

# Palladium charcoal-catalyzed, ligandless Suzuki reaction by using tetraarylborates in water

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**Abstract**—In water and without using any ligand, palladium charcoal-catalyzed Suzuki coupling reaction of tetraarylborates with aryl bromides could be achieved in excellent yield. A concise mechanism consisting of four catalytic cycles is depicted in this paper. © 2005 Elsevier Ltd. All rights reserved.

The Suzuki reaction has found a wide application in modern synthetic organic chemistry for the preparation of biaryl compounds.<sup>1</sup> Although, many efficient palladium catalysts with novel ligands have been discovered for the reaction, chemists have recently paid great attention to the ligandless protocol catalyzed by palladium catalysts such as Pd(OAc)<sub>2</sub> or PdCl<sub>2</sub>.<sup>2</sup> With the advantage of its relatively inexpensive, stable, easily removable and reusable characteristics, palladium charcoal is the most suitable catalyst for this type of reaction in terms of green chemistry. Some excellent results of the coupling reactions of aryl halides/triflates with arylboronic acids catalyzed by Pd/C have been reported since 1994.<sup>3</sup>

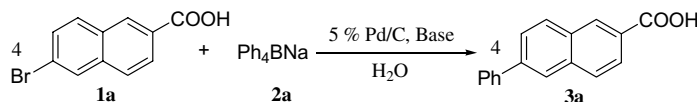
As a new type of borate source, sodium tetraphenylborate is a stable and commercially available reagent for the Suzuki reaction, and efforts to carry out the reaction with Pd(PPh<sub>3</sub>)<sub>4</sub> or Pd(OAc)<sub>2</sub> have been published.<sup>4</sup> It has been discovered that its four phenyl groups can all be coupled with aryl halides to generate the product efficiently.<sup>5</sup> A reasonable mechanism for the reaction has not yet been reported, although a few attempts have been made.<sup>4a</sup> All these findings inspired us to report our recent results for the study of the Pd/C-catalyzed, ligandless Suzuki reaction of sodium tetraarylborates in water.

During our investigation for preparing the biaryl compounds by employing this reaction, we found that Pd/C could enhance the coupling of 6-bromo-2-naphthoic acid (**1a**) with sodium tetraphenylborate (**2a**). Surprisingly, the reaction proceeded smoothly in water without using any phosphine ligand. Under this mild condition, the reaction went to completion in more than 90% yield even in the presence of 0.0025 mol% Pd/C when the reaction time was prolonged from 1 h to 7 h (Table 1, entries 1 and 2), but it did not occur in the absence of Pd/C. Comparison of inorganic bases utilized showed that sodium bases were more suitable than the potassium ones. For example, the reaction proceeded in high yield within a short time in the presence of Na<sub>2</sub>CO<sub>3</sub> or Na<sub>3</sub>PO<sub>4</sub>, while it was less satisfactory in the case of K<sub>2</sub>CO<sub>3</sub> or K<sub>3</sub>PO<sub>4</sub> (Table 1, entries 7 vs 8, 13 vs 14). The possible reason for the difference might be due to the low solubility of in situ formed potassium tetraphenylborate in water.

We then continued our work with other selected bromoaryl carboxylic acids or phenols to further study the scope and limitations of the reaction and noticed that most of the results were excellent as demonstrated in Table 2.<sup>6</sup> In many cases, the biaryl carboxylic acids were quantitatively obtained from aryl bromides either bearing electron-donating groups (Table 2, **3d**<sup>5</sup>) or electron-withdrawing groups (Table 2, **3f,h**<sup>7</sup>). 4-Phenylphenol<sup>3g</sup> was also obtained in excellent yield (Table 2, **3i**). Only sterically hindered *ortho*-bromo starting materials such as 2-bromobenzoic acid or 2-bromophenylacetic acid gave low to moderate yields even at prolonged reaction times.

**Keywords:** Suzuki coupling; Palladium charcoal; Ligandless; Mechanistic study.

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**Table 1.** Suzuki reaction of sodium tetraphenylborate in the presence of Pd/C<sup>a</sup>

Entry	Base	Pd/C (mol%)	Time (h)	Yield <sup>b</sup> (%)	TON
1	NaOH	0.05	1	99	1980
2	NaOH	0.0025	7	92	36,800
3	KOH	0.05	24	20	400
4	NaOAc	0.05	1	28	560
5	NaHCO <sub>3</sub>	0.05	1	88	1760
6	KHCO <sub>3</sub>	0.05	24	59	1180
7	Na <sub>2</sub> CO <sub>3</sub>	0.0025	1	94	37,600
8	K <sub>2</sub> CO <sub>3</sub>	0.05	24	9	180
9	CS <sub>2</sub> CO <sub>3</sub>	0.05	24	Trace	—
11	Na <sub>2</sub> HPO <sub>4</sub>	0.05	1	69	1380
12	K <sub>2</sub> HPO <sub>4</sub>	0.05	24	92	1840
13	Na <sub>3</sub> PO <sub>4</sub>	0.05	1	99	1980
14	K <sub>3</sub> PO <sub>4</sub>	0.05	24	Trace	—

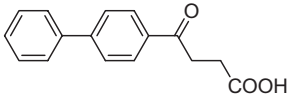
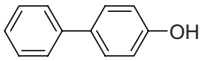
<sup>a</sup> Reaction conditions: 0.27 equiv (based on **1a**) sodium tetraphenylborate (**2a**), 2.00 equiv base, reflux under air.

<sup>b</sup> Yields determined by HPLC analysis.

**Table 2.** Pd/C-catalyzed cross-coupling of various aryl bromides with sodium tetraphenylborate<sup>a</sup>

Compd	Product	Pd/C (mol %)	Yield <sup>b</sup> (%)	TON
<b>3b</b>		0.01	95	9500
		0.005	87	17,400
<b>3c</b>		0.05	97	1940
		0.01	27	2700
<b>3d</b>		0.05	>99	>1980
		0.01	90	9000 <sup>c</sup>
<b>3e</b>		0.05	94	1880
<b>3f</b>		0.05	>99	>1980
<b>3g</b>		0.05	94	1880
<b>3h</b>		0.01	99	9900
<b>3i</b>		0.005	>99	>19,800
<b>3j</b>		0.1	74	740 <sup>d</sup>

Table 2 (continued)

Compd	Product	Pd/C (mol %)	Yield <sup>b</sup> (%)	TON
<b>3k</b>		0.05	98	1960
		0.01	89	8900
<b>3l</b>		0.05	99	1980

<sup>a</sup> Reaction conditions: 0.27 equiv **2a** (based on **1**), 2.00 equiv Na<sub>2</sub>CO<sub>3</sub>, reflux under air for 1 h.

<sup>b</sup> Yields determined by HPLC analysis.

<sup>c</sup> Reaction time was 3 h.

<sup>d</sup> Reaction time was 24 h.

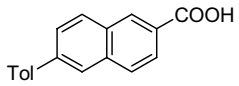
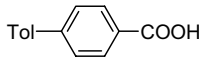
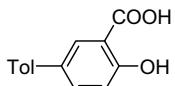
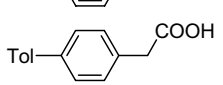
Considering that many non-steroidal anti-inflammatory drugs of arylalkyl carboxylic acid type are biaryl compounds, we then applied this new synthetic strategy for the syntheses of two commercially available drugs, Felbinac<sup>8</sup> and Fenbufen.<sup>9</sup> The preparation of both molecules could easily be scaled up to more than 100 g scale in excellent yields (Table 2, **3i** and **k**).

As we expected, sodium tetrakis(4-tolyl)borate could also be smoothly coupled with aryl bromides to give similar results as the case for sodium tetraphenylborate (Table 3).

It is noteworthy that the recovered Pd/C possessed high catalytic activity for the coupling reaction, which was monitored by the reaction of 4-bromobenzoic acid and sodium tetraphenylborate (Table 4). Although, the catalytic activity was gradually diminished, the yield was still 76% even in the fourth reuse without any activating procedure.

Starting from 4-bromophenol or 6-bromo-2-naphthoic acid, it was very interesting to note that the amount of base utilized greatly affected the yield in the reaction as shown in Table 5. The acidity of phenols in water is

Table 3. Pd/C-catalyzed cross-coupling of aryl bromides with sodium tetrakis(4-tolyl)borate<sup>a</sup>

Compd	Product	Yield <sup>b</sup> (%)	TON
<b>4a</b>		>99	>1980
<b>4b</b>		97	1940
<b>4c</b>		66	1320
<b>4d</b>		>99	>1980

<sup>a</sup> Reaction conditions: 0.27 equiv **2b** (based on **1**), 0.05 mol% 5% Pd/C, 2.00 equiv Na<sub>2</sub>CO<sub>3</sub>, reflux under air for 1 h.

<sup>b</sup> Yields determined by HPLC analysis.

Table 4. Coupling of 4-bromobenzoic acid with sodium tetraphenylborate using recovered Pd/C as catalyst<sup>a</sup>

Entry	Pd/C	Yield (%) <sup>b</sup>
1	Fresh	95
2	First reuse	88
3	Second reuse	84
4	Third reuse	81
5	Fourth reuse	76

<sup>a</sup> Reaction conditions: 0.27 equiv Ph<sub>4</sub>BNa (based on **1b**), 2.00 equiv Na<sub>2</sub>CO<sub>3</sub>, reflux under air for 1 h.

<sup>b</sup> Yields determined by HPLC analysis.

Table 5. Effects of base amounts in the cross-coupling<sup>a</sup>

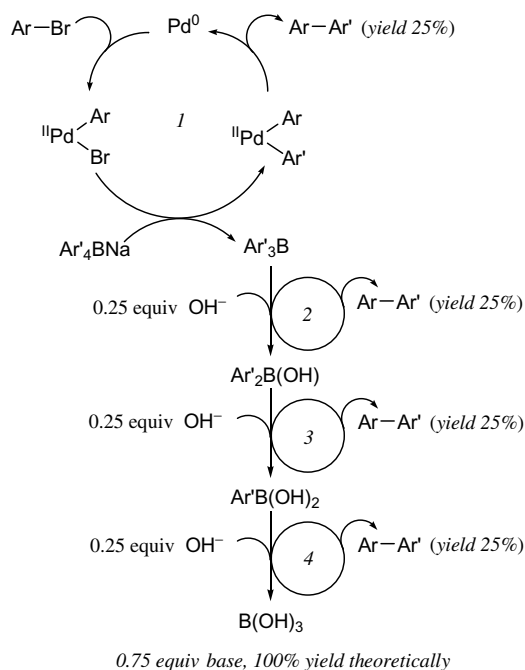
Entry	Aryl bromide	Base (mole equiv)	Time (h)	Yield (%) <sup>b</sup>
1	<b>1a</b>	NaOH (1.75)	1	95
2	<b>1a</b>	NaOH (0.75)	1	92
3	<b>1a</b>	NaOH (0.50)	24	73
4	<b>1a</b>	NaOH (0.25)	24	45
5	<b>1a</b>	NaOH (0)	24	21
6	<b>1a</b>	NaHCO <sub>3</sub> (0.75)	1	77
7	<b>1a</b>	Na <sub>2</sub> CO <sub>3</sub> (0.375)	1	81
8	<b>1a</b>	Na <sub>3</sub> PO <sub>4</sub> (0.375)	1	78
9	<b>1l</b>	NaOH (0)	24	25
10	<b>1l</b>	NaOH (0.50)	24	74
11	<b>1l</b>	NaOH (0.75)	5	95
12	<b>1l</b>	Na <sub>2</sub> CO <sub>3</sub> (0.375)	5	90

<sup>a</sup> Reaction conditions: 0.25 equiv **2a** (based on **1**), 0.05 mol% 5% Pd/C, 10 mL H<sub>2</sub>O, reflux under argon.

<sup>b</sup> Yields determined by HPLC analysis.

weaker than that of H<sub>2</sub>CO<sub>3</sub> in the case of 4-bromophenol. 6-Phenyl-2-naphthoic acid (**3a**), on the other hand, was precipitated immediately after it was formed in the reaction due to its poor solubility. Using 1.75, 0.75, 0.50, 0.25, or 0 mole equiv of NaOH yielded **3a** in 95%, 92%, 73%, 45%, and 21%, respectively (Table 5, entries 1–5). Similar results were obtained by using NaHCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, or Na<sub>3</sub>PO<sub>4</sub> (Table 5, entries 6–8). For other acidic starting materials such as 4-bromophenylacetic acid, this phenomenon could not be observed.

In view of this finding, a concise mechanism is depicted in Scheme 1. After aryl bromide first undergoes oxidative addition with Pd [0], it is coupled with one aryl group of Ar'<sub>4</sub>BNa to give 25% product (based on ArBr). The generated Ar'<sub>3</sub>B, Ar'<sub>2</sub>B(OH), or Ar'B(OH)<sub>2</sub> will take



**Scheme 1.** Proposed mechanism of Pd/C-catalyzed cross-coupling of aryl bromide with sodium tetraarylboration.

part in the next catalytic cycle in the presence of base. Totally, 0.25 equiv  $\text{Ar}'_4\text{BNa}$  and 0.75 equiv base are needed and nearly 100% product is formed after four catalytic cycles. Unfortunately, we could not directly detect  $\text{Ph}_3\text{B}$  and  $\text{Ph}_2\text{B}(\text{OH})$  during the reaction due to their instability when  $\text{Ph}_4\text{BNa}$  was used. Barnes and co-workers<sup>10</sup> have, on the other hand, studied the kinetic decomposition of  $\text{Ph}_4\text{BNa}$ ,  $\text{Ph}_3\text{B}$  and  $\text{Ph}_2\text{B}(\text{OH})$  catalyzed by copper in aqueous alkaline solutions. We also noticed that when insufficient amount of base was used, benzene and phenylboronic acid, generated by the decomposition of phenylborate species in the mixture, could be detected.

In summary, we would like to report a novel Pd/C-catalyzed, ligandless Suzuki reaction in water by using tetraarylboration. The reaction proceeds in excellent yield particularly in the presence of sodium hydroxide or carbonate, etc. Based upon the results found in the coupling of 6-bromo-2-naphthoic acid and 4-bromophenol with  $\text{Ph}_4\text{BNa}$  in the presence of different amounts of base, we would like to first report a concise mechanism consisting of four catalytic cycles for the reaction. This mild and environmental friendly reaction is suitable for the preparation of various biaryl carboxylic acids or phenols.

#### Acknowledgements

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#### Supplementary data

General experimental procedures and characterization of all coupling products were depicted. For the mecha-

nistic study, details about the isolation and determination of the two by-products, benzene and  $\text{PhB}(\text{OH})_2$ , were also given. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.022.

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- It was very difficult to get the isolated yields due to the similar  $R_f$  values of all aryl bromides and the coupling products on TLC plates. In order to obtain pure products by recrystallization or flash chromatography as standards for HPLC analyses, we should first carry out the reactions to completion using a sufficient amount of catalyst. Typical procedure: a 50 mL flask equipped with a stirring bar and a

condenser was charged with water (10 mL), Na<sub>2</sub>CO<sub>3</sub> (212 mg, 2.00 mmol), aryl bromide (**1**) (1.00 mmol), sodium tetraarylborate (**2**) (0.27 mmol), and 5% Pd/C (50% water wet, 2 mg, 0.05 mol%). The mixture was refluxed for 1 h, quenched with 3 M HCl. The precipitate was filtered, washed with water and dried. It was dissolved in THF to remove Pd/C by filtration and directly used for yield determination by HPLC. The unknown coupling products (**3a**, **3f** and **4a**) were ascertained by <sup>1</sup>H NMR, <sup>13</sup>C

NMR, and elemental analyses. Others were characterized by <sup>1</sup>H NMR and <sup>13</sup>C NMR.

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