, 138.20, 138.1, 137.6, 136.1, 136.0, 135.0, 134.7, 134.3, 134.11, 134.09, 133.9, 133.7, 133.5, 132.5, 132.3, 132.2, 131.9, 131.7, 131.3, 131.1, 128.3, 128.2, 128.12, 128.06, 127.7, 127.6, 127.3, 127.2, 126.9, 126.5, 126.2, 126.1, 124.9, 21.23, 21.17. <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>)  $\delta$  -12.6. MS (ESI) *m/z*: 775 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>58</sub>H<sub>47</sub>P: C, 89.89; H, 6.11. Found: C, 89.85; H, 6.28.
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16. *Representative experimental procedure for Table 1, entry 7*: KF (3.49 g, 60 mmol) was dried in vacuo in a 50 mL flask with heating (heat gun), then *o*-tolylboronic acid (3.27 g, 24 mmol), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2.6 mg, 0.0025 mmol), and phosphine **3** (4.6 mg, 0.006 mmol) were added. The whole system was evacuated and backfilled with argon three times, and the THF solution of 2-chloro-1,3-dimethylbenzene (2.7 M, 10 mL) was added. The reaction mixture was stirred at room temperature for 10 min, and then conducted in refluxing THF for 23 h. After the reaction, the mixture was diluted with EtOAc, and was filtered. Purification by silica gel column chromatography (hexane/CHCl<sub>3</sub> = 4:1) quantitatively afforded a desired biaryl<sup>5b</sup> (4.24 g) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.41–7.33 (m, 3H), 7.30–7.21 (m, 3H), 7.16–7.13 (m, 1H), 2.10 (s, 3H), 2.08 (s, 6H). MS (EI) *m/z*: 196 (M<sup>+</sup>).
17. The P/Pd = 1.2, 2.0 and 3.0 in the reaction condition of Table 1 at entry 1 gave the 2,2',6'-trimethylbiphenyl in 92%, 86%, and 87% yields, respectively. The ratio of 1.2 was used from the viewpoint of reaction efficiency.
18. *Representative experimental procedure for Table 2, entry 7*: KF (697 mg, 12 mmol) was dried in vacuo in a 25 mL flask with heating (heat gun), then *o*-tolylboronic acid (816 mg, 6 mmol), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2.6 mg, 0.0025 mmol), and phosphine **3** (4.6 mg, 0.006 mmol) were added. The whole system was evacuated and backfilled with argon three times, and the THF solution of 2-chloro-3-methoxybenzaldehyde (0.8 M, 10 mL) was added. The reaction mixture was stirred at room temperature for 10 min, and then conducted in refluxing THF for 13 h. After the reaction, the mixture was diluted with EtOAc, and was filtered. Purification by silica gel column chromatography (hexane/CHCl<sub>3</sub> = 4:1) quantitatively afforded a desired biaryl<sup>23</sup> (1.15 g) as white needles. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.62 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H), 7.35–7.24 (m, 3H), 7.21–7.19 (m, 1H), 7.14–7.12 (m, 1H), 3.78 (s, 3H), 2.07 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  192.5, 157.2, 137.4, 135.3, 134.8, 133.3, 131.0, 130.0, 129.0, 128.4, 125.6, 119.1, 116.1, 56.1, 20.2. MS (EI) *m/z*: 226 (M<sup>+</sup>, 100%).
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21. *Representative experimental procedure for Table 3, entry 1*: Cs<sub>2</sub>CO<sub>3</sub> (358 mg, 1.1 mmol) was dried in vacuo in a 20 mL Schlenk tube with heating (heat gun), and to the flask were added Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (15.5 mg, 0.015 mmol) and phosphine **3** (27.9 mg, 0.036 mmol). The whole system was evacuated and backfilled with argon three times, and the 1,4-dioxane (1 mL) and *p*-chlorotoluene (0.118 mL, 1 mmol) were added. The mixture was conducted at 75 °C (bath temperature) for 5 min, and methyl acrylate (0.18 mL, 2 mmol) was added. The reaction was carried out at 120 °C (bath temperature) for 16 h. After the reaction, the mixture was diluted with Et<sub>2</sub>O, and was filtered. Purification by silica gel column chromatography (hexane/CHCl<sub>3</sub> = 4:1) afforded methyl (*E*)-*p*-methylcinnamate<sup>24</sup> in 50% yield (88 mg) as white needles. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.67 (d, *J* = 16 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.39 (d, *J* = 16 Hz, 1H), 3.80 (s, 3H), 2.38 (s, 3H). MS (EI) *m/z*: 176 (M<sup>+</sup>).
22. The reaction system in Table 3 was undertaken with styrene, methyl methacrylate, 1-hexene, and methyl vinylketone. The styrene gave the desired (*E*)-1-methyl-4-styrylbenzene in 41% yield. However, little amounts of the target molecule were observed in use of methyl methacrylate (<4% yield), and no cross-coupling with 1-hexene and methyl vinylketone proceeded.
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