

# Microwave-promoted palladium catalysed Suzuki cross-coupling reactions of benzyl halides with arylboronic acid

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Simple catalytic systems for the coupling of benzyl halides with phenylboronic acid under microwave conditions were tested. Microwave-promoted Suzuki reaction of arylboronic acid with benzyl halides catalysed by  $\text{PdCl}_2(\text{PPh}_3)_2$  in the mixed solvents DMF/ $\text{H}_2\text{O}$  is reported to give diaryl methane derivatives in good to high yield.

**Keywords:** Suzuki cross-coupling reactions, benzyl halides, diaryl methanes, microwave irradiation microwave

The palladium catalysed Suzuki–Miyaura cross-coupling reaction<sup>1</sup> between arylboronic acids and aryl halides or triflates has proved to be a very popular and versatile method for forming the carbon–carbon single bonds of biaryls.<sup>2,3</sup> Diaryl methane derivatives are important building blocks in organic synthesis because of their industrial applications. Organoboron reagents exhibit greater functional group compatible with organo zinc or Grignard reagents. Moreover, the innocuous nature of boronic acids, which are generally nontoxic and thermally air and moisture-stable, is a practical advantage of the Suzuki reaction relative to other coupling processes. Negishi and co-workers had earlier reported Pd(0)- and Ni(0)-catalysed syntheses of unsymmetrical diarylmethanes via the corresponding benzylzinc bromides or benzylmagnesium chlorides with aryl bromides or iodides.<sup>4</sup> There are other instances in which Pd(0)-catalysed couplings of benzylic halides under Stille-type conditions have been reported.<sup>5</sup> Other Suzuki coupling reactions of benzyl halides have been described.<sup>6–15</sup>

Several non-traditional methods have been developed for the Suzuki–Miyaura synthesis of unsymmetrical biaryls such as high intensity ultrasound<sup>16–17</sup> and especially microwave irradiation,<sup>18–22</sup> which also promotes the reaction of aryl chlorides and acid chlorides.

The main goal of our work was to see if the Suzuki–Miyaura coupling of arylboronic acids with benzylic halides can be promoted by microwave irradiation. The second aim was also to find out if this reaction can also be used for the preparation of unusually substituted diarylmethane derivatives, as shown in Scheme 1.

The microwave-assisted crossing-coupling reaction of phenylboronic acid with 2-bromomethyl naphthalene, affording 2-naphthyl phenyl methane, was chosen as a model reaction. The effect of catalysts, base, reaction time, and mole ratios, were examined.

The catalytic study (Table 1) showed that in the absence of catalyst, there was no reaction even after microwave irradiation of 30min (Table 1, entry 9). On the other hand Pd ( $\text{PPh}_3$ )<sub>2</sub>Cl<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> were found to be the best catalyst system and the crossed coupled product was isolated in 90% yield (Table 1, entries 5 and 6), moderate yields (60% and 84%) of the 2-naphthylphenylmethane were obtained in the presence of 2 and 5mol% of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as catalyst using different base (Table 1, entries 1–4). However, using 5mol% of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> the reaction was complete in a short time (13 min) and an excellent yield of 2-naphthylphenylmethane was

obtained (90%). It is important to note that when the amount of catalyst is increased from entry 2 to 5 or 7 mmol%, the yield of the product did not improve using K<sub>2</sub>CO<sub>3</sub> as base even after irradiation the reaction mixture for 15min (Table 1, entries 11 and 12).

We investigated the different mole ratios on microwave-assisted crossing-coupling reaction of phenylboronic acid with 2-bromomethylnaphthalene, the results show the best mole ratio is phenylboronic acid: 2-bromomethylnaphthalene: K<sub>2</sub>CO<sub>3</sub>: [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] = 1:1.2:2.5:0.05.

Applying the optimised conditions, we synthesised the **3a–j** under microwave irradiation. The results are listed in Table 2.

Note that benzyl bromides underwent smooth coupling with phenylboronic acid, whereas other halogens present on the aromatic ring remained unaffected (Table 2, entries **3b** and **3h**). However, aromatic bromides underwent the Suzuki cross-coupling reaction selectively (Table 2, entry **3d**) under microwave irradiation. Without microwave irradiation **3d** was not obtained.

## Experimental

**CAUTION:** The palladium catalyst must be well distributed in the reaction mixture and the reaction equipment must not be closed.

Microwave irradiation was carried out with a commercial domestic microwave oven Glanzwp 750B at 2450Hz. Melting points were determined with an electric-melting point apparatus and are uncorrected. IR spectra were recorded in KBr on an Alpha Centauri FT-IR spectrophotometer and <sup>1</sup>H NMR spectra were recorded on a BRUKER PT 200MHz or 400 MHz instrument using CDCl<sub>3</sub> as solvent and TMS as internal reference. Mass spectra were recorded on a QP-1000A GC-MS using the electron impact mode (70ev) or Bruker Daltonics APEX II 47eFT-ICR. All solvents were used without further purification.

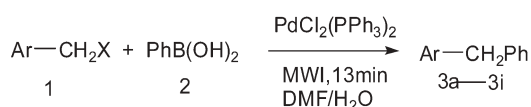
**Table 1** Effect of catalyst on Suzuki cross-coupling of 2-bromomethyl naphthalene with phenylboronic acid in DMF/ $\text{H}_2\text{O}$  under microwave irradiation<sup>a</sup>

Entry	Catalyst/mmol% Pd (PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	Base	Time/min	Yields /% <sup>b</sup>
1	5	NaOH	13	60
2	5	KF/Al <sub>2</sub> O <sub>3</sub>	13	80
3	5	KF	13	84
4	5	Na <sub>2</sub> CO <sub>3</sub>	13	70
5	5	K <sub>2</sub> CO <sub>3</sub>	13	90
6	7	K <sub>2</sub> CO <sub>3</sub>	13	90(86%)
7	3	K <sub>2</sub> CO <sub>3</sub>	13	82
8	2	K <sub>2</sub> CO <sub>3</sub>	13	70
9	0	K <sub>2</sub> CO <sub>3</sub>	30	—
10	5	K <sub>2</sub> CO <sub>3</sub>	11	78
11	5	K <sub>2</sub> CO <sub>3</sub>	15	90
12	5	K <sub>2</sub> CO <sub>3</sub>	20	90

<sup>a</sup> Conditions: 2-bromomethyl naphthalene (1.2 mmol), phenylboronic acid (1 mmol), base (2.5 mmol), 675W.

<sup>b</sup> Yield of isolated product.

<sup>c</sup> Reaction temperature 130 °C, reaction time 10 h, without microwave irradiation.



**Scheme 1**

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**Table 2** fast palladium catalysed coupling reaction under microwave irradiation<sup>a</sup>

Product	ArCH <sub>2</sub> X	Yields (%) <sup>b</sup>	M.p. °C/Lit
<b>3a</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Br	92	Oil <sup>23</sup>
<b>3a</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl	85	Oil <sup>23</sup>
<b>3b</b>	3-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br	88	Oil <sup>24</sup>
<b>3c</b>	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br	82	Oil <sup>25</sup>
<b>3d</b>	4-Br-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br	86	84–85 (86–87 <sup>26</sup> )
<b>3e</b>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br	90	30(31 <sup>27</sup> )
<b>3f</b>	4-BrCH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br	92	85–86(86 <sup>26</sup> )
<b>3g</b>	2-C <sub>10</sub> H <sub>7</sub> CH <sub>2</sub> Br	90	57–58(58 <sup>28</sup> )
<b>3h</b>	4-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br	91	Oil <sup>23</sup>
<b>3i</b>	1-C <sub>10</sub> H <sub>7</sub> CH <sub>2</sub> Br	84	52–54

<sup>a</sup> Conditions: benzylhalide (1.2 mmol), phenylboronic acid (1 mmol), K<sub>2</sub>CO<sub>3</sub> (2.5 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5% mmol), 13 minutes at 675 W.

<sup>b</sup> Yield of isolated product.

PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was prepared according to ref.29., ArCH<sub>2</sub>X was prepared according to ref.30. The remaining chemicals were obtained from commercial sources.

#### General procedure

Base K<sub>2</sub>CO<sub>3</sub> (2.5 mmol, and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 mmol) catalyst were added to the solution of phenylboronic acid (1 mmol) and benzyl halide (1.2 mmol) in 12 mL solvent of N,N-diethyl formamide (DMF) (10 mL) and H<sub>2</sub>O (2 mL). The reaction mixture was stirred and then irradiated for 13 minutes at 675W under a nitrogen atmosphere. It was cooled, the precipitate was filtrated and filtrate was poured into a saturated aqueous sodium chloride solution (50 mL) and extracted with diethyl ether (3×15 mL). The extract was then dried over magnesium sulfate. The solution was concentrated to yield the crude product, which was separated by column chromatography on silica gel (eluent: petroleum/ethyl acetate = 10:1) and identified by spectroscopic analyses.

**3i**: M.p. 52–54 °C. IR: ν = 3058, 3023, 2906, 2852, 1595, 1490, 1449, 1394, 1160, 791, 772, 734, 703 cm<sup>-1</sup>. <sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>): δ<sub>H</sub> = 7.45–7.20 (m, 9H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.83–8.04 (m, 2H), 4.48 (s, 2H). HRMS calcd C<sub>17</sub>H<sub>14</sub>: 218.1095, found: 218.1088.

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