

# Convenient Synthesis of Arylboronates through a Synergistic Pd/Cu-Catalyzed Miyaura Borylation Reaction under Atmospheric Conditions

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A highly efficient and practical borylation reaction of aryl iodides with bis(pinacolato)diboron has been established. By using  $Pd(OAc)_2$ , CuI, and  $PPh_3$  as a ligand at room temperature under air in the presence of  $Cs_2CO_3$ , the protocol proved

to be general. Various functionalized arylboronates were obtained in moderate to excellent yields. In addition, a possible reaction mechanism was proposed.

## Introduction

Arylboronic acids and their esters are important and useful reagents that are widely used in organic synthesis for functional-group transformations.<sup>[1]</sup> They play a key role as coupling partners in Suzuki–Miyaura cross-coupling reactions. The advantages of these organoboron compounds in cross-coupling processes include their high stability and low toxicity. Arylboronic acids and esters are typically produced by the reaction of trialkyl borates with either organolithium or Grignard reagents. However, these methods are incompatible with sensitive functional groups and require rigorous anhydrous reaction conditions.

Owing to these disadvantages, several alternative routes to synthesize borylation products have been developed. Many of them use transition-metal-catalyzed borylation reactions. Pd- and Ni-catalyzed borylation reactions of aryl halides have been used in the preparation of arylboronates.<sup>[1a,2]</sup> C–H borylations of aromatic substrates catalyzed by iridium have been reported.<sup>[3]</sup> Cu-catalyzed borylation for the synthesis of arylboronates was found to be efficient and economical.<sup>[4]</sup> Also, transition-metal-free borylations have been studied.<sup>[5]</sup> However, they require an inert gas and have either long reaction times or high reaction temperatures.

In this work, we discovered a new transition-metal catalytic system for the Miyaura borylation for which an airsensitive technique is not required. This simple and efficient system consisting of Pd and Cu can catalyze the borylation

M.htm Supporting information for this article is gwildble on the of aryl iodides with bis(pinacolato)diboron at room temperature under atmospheric conditions to achieve arylboronates and their derivatives. Moderate to excellent yields were obtained under this synergistic catalysis.

### **Results and Discussion**

We initially used phenyl iodide and bis(pinacolato)diboron as substrates in a catalytic combination between Pd(OAc)<sub>2</sub> and CuI. For the present borylation reaction under ambient conditions, a moderate vield was obtained (Table 1, Entry 1). The yield of product **3a** declined to 13% in the absence of PPh<sub>3</sub> and to 30% with only Pd(OAc)<sub>2</sub> (Table 1, Entries 2 and 3). A catalytic system consisting of only CuI/PPh<sub>3</sub> or CuI was found ineffective for this borylation reaction (Table 1, Entries 4 and 5). Moreover, no reaction was observed in the absence of both Pd(OAc)<sub>2</sub> and CuI (Table 1, Entries 6 and 7). We subsequently investigated the effect of the amount of air-stable PPh<sub>3</sub> ligand on the reaction and interestingly found that decreasing the amount of PPh<sub>3</sub> positively affected the yield of 3a (Table 1, Entries 8–13). A 60% yield of the borylation product was afforded even with the use of 2 mol-% of PPh<sub>3</sub> in the presence of 0.5 mL of water (Table 1, Entry 13). The amount of CuI was next examined (Table 1, Entries 13-18). We observed an improved product yield (65%) upon using 20 mol-% of CuI (Table 1, Entry 16). In addition, we screened various Pd sources to examine their effects on the reaction (Table 1, Entries 19–22). Notably, Pd(PPh<sub>3</sub>)<sub>4</sub> delivered a higher product yield (79%). However, this reagent requires an inert gas for storing and handling, whereas Pd(OAc)<sub>2</sub> is air- and moisture-stable and hence does not require any air-sensitive technique, which is the main interest of this research. We thus chose Pd(OAc)<sub>2</sub> (2 mol-%), CuI (20 mol-%), and PPh<sub>3</sub> (2 mol-%) for further evaluation of the other effects.

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Table 1. Screening of reaction conditions for the Pd/Cu-catalyzed borylation of iodobenzene and bis(pinacolato)diboron.<sup>[a]</sup>

Table 2. Screening of co-catalysts for the borylation reaction.[a]

$\langle \rangle$	-I + C B-B		d source ul, PPh <sub>3</sub>	−B O
<b>1a</b> (1.0 equ	2 uiv.) (1.5 equ	uiv.) atmosph	IF (2 mL) .t., 24 h heric conditions	3a
Entry	Pd source	CuI [mol-%]	PPh <sub>3</sub> [mol-%]	Yield <sup>[b]</sup> [%]
1	$Pd(OAc)_2$	10	13	51
2	$Pd(OAc)_2$	10	_	13
3	$Pd(OAc)_2$	_	_	30
4	_	10	13	28
5	_	10	_	4
6	_	_	_	0 <sup>[d]</sup>
7	_	_	13	0 <sup>[d]</sup>
8[c]	$Pd(OAc)_2$	10	30	57
9[c]	$Pd(OAc)_2$	10	18	58
10 <sup>[c]</sup>	$Pd(OAc)_2$	10	13	62
11 <sup>[c]</sup>	$Pd(OAc)_2$	10	10	60
12 <sup>[c]</sup>	$Pd(OAc)_2$	10	5	60
13 <sup>[c]</sup>	$Pd(OAc)_2$	10	2	60
14[c]	$Pd(OAc)_2$	2.5	2	47
15 <sup>[c]</sup>	$Pd(OAc)_2$	5	2	56
16 <sup>[c]</sup>	$Pd(OAc)_2$	20	2	65
17 <sup>[c]</sup>	$Pd(OAc)_2$	30	2	65
18 <sup>[c]</sup>	$Pd(OAc)_2$	50	2	63
19[c]	PdCl <sub>2</sub>	20	2	53
20 <sup>[c]</sup>	$Pd(PPh_3)_2Cl_2$	20	2	55
21 <sup>[c]</sup>	Pd <sub>2</sub> dba <sub>3</sub>	20	2	56
22 <sup>[c]</sup>	$Pd(PPh_3)_4$	20	2	79

[a] Reaction conditions, unless otherwise stated: Pd source (0.012 mmol), CuI, PPh<sub>3</sub>, aryl iodide (0.6 mmol), bis(pinacolato)diboron (0.9 mmol), KOtBu (0.9 mmol), THF (2 mL), air, room temperature, 24 h. [b] Yield was determined by GC integration relative to hexamethylbenzene as an internal standard. [c] Water (0.5 mL) was added. [d] No reaction was detected by TLC/GC–MS.

We next screened a variety of co-catalysts. Various copper salts and other metal sources were investigated. The results are summarized in Table 2. CuCl and Cu(OTf)<sub>2</sub> (Tf = trifluoromethylsulfonyl) gave a product yield similar to that obtained with CuI (65%). In contrast, other metal co-catalysts, such as NiCl<sub>2</sub>, Ni(OAc)<sub>2</sub>, ZnCl<sub>2</sub>, AgOAc, and Ag<sub>2</sub>CO<sub>3</sub>, and the absence of a co-catalyst gave poor results. We chose CuI as a co-catalyst to avoid the interference of other anionic species in the reaction.

Then, we studied the effect of inorganic bases and equivalency (Table 3, Entries 1–13). The highest product yield was obtained with the use of 1.5 equiv. of  $Cs_2CO_3$ . In contrast, the absence of base resulted in a drastically lower yield of **3a** (Table 3, Entry 14).

The optimized reaction conditions furnished 3a with various types of solvents (Table 4). A quantitative yield was afforded upon using acetonitrile as the solvent (Table 4, Entry 8). In addition, we performed the reaction by using a mixture of water (0.5 mL) and acetonitrile (2 mL). As a result, the yield slightly declined to 91% (Table 4, Entry 10). We also examined the effect of reaction time and found that a quantitative yield could be obtained after 2 h (Table 5, Entry 6).



[a] Reaction conditions:  $Pd(OAc)_2$  (0.012 mmol), co-catalyst (0.12 mmol), PPh<sub>3</sub> (0.012 mmol), aryl iodide (0.6 mmol), bis-(pinacolato)diboron (0.9 mmol), KOtBu (0.9 mmol), THF (2 mL), H<sub>2</sub>O (0.5 mL), air, room temperature, 24 h. [b] Yield was determined by GC integration relative to hexamethylbenzene as an internal standard.

Table 3. Screening of bases for the Pd/Cu-catalyzed borylation reaction.  $^{\left[ a\right] }$ 

<b>1a</b> (1.0 equiv.)	Pd(OAc) Cul (2 PPh <sub>3</sub> B-B O 2 (1.5 equiv.) Pd(OAc) PPh <sub>3</sub> Dase (1 THF (2 mL) r.t. atmosphe	2 (2 mol-%) 0 mol-%) (2 mol-%) 1.5 equiv.) , H <sub>2</sub> O (0.5 mL) , 24 h ric conditions
Entry	Base	Yield <sup>[b]</sup> [%]
1	LiOtBu	57
2	NaOtBu	59
3	KOtBu	65
4	$K_3PO_4$	74
5	$K_2CO_3$	75
6	$Cs_2CO_3$	82
7	$Ag_2CO_3$	26
8	NaOH	58
9	KOH	57
10	CsOH·H <sub>2</sub> O	53
11	KOAc	69
12	KOMe	67
13	NEt <sub>3</sub>	65
14	_	5

[a] Reaction conditions:  $Pd(OAc)_2$  (0.012 mmol), CuI (0.12 mmol), PPh<sub>3</sub> (0.012 mmol), aryl iodide (0.6 mmol), bis(pinacolato)diboron (0.9 mmol), base (0.9 mmol), THF (2 mL), H<sub>2</sub>O (0.5 mL), air, room temperature, 24 h. [b] Yield was determined by GC integration relative to hexamethylbenzene as an internal standard.

We proceeded to apply this borylation reaction to various ratios of acetonitrile/water so that this protocol could meet the character of green chemistry (Table 6). Poor yields were obtained if the volume of water was increased, and the Table 4. Screening of solvents for the Pd/Cu-catalyzed borylation reaction.  $\ensuremath{^{[a]}}$ 



Entry	Solvent (mL)	Yield <sup>[b]</sup> [%]
1	dioxane (2)	68
2	DMF (2)	73
3	MeOH (2)	72
4	THF (2)	67
5	THF/H <sub>2</sub> O (2:0.5)	82
6	EtOH (2)	70
7	DMSO (2)	75
8	$CH_3CN(2)$	97
9	$H_2O(2)$	16
10	CH <sub>3</sub> CN/H <sub>2</sub> O (2:0.5)	91

[a] Reaction conditions:  $Pd(OAc)_2$  (0.012 mmol), CuI (0.12 mmol), PPh<sub>3</sub> (0.012 mmol), aryl iodide (0.6 mmol), bis(pinacolato)diboron (0.9 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.9 mmol), solvent (2 mL), air, room temperature, 24 h. [b] Yield was determined by GC integration relative to hexamethylbenzene as an internal standard.

Table 5. Effect of reaction time on the Pd/Cu-catalyzed borylation reaction.<sup>[a]</sup>



[a] Reactions were performed in air at room temperature for the time indicated with  $Pd(OAc)_2$  (0.012 mmol), CuI (0.12 mmol), PPh<sub>3</sub> (0.012 mmol), aryl iodide (0.6 mmol), bis(pinacolato)diboron (0.9 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.9 mmol), and CH<sub>3</sub>CN (2 mL). [b] Yield was determined by GC integration relative to hexamethylbenzene as an internal standard.

use of only water afforded a very low yield. Moreover, the product yield was found to be independent of the amount of solvent (Table 7).

On the basis of the above optimization results, we chose the following reaction conditions: a mixture of  $Pd(OAc)_2$  (2 mol-%), CuI (20 mol-%), PPh<sub>3</sub> (2 mol-%), and Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv.) in acetonitrile (2 mL) stirred at room temperature for 2 h, which provided **3a** in 97% yield.

Under the optimal reaction conditions, the scope of the substrates was next examined. Only aryl iodides were effective substrates, whereas aryl chlorides and bromides gave Table 6. Effect of water concentrations in  $CH_3CN$  on the Pd/Cucatalyzed borylation reaction.<sup>[a]</sup>

<b>1a</b> (1.0 equiv.)	+ $+ \begin{pmatrix} 0 & 0 \\ B - B' & 0 \\ 2 \\ (1.5 \text{ equiv.}) \end{pmatrix}$	Pd(OAc) <sub>2</sub> (2 mol-%) Cul (20 mol-%) PPh <sub>3</sub> (2 mol-%) Cs <sub>2</sub> CO <sub>3</sub> (1.5 equiv.) CH <sub>3</sub> CN, H <sub>2</sub> O r.t., 2 h atmospheric conditions	
Entry	CH <sub>3</sub> CN [mL]	H <sub>2</sub> O [mL]	Yield <sup>[b]</sup> [%]
1	2.5	0	72
2	2.0	0.5	91
3	1.5	1	81
4	1.0	1.5	47
5	0.5	2	17
6	0	2.5	18

[a] Reaction conditions:  $Pd(OAc)_2$  (0.012 mmol), CuI (0.12 mmol), PPh<sub>3</sub> (0.012 mmol), aryl iodide (0.6 mmol), bis(pinacolato)diboron (0.9 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.9 mmol), air, room temperature, 2 h. [b] Yield was determined by GC integration relative to hexameth-ylbenzene as an internal standard.

Table 7. Effect of solvent concentrations on the Pd/Cu-catalyzed borylation reaction.  $^{\rm [a]}$ 



[a] Reaction conditions:  $Pd(OAc)_2$  (0.012 mmol), CuI (0.12 mmol), PPh<sub>3</sub> (0.012 mmol), aryl iodide (0.6 mmol), bis(pinacolato)diboron (0.9 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.9 mmol), CH<sub>3</sub>CN (*n* mL), air, room temperature, 2 h. [b] Yield was determined by GC integration relative to hexamethylbenzene as an internal standard.

Table 8. Investigation of the substrate scope of the Pd/Cu-catalyzed borylation reaction.<sup>[a]</sup>



[a] Reaction conditions:  $Pd(OAc)_2$  (0.012 mmol), CuI (0.12 mmol), PPh<sub>3</sub> (0.012 mmol), aryl iodide (0.6 mmol), bis(pinacolato)diboron (0.9 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.9 mmol), CH<sub>3</sub>CN (2 mL), air, room temperature, 2 h. [b] Yield was determined by GC integration relative to hexamethylbenzene as an internal standard.

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the corresponding products in very low yields (Table 8, Entries 1 and 2). This result suggests that this protocol can be

Table 9. Screening of aryl iodides for the Pd/Cu-catalyzed borylation reaction.  $^{\left[ a\right] }$ 



[a] Reaction conditions: Pd(OAc)<sub>2</sub> (0.012 mmol), CuI (0.12 mmol), PPh<sub>3</sub> (0.012 mmol), aryl iodide (0.6 mmol), bis(pinacolato)diboron (0.9 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.9 mmol), CH<sub>3</sub>CN (2 mL), air, room temperature, 24 h. pin =  $1,2-O_2C_2Me_4$ . [b] Yield of isolated product. [c] Yield calculated by GC.

useful for chemoselective borylation at the C–I bond if other halogen substituents are present.

The present method could be applied successfully to a variety of aryl iodides bearing various types of functionalities. The results are summarized in Table 9. The scope of the aryl iodide derivatives was found to be remarkably broad. Excellent yields were obtained for substrates with both electron-donating and electron-withdrawing substituents (Table 9, Entries 2 and 3). The borylation reaction performed in air showed good tolerance for various functional groups, including hydroxide (**3d**), trifluoromethyl (**3e**), ketone (**3f**), amide (**3g**), and ester (**3h**) groups (Table 9, Entries 4–8).

Interestingly, excellent chemoselectivity was observed upon using 1-chloro-4-iodobenzene (1i) and 1-bromo-4iodobenzene (1j), as only monoborylated products 3i and 3j were obtained (Table 9, Entries 9 and 10). The remaining halogen and substituent groups are ready for further transformations. This advantage could find general usage in organic synthesis and polymerization. Introducing alkyl or dialkyl groups at the *ortho* positions of the aryl iodides (i.e., as in 1k and 1l) resulted in moderate yields (Table 9, Entries 11 and 12), presumably because the steric hindrance of the *ortho* substituents can hamper the oxidative addition step of the catalytic cycle. Additionally, heteroaromatic iodide 1m also gave the corresponding product 3m in a high yield (Table 9, Entry 13).

The mechanism of this transformation is assumed to involve oxidative addition of the aryl iodide and Pd<sup>0</sup> to form Pd<sup>II</sup> complex **5**, as presented in Scheme 1. Complex **5** reacts with an alkoxide base to form ArPd<sup>II</sup>–OR species **6**, which is more reactive than the ArPd<sup>II</sup>–X adduct.<sup>[1a]</sup> Copper iodide acting as a transmetalating agent reacts with the base and ligand to form L–Cu–OR intermediate **7**.<sup>[4b]</sup> Ligand exchange has been reported to occur between **7** and bis(pinacolato)diboron to afford intermediate **8**.<sup>[4b]</sup> Subsequently, **6** and **8** undergo transmetalation to form complex **9**, which induces regeneration of copper intermediate **7**. Finally, reductive elimination of **9** produces a new C–B bond of the corresponding borylation product. Further studies on the mechanism of this Pd/Cu-catalyzed borylation reaction are in progress in our laboratory.

#### Conclusions

An efficient Pd/Cu-catalyzed protocol for the borylation of aryl and heteroaryl iodides was developed. The synergistic catalysis can be performed in air at room temperature. This method serves as an inexpensive and convenient synthetic route to afford arylboronates. Chemoselectivity was observed in this catalytic combination. Furthermore, the reaction conditions are compatible with various sensitive functional groups, and high product yields are obtained.

**Supporting Information** (see footnote on the first page of this article): Experimental Section and copies of the <sup>1</sup>H, <sup>13</sup>C, and <sup>11</sup>B NMR spectra.



Scheme 1. Proposed plausible mechanism for the Pd/Cu-catalyzed Miyaura borylation reaction.

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