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## COMMUNICATION

## Copper Nanoparticle-Catalyzed Borylation of Alkyl Bromides with Organodiboron Compound

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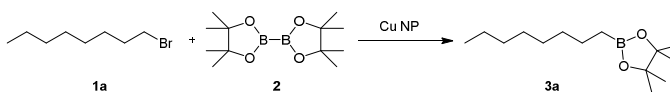
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**Borylation of primary and secondary alkyl bromides with bis(pinacolato)diboron was carried out in the presence of commercially available copper nanoparticles as catalysts. The reaction went to completion in the absence of phosphines at room temperature. The catalytic system showed high activity, broad substrate scope, and good functional group tolerance.**

The Suzuki–Miyaura cross-coupling reaction, catalyzed by a palladium(0) complex, and where the coupling partners are a boronic acid and a halide, shared the Nobel Prize for Chemistry 2010 because it was one of the most significant methodologies for the synthesis of biaryl compounds.<sup>1</sup> Over the past decades, the synthetically useful organoboron-containing compounds have been actively developed.<sup>2</sup> Recently, the transition metal-catalyzed borylation of the C–H bond has attracted much attention as an alternative method for the synthesis of the C–B bond.<sup>3</sup> Among the different transition metal–catalysts used for borylation reactions, palladium, nickel, and copper complexes are by far the most widely studied, mainly because of their extensive applicable scope, and compatibility with many functional groups.<sup>4–6</sup> However, most of the catalytic systems involve the use of toxic ligands such as phosphine compounds. Therefore, there is a need for the development of environment-friendly and economically more convenient catalytic systems. In this regard, the use of copper-based catalysts<sup>5</sup> is particularly attractive because they are inexpensive, readily available, and environmentally friendly. The use of an inexpensive Cu catalyst for the borylation of alkyl halides at room temperature was reported by Liu and Ito *et al.*<sup>6, 7</sup> Recently, the ligand-free copper-catalyzed borylation of benzyl halides with bis(pinacolato)diboron in DMF at 80 °C was reported by Yan.<sup>5c</sup> Previous studies on the copper-catalyzed cross-coupling reactions<sup>5, 6</sup> provided important motives to use copper nanoparticles (Cu NPs) as catalysts in the coupling reactions of alkyl halides with diboron reagents. It has been recently reported<sup>8</sup> that copper(II) oxide nanoparticles (CuO NPs) supported on magnesia exhibits complete chemoselectivity towards the monoborylation of alkynes in the presence of alkenes and triphenylphosphine. However, until now, the catalysis of such transformations by Cu NPs has not been reported yet. Therefore, we decided to study the use of Cu NPs in the borylation of alkyl halides with alkoxy diboron compounds. It was

found that Cu NPs were quite effective catalysts in the borylation of primary and secondary alkyl bromides with bis(pinacolato)diboron. Herein we communicate our preliminary results. Cu NPs could efficiently catalyze the cross-coupling of alkyl boronate with nonactivated alkyl bromides in the absence of phosphines at room temperatures.

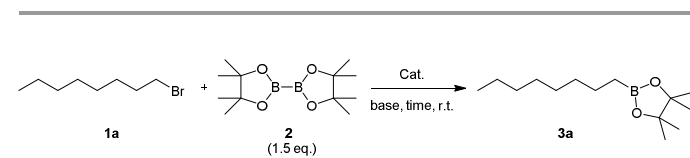


Scheme 1. Synthesis of alkylboronate via copper-nanoparticle catalyzed borylation of alkyl bromide.

The reaction of 1-bromooctane (**1a**) with bis(pinacolato)diboron (**2**) to produce pinacol alkylboronate (**3a**) was chosen as a model reaction in Scheme 1. We carried out the optimization of the catalyst system. The same catalyst that we have studied our previous report<sup>9</sup> was used. The results are summarized in Table 1. The treatment of **1a** with **2** in the presence of 15 mol% of Cu NPs and 2 equiv of LiOtBu in DMF at 25 °C for 18 h was found to produce the corresponding alkylboronate **3a** in a good yield (99%, entry 1). The reaction time could be decreased to 3 h without any loss in the yield (99%, entry 2). To improve the yield, different bases such as LiOMe, K<sub>2</sub>CO<sub>3</sub>, NaOH, and NaOMe were studied (entries 3 ~ 6). It was observed that the base LiOMe afforded good yields of the desired product (90%). However, other bases such as K<sub>2</sub>CO<sub>3</sub>, NaOH, and NaOMe were not as effective (yields: 32~ 69%). LiOtBu was found to be the best base giving a yield of 99 % (entry 2), but it was effective only for normal alkyl bromides. Thus, we chose LiOMe as the base in our reaction. The effect of various solvents on the reaction system was also examined (entries 7 ~ 9). It was observed that solvents, such as THF, toluene, and MeCN, were proven to be inefficient for this transformation, but the reasons for this are not very clear. DMF was found to give the best results and was used for further studies. When wet DMF was used as a solvent with a reaction time of 3 h, the yield decreased to ca. 80%. Liu *et al.*<sup>6</sup> reported that the addition of 4 equivalents of water reduced the yield from 91% to 77%. Thus, the reaction became slow in the presence of

water. Interestingly, in our case, the yield recovered to 91% for a reaction time of 6 h. The necessity of Cu NPs in the reaction was confirmed by the observation that no reaction was observed in their absence (entry 10). We also examined other metal compounds such as Pd(OAc)<sub>2</sub>, NiCl<sub>2</sub>, and CuO NPs as a catalyst under the optimized reaction conditions (entries 11 ~ 13). In the presence of Pd(OAc)<sub>2</sub>, no reaction was observed. However, in the presence of NiCl<sub>2</sub> and CuO NPs, the formation of **3a** was observed in 3% and 31% yields, respectively. Although our previous study<sup>9</sup> showed that CuO NPs were also an active catalyst in the C-C coupling reaction in the presence of Grignard reagents, the borylation reaction using CuO NPs was sluggish. Among the catalysts studied, no other catalysts afforded a higher yield than Cu NPs used. The possibility of contamination by palladium or nickel in the catalytic reaction was eliminated.<sup>10</sup>

Table 1. Screening reaction conditions



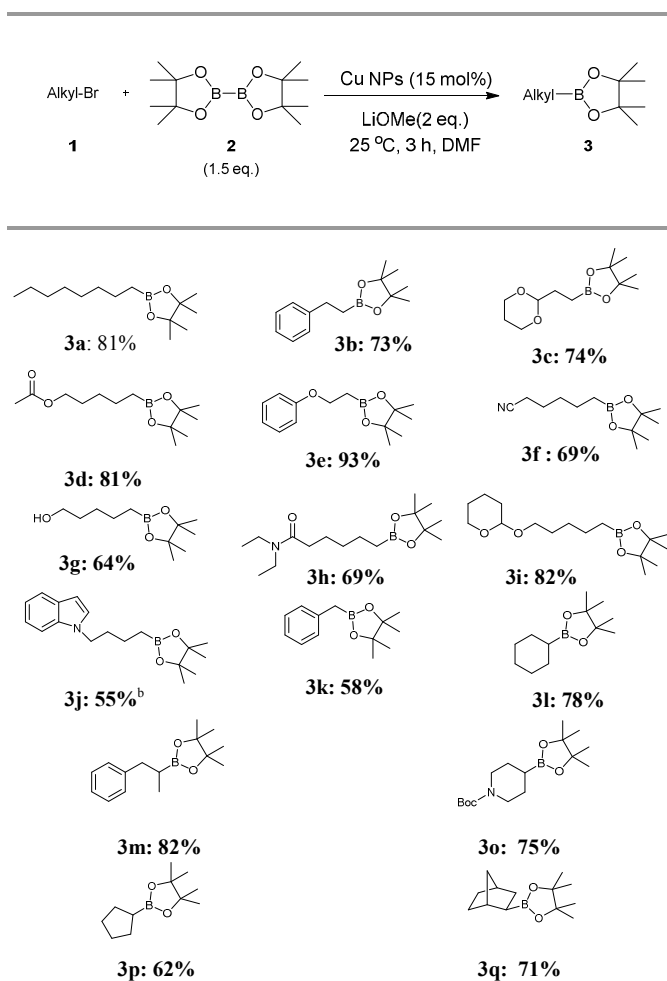
entry	Cat.	Cat. (mol%)	Base (2 eq.)	Solvent (1 mL)	Time (h)	Yield (%) <sup>a</sup>
1	Cu NP	15	LiOt-Bu	DMF	18	99
2	Cu NP	15	LiOt-Bu	DMF	3	99
3	Cu NP	15	LiOMe	DMF	3	90
4	Cu NP	15	NaOMe	DMF	3	32
5	Cu NP	15	K <sub>2</sub> CO <sub>3</sub>	DMF	3	43
6	Cu NP	15	NaOH	DMF	3	69
7	Cu NP	15	LiOMe	THF	3	0
8	Cu NP	15	LiOMe	Toluene	3	0
9	Cu NP	15	LiOMe	MeCN	3	0
10	No cat.		LiOt-Bu	DMF	3	0
11	Pd(OAc) <sub>2</sub>	15	LiOMe	DMF	3	0
12	NiCl <sub>2</sub>	15	LiOMe	DMF	3	3
13	CuO NP	15	LiOMe	DMF	3	31

<sup>a</sup> Determined by GC analysis using 1,3,5-trimethylbenzene as an internal standard.

With the optimized conditions in hand, we next investigated the substrate scope of the borylation of the alkyl bromides using **2** (Table 2).

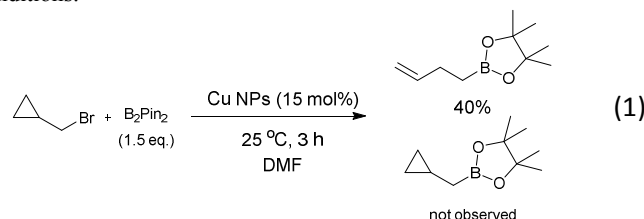
The yield ranged from 55% to 93%. The presence of functional groups (**3a-3k**), such as acetal, ester, hydroxy, amide, and cyano groups, and an ether linkage in the starting alkyl bromides **1** did not interfere with the outcome of the borylation with **1**. In particular, it is notable that even without a protecting group, the borylation reaction proceeds in the presence of a hydroxyl group (**3g**).<sup>6</sup> Compounds containing heterocyclic arenes, such as pyran and indole (**3i-3j**) are good substrates for the borylation. Interestingly, (2-bromoethoxy)benzene, which is known to undergo a C-O bond cleavage in the reaction with a Grignard reagent in the presence of Cu NPs,<sup>9</sup> afforded a high yield (93%) of the borylation product (entry 4). Compared to a homogeneous copper system (CuI and PPh<sub>3</sub>),<sup>7</sup> the Cu NP system showed a higher activity for some substrates having functional groups such as a hydroxyl, or an amide, but showed lesser activity for other substrates having nitrile, indole, or benzyl groups. However, it seems that the overall reactivity of the

Cu NP system seemed to be similar to that of the homogeneous copper system.

Table 2. Reaction scope of substrates<sup>a</sup>

<sup>a</sup> Yield of isolated product. <sup>b</sup> Reaction time was 6 h.

We also studied the borylation of secondary alkyl bromides under our optimized reaction conditions (**3i-3q**). For the borylation of *exo*-2-bromonorbornane, an overall retention of configuration was observed (**3q**).<sup>6</sup> Unactivated secondary alkyl halides could be borylated with good yields (62-82%). Cyclic and acyclic secondary bromides were easily borylated and a protected amine was also a good substrate. For cyclohexyl bromide, the yield was 78% at 25 °C for 3 h. This yield was higher than that (60%) observed in the presence of CuI and PPh<sub>3</sub> at 25 °C for 24 h by Liu et al<sup>6</sup> although they observed a 79% yield at a higher reaction temperature (37 °C). Thus, our catalytic system was highly effective for the borylation of primary and secondary alkyl bromides, but primary alkyl chlorides and tertiary alkyl halides were found to be inert under our reaction conditions.



To validate the reaction mechanism further, we carried out an experiment (eq. 1). When the borylation of cyclopropylmethyl bromide was carried out in the presence of Cu NPs, 3-butenylboronate was isolated in 40% yield and no simple boryl substitution product was observed. In contrast to the case of Cu NP-catalyzed coupling reaction in the presence of a Grignard reagent,<sup>9</sup> the observation of the ring-opening product provided an evidence for the formation of a radical intermediate, which suggests that the reaction probably proceeds via a radical pathway.

## Conclusions

We have developed a remarkably simple and general Cu NP-catalyzed borylation reaction under phosphine-free conditions. The Cu NPs used in this study are commercially available, and the catalytic system does not require any pretreatment or preformed supports and ligands. The catalytic system is quite effective for the borylation of unactivated primary and secondary alkyl bromides with organodiboron compounds. In view of the broad substrate scope, functional group tolerance, high reaction efficiencies, and high product yields, the Cu NP-catalyzed cross-coupling reaction can be expected to find wide synthetic applications. Further mechanistic studies are in progress.

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## Notes and references

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