

Ligand-Free Copper-Catalyzed Borylation of Aryl and Benzyl Halides with Bis(pinacolato)diboron

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Abstract: The CuBr-catalyzed cross-coupling reaction of aryl iodides with B₂pin₂ in the absence of ligand has been developed for the preparation of arylboronates. The reaction was also suitable for the borylation of aryl bromides and benzyl halides, albeit in moderate yields.

Keywords: Aryl and benzyl halides, arylboronates, borylation.

INTRODUCTION

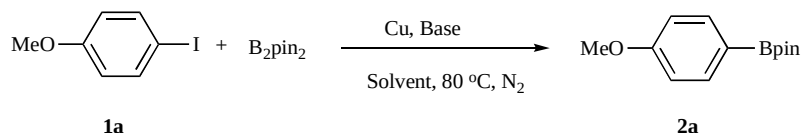
Arylboronic acids or arylboronates are very important intermediates in organic synthesis [1]. They have found wide applications in transition-metal-catalyzed cross-coupling reactions [2]. Due to their high stability and low toxicity, increasing attention has recently also been devoted to their applications in molecular recognition and pharmaceutical candidates [3]. The traditional route to these boron reagents involves the addition of aryl Grignard reagents or aryllithium reagents to trialkyl borates, followed by hydrolytic workup [4]. This methodology, although still widely used in industry as well as in academia, suffers some major drawbacks that are rigorous anhydrous conditions and the limitation of substrates. In 1995, Miyaura and co-workers developed a robust and highly efficient palladium-catalyzed method for the preparation of arylboronates [5a]. Palladium(0) species, generated in situ from PdCl₂(dppf), has been reported to be active catalysts for the cross-coupling reactions of diboron reagents with aryl iodides or bromides in homogeneous systems. Other palladium catalytic systems have also been developed in the borylation of aryl halides and aryl triflates with bis(pinacolato)diboron or pinacolborane [5]. Although these palladium catalysts exhibited high efficiency in the Miyaura borylation, the development of less expensive and environmentally more benign catalysts is more attractive for organic synthesis. A remarkable progress has recently been made in copper-catalyzed borylation of aryl halides [6]. In 2006, Ma and co-workers reported CuI-catalyzed cross-coupling reaction of aryl iodides with pinacolborane in the presence of sodium hydride at room temperature [6a]. However, their reaction required more reactive sodium hydride as a base and showed poor conversion for aryl bromides. In 2009, Marder and co-workers developed a simple and efficient process for the borylation of aryl halides with diboron reagents catalyzed by CuI and *n*Bu₃P under mild conditions [6b]. The reaction showed the broad scope of substrates and was also suitable for electron-rich and sterically hindered aryl bromides. This method represents a

cost-effective and environmentally friendly alternative to the widely employed palladium-catalyzed Miyaura borylation. However, the reaction must be handled in the glove box, because *n*Bu₃P is sensitive to air and water, which, to some extent, may increase the cost and limit the scope of applications. Therefore, it is desirable to find novel and ligand-free catalytic procedures for the preparation of arylboronates. Herein, we wish to report a ligand-free copper-catalyzed borylation of aryl halides with the diboron pinacol ester under mild conditions.

RESULTS AND DISCUSSION

On the outset of this investigation, 4-iodoanisole **1a** was chosen as model substrate with B₂pin₂ to screen suitable reaction conditions. According to the CuI-catalyzed borylation procedures reported by Ma and Marder, we found that the borylation indeed took place in the presence of CuI and *t*BuONa in THF, albeit in low yield (Table 1, entry 1). Next, a range of solvents were screened, such as PhMe, MeCN, Dioxane, DMF and DMSO. To our delight, the reaction afforded the borylation product **2a** with 19% and 56% yields in MeCN and DMF, respectively (Table 1, entries 3, 5). Other solvents were unsuitable for this reaction (Table 1, entries 2, 4, 6). Several other copper catalysts were then examined. The yield could be slightly improved by CuBr, whereas CuCl and Cu₂O resulted in diminished yields (Table 1, entries 7-9). It was found that Cu(II) did not show catalytic activity for the reaction (Table 1, entry 10). Switch of *t*BuONa to *t*BuOK led to slightly decrease yield (Table 1, entry 11). Other inorganic bases, such as KOAc, K₂CO₃ and K₃PO₄ might be too weak for this reaction, only trace amounts of the desired product were observed as shown by GC-Mass analysis (Table 1, entries 12-14). Surprisingly, Cs₂CO₃ was found to promote the reaction with 56 % yield (Table 1, entry 15). Increasing the catalyst loading and the amount of B₂pin₂ could slightly improve the yields (Table 1, entries 16-17). However, the yields of the reaction were slightly decreased by changing reaction temperature (Table 1, entries 18-19). Finally, for comparison the reaction was carried out in the absence of CuBr, no product **2a** could be detected (Table 1, entry 20).

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Table 1. Optimization of Copper-Catalyzed Borylation of 4-Iodoanisole **1a with B₂pin₂^a**

Entry	Cu Cat.(equiv)	Base (equiv)	Solvent	t (h)	Yield(%) ^b
1	CuI(0.1)	<i>t</i> BuONa(1.5)	THF	24	10
2	CuI(0.1)	<i>t</i> BuONa(1.5)	PhMe	24	Trace
3	CuI(0.1)	<i>t</i> BuONa(1.5)	MeCN	24	19
4	CuI(0.1)	<i>t</i> BuONa(1.5)	Dioxane	24	Trace
5	CuI(0.1)	<i>t</i> BuONa(1.5)	DMF	12	56
6	CuI(0.1)	<i>t</i> BuONa(1.5)	DMSO	24	Trace
7	CuBr(0.1)	<i>t</i> BuONa(1.5)	DMF	12	60
8	CuCl(0.1)	<i>t</i> BuONa(1.5)	DMF	12	46
9	Cu ₂ O(0.1)	<i>t</i> BuONa(1.5)	DMF	24	21
10	Cu(acac) ₂ (0.1)	<i>t</i> BuONa(1.5)	DMF	24	Trace
11	CuBr(0.1)	<i>t</i> BuONa(1.5)	DMF	12	50
12	CuBr(0.1)	KOAc(1.5)	DMF	24	Trace
13	CuBr(0.1)	K ₂ CO ₃ (1.5)	DMF	24	Trace
14	CuBr(0.1)	K ₃ PO ₄ (1.5)	DMF	24	Trace
15	CuBr(0.1)	Cs ₂ CO ₃ (1.5)	DMF	24	56
16	CuBr(0.2)	<i>t</i> BuONa(1.5)	DMF	12	67
17 ^c	CuBr(0.2)	<i>t</i> BuONa(1.5)	DMF	12	70
18 ^d	CuBr(0.2)	<i>t</i> BuONa(1.5)	DMF	24	56
19 ^e	CuBr(0.2)	<i>t</i> BuONa(1.5)	DMF	12	65
20 ^f	none	<i>t</i> BuONa(1.5)	DMF	12	0

^aUnless otherwise noted, the reaction conditions are as follows: **1a** (0.3 mmol), B₂pin₂ (1.5 equiv), Base (1.5 equiv), Solvent (2 mL), 80 °C, under N₂, ^bIsolated yield, ^cB₂pin₂ (2.0 equiv), ^d60 °C, ^e100 °C, ^fThe reaction was carried out in the absence of CuBr.

Under the optimized conditions, the substrate scope of this reaction was investigated (Table 2). The reaction with *ortho*-, *meta*-, and *para*-electron-donating substituted aryl iodides proceeded smoothly and afforded the corresponding borylation compounds in moderate yields (Table 2, entries 1-6). However, for acetyl and nitro-substituted aryl iodide, only small amounts of the desired products were detected by GC-Mass, and were not readily isolated (Table 2, entries 7, 8). The reaction with chloro-substituted aryl iodide afforded the lower yields under the standard conditions (Table 2, entry 9).

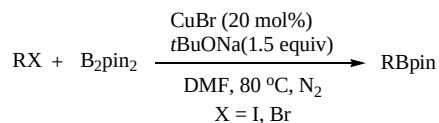
The procedure was also applicable to the borylation of benzyl halides. Benzyl bromide proceeded efficiently under the optimized conditions and gave 78% yield, while a lower yield was obtained for benzyl chloride (Table 2, entries 10, 11). Next we conceived to extend the coupling reaction to less active aryl bromides. The borylation of aryl bromides indeed took place under the standard conditions, but the reactions took longer and gave the lower yields than the borylation of aryl iodides (Table 2, entries 12-14).

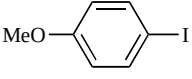
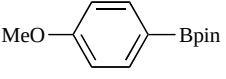
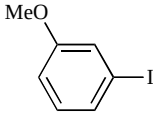
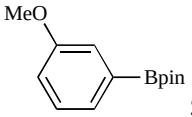
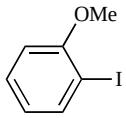
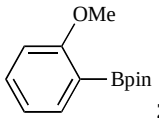
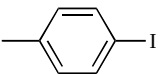
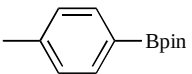
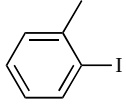
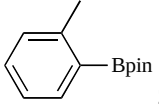
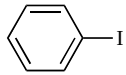
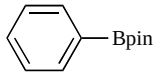
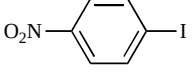
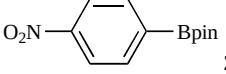
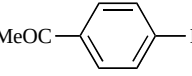
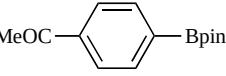
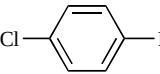
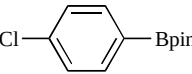
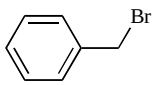
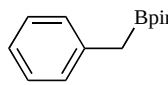
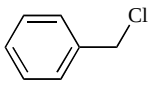
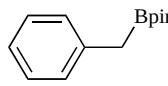
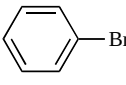
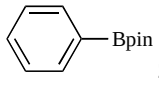
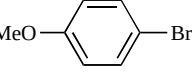
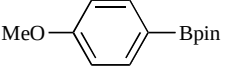
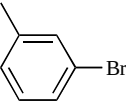
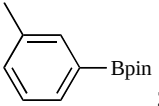
Although the detailed mechanism for this process awaits further investigation, we believe that the reaction goes through the formation of the corresponding copper-boryl

intermediate, as pointed out by Marder, etc. [7]. A tentative mechanism is proposed in Scheme 1. This reaction is initiated by the generation of borylcopper(I) intermediate **B** through the σ -bond metathesis reaction between diboron reagents and the active species **A** generated in situ from the precatalyst CuBr in the presence of sodium *tert*-butoxide. Borylcopper(I) intermediate **B** might be stabilized by the coordination of DMF to copper(I) in the absence of ligand. Next, σ -bond metathesis between borylcopper(I) intermediate **B** and an aryl halide affords the borylation product along with a CuX species. On the other hand, Oxidative addition of borylcopper(I) intermediate **B** with an aryl halide forms ArCu(III) intermediate **C**, followed by reductive elimination to give the borylation product and regenerate the catalyst CuX, based on Ullmann-type coupling reactions and the Miyaura-borylation reaction.

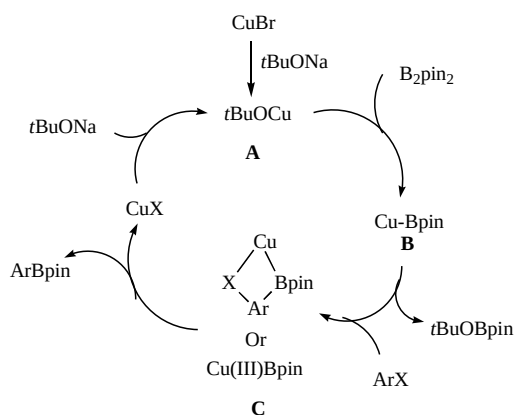
EXPERIMENTAL

Copper catalysts and aryl and benzyl halides were purchased from Alfa Aesar. Chloroform-*d* was purchased from Cambridge Isotope Laboratories. All solvents were distilled prior to use. THF was freshly distilled from Na before use. All reactions with air- and moisture-sensitive

Table 2. CuBr-Catalyzed Borylation of Aryl and Benzyl Halides with B₂pin₂^a

Entry	RX(1)	Products(2)	t (h)	Yield(%) ^b
1	 1a	 2a	12	67
2	 1b	 2b	12	60
3	 1c	 2c	12	53
4	 1d	 2d	24	60
5	 1e	 2e	24	48
6	 1f	 2f	24	63
7	 1g	 2g	24	Trace
8	 1h	 2h	24	Trace
9	 1i	 1i	24	30
10	 1j	 2j	12	78
11	 1k	 2j	24	32
12	 1l	 2f	36	51
13	 1m	 2a	36	58
14	 1n	 2n	36	52

^aUnless otherwise noted, the reaction conditions are as follows: **1** (0.5 mmol), B₂pin₂ (1.5 equiv), tBuONa (1.5 equiv), Solvent (3 mL), 80 °C, under N₂. ^bIsolated yield.



Scheme 1. Mechanistic Rationale.

components were performed under a nitrogen atmosphere in a flame-dried reaction flask. For chromatography, 200-300 mesh silica gel (Qingdao, China) was employed. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured on Bruker 400 M spectrometers and ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Bruker 300 M spectrometers. CDCl_3 was used as solvent with tetramethylsilane (TMS) as internal standard.

General Procedure for the Borylation of Aryl and Benzyl Halides

Aryl or benzyl halides (0.5 mmol), bis(pinacolato) diboron (1.5 equiv), CuBr (0.2 equiv) and tBuONa (1.5 equiv) were weighed in a 25 mL Schlenk round bottle flask under nitrogen atmosphere. The system was degassed four times by oil pump and then 3 mL DMF was added by syringe. The resulting reaction solution was stirred at 80 °C under the nitrogen. The reaction progress was monitored by GC-Mass. After the completion of the reaction, the solution was extracted with ethyl acetate (3×10 mL), then washed with H_2O and brine, dried (MgSO_4), and concentrated to dryness. Purification on silica gel (Petroleum ether / EtOAc, 10:1~30:1) gave the product.

Spectral Data for the Products

2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2a [6] (Table 2, entry 1)

^1H NMR (400 MHz, CDCl_3) δ ppm: 7.76 (d, $J = 1.8$ Hz, 2H), 6.89 (q, $J = 1.8$ Hz, 2H), 3.82 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 162.1, 136.5, 113.3, 83.5, 55.0, 24.8.

2-(3-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2b [6] (Table 2, entry 2)

^1H NMR (400 MHz, CDCl_3) δ ppm: 7.40 (d, $J = 11.2$ Hz, 1H), 7.33-7.28 (m, 2H), 7.02-6.99 (m, 1H), 3.83 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 159.0, 128.9, 127.1, 118.6, 117.9, 83.8, 55.2, 24.8.

2-(2-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2c [6] (Table 2, entry 3)

^1H NMR (400 MHz, CDCl_3) δ ppm: 7.69-7.66 (m, 1H), 7.41-7.37 (m, 1H), 6.94 (t, $J = 7.4$ Hz, 1H), 6.85 (d, $J = 8.3$

Hz, 1H), 3.83 (s, 3H), 1.35 (s, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 164.1, 136.7, 132.4, 120.2, 110.4, 83.4, 55.8, 24.8.

4,4,5,5-Tetramethyl-2-p-tolyl-1,3,2-dioxaborolane 2d [6] (Table 2, entry 4)

^1H NMR (400 MHz, CDCl_3) δ ppm: 7.70 (d, $J = 7.5$ Hz, 2H), 7.18 (d, $J = 7.5$ Hz, 2H), 2.36 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 141.4, 134.8, 128.5, 83.6, 24.8, 21.7.

4,4,5,5-Tetramethyl-2-o-tolyl-1,3,2-dioxaborolane 2e [6] (Table 2, entry 5)

^1H NMR (400 MHz, CDCl_3) δ ppm: 7.77 (d, $J = 1.4$ Hz, 1H), 7.33-7.29 (m, 1H), 7.16-7.14 (m, 2H), 2.54 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 144.8, 135.8, 130.8, 129.7, 124.7, 83.4, 24.9, 22.2.

4,4,5,5-Tetramethyl-2-phenyl-1,3,2-dioxaborolane 2f [6] (Table 2, entry 6)

^1H NMR (400 MHz, CDCl_3) δ ppm: 7.81 (d, $J = 6.7$ Hz, 2H), 7.47-7.43 (m, 1H), 7.38-7.35 (m, 2H), 1.34 (s, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 131.7, 131.2, 127.7, 83.7, 24.8.

2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2i [6] (Table 2, entry 9)

^1H NMR (400 MHz, CDCl_3) δ ppm: (d, 2H, $J = 8.4$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz), 1.34 (s, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 137.4, 136.1, 127.9, 120.7, 83.9, 24.8.

2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2j [6] (Table 2, entry 10)

^1H NMR (300 MHz, CDCl_3) δ ppm: 7.28-7.14 (m, 5H), 2.32 (s, 2H), 1.25 (s, 12H). ^{13}C NMR (75 MHz, CDCl_3) δ ppm: 138.6, 129.0, 128.5, 128.4, 128.3, 124.9, 83.4, 38.0, 24.7.

4,4,5,5-tetramethyl-2-m-tolyl-1,3,2-dioxaborolane 2n [6] (Table 2, entry 14)

^1H NMR (400 MHz, CDCl_3) δ ppm: 7.64-7.60 (m, 2H), 7.28-7.26 (m, 2H), 2.35 (s, 3H), 1.34 (s, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 137.1, 135.3, 132.0, 131.8, 127.7, 83.7, 24.8, 21.2.

CONCLUSION

In conclusion, we have demonstrated a ligand-free CuBr-catalyzed borylation of aryl halides with B_2pin_2 under mild conditions. It was considered that DMF used as a ligand might stabilize borylcopper(I) intermediate **B**. Although the reaction afforded the only moderate yields, there was a broad scope of substrates, especially including aryl bromides and benzyl halides. Further investigation of the detailed mechanism and the scope of substrates is currently underway in our lab.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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