



## Original article

## Expedient copper-catalyzed borylation reactions using amino acids as ligands

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## ABSTRACT

Amino acids were found to be as good ligands for copper-catalyzed borylation reactions of primary and secondary alkyl halides, and the B<sub>2</sub>pin<sub>2</sub> acted as bi-boron source for borylation. The high reaction efficiency and mild conditions make the new catalyst system a useful alternative to the recently developed methods for the preparation of alkylboronic esters.

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## 1. Introduction

Boron chemistry is one of the most important subjects in organic chemistry, and it attracted increasing attention because of their intrinsic scientific importance and industrial applications. Much attention has been focused on looking for easy and efficient ways to prepare organoboron reagents, which is an important reagent family in organic synthesis [1]. The traditional C–B formation *via* addition reaction of borane with alkenes or alkynes was conducted under harsh conditions. More recently, the C–B cross-coupling reaction of alkyl halides showed many advantages [2]. Due to the low price and toxicity, Cu salts have been widely reported as catalysts for cross-coupling reactions, which are valuable reactions for synthetic organic chemistry [3]. Copper-catalyzed reaction showed advantages including low toxicity, mild reaction conditions and wide substrate tolerance, but may suffer from several limitations such as low conversion efficiency [4]. Nonetheless, Marder and Liu *et al.* recently reported that CuI in the presence of phosphines catalyzed the borylation of primary and secondary alkyl halides and pseudo halides [5]. Previously, we reported that amino acid ligands could promote several types of transition metal-catalyzed reactions [6]. The amino acids as

ligands are especially interesting, because they are inexpensive, conveniently available, environmentally benign, and structurally diverse. Therefore, we recently initiated a project to study the copper-catalyzed borylation reactions with amino acids as ligands. Herein, we disclosed a method for mild copper-catalyzed borylation using amino acids as ligands, which showed low cost, low toxicity and high conversion efficiency.

## 2. Experimental

General procedure of amino acid/Cu borylation reaction: a mixture of bis(pinacolato)diboron (B<sub>2</sub>pin<sub>2</sub>, **1a**) (0.25 mmol), alkyl halide (0.38 mmol), Cu salt (10 mol% for B<sub>2</sub>pin<sub>2</sub>) and ligand (13 mol% for B<sub>2</sub>pin<sub>2</sub>), in 0.5 mL solvent is reacted under argon at 25 °C for 18 h. Then the solvent is evaporated, the residue is purified by chromatography to afford pure product.

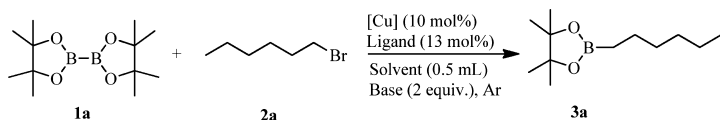
## 3. Results and discussion

Initially we repeated the previous procedure to couple diboron reagent of B<sub>2</sub>pin<sub>2</sub> with alkyl electrophile (Table 1, entry 1), and comparable yield (81%) was obtained. After a careful examination of the crude extract of the reaction mixture, we found excessive B<sub>2</sub>pin<sub>2</sub> were consumed. Therefore, we changed to use excessive bromohexane (0.38 mmol) in this reaction. A significantly high yield (128%) was observed, as calculated on the basis of B<sub>2</sub>pin<sub>2</sub> as

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**Table 1**  
Optimization studies for “Cu” catalyze the reaction of diboron reagent (**1a**) with alkyl electrophile (**1b**).<sup>a</sup>



Entry	Catalyst	Ligand	Base	Solvent	Yield (%) <sup>b</sup>
1	CuI	PPh <sub>3</sub>	<i>t</i> -BuOLi	DMF	81 <sup>c,d</sup>
2	CuI	PPh <sub>3</sub>	Li <sub>2</sub> CO <sub>3</sub>	DMF	Trace <sup>c,d</sup>
3	CuI	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	DMF	17 <sup>c,d</sup>
4	CuI	PPh <sub>3</sub>	<i>t</i> -BuOLi	DMF	(128 <sup>c</sup> )85
5	Cu(OAc) <sub>2</sub>	PPh <sub>3</sub>	<i>t</i> -BuOLi	DMF	92
6	Cu(CF <sub>3</sub> SO <sub>3</sub> ) <sub>2</sub>	PPh <sub>3</sub>	<i>t</i> -BuOLi	DMF	95
7	CuI	PPh <sub>3</sub>	<i>t</i> -BuOLi	Toluene	78
8	Cu(OAc) <sub>2</sub>	PPh <sub>3</sub>	<i>t</i> -BuOLi	Toluene	80
9	CuI	PPh <sub>3</sub>	<i>t</i> -BuOLi	DMF	96 <sup>e</sup>
10	CuI	DPEPhos	<i>t</i> -BuOLi	DMF	83
11	CuI	Johnphos	<i>t</i> -BuOLi	DMF	82
12	CuI	DPPP	<i>t</i> -BuOLi	DMF	43
13	CuI	DPPB	<i>t</i> -BuOLi	DMF	62
14	CuI	Dimethylglycine	<i>t</i> -BuOLi	DMF	75

<sup>a</sup> Conditions: “Cu” (10 mol% for bis(pinacolato)diboron), ligand [13 mol% for bis(pinacolato)diboron], **1a** (0.25 mmol), **2a** (0.38 mmol), solvent (0.5 mL), Ar, 25 °C, 18 h.

<sup>b</sup> Yield based on alkyl bromide and determined by GC-MS.

<sup>c</sup> Yield based on bis(pinacolato)diboron as mono-boron source.

<sup>d</sup> Reaction condition bis(pinacolato)diboron was excessive, **1a** (0.38 mmol), **2a** (0.25 mmol).

<sup>e</sup> KI was added.

mono-boron source (entry 2). The yield in excess of 100% indicated that the by products of B<sub>2</sub>pin<sub>2</sub> should be involved in the reaction. So, we calculated the yield based on alkyl bromide, and obtained the 85% yield, meaning much higher efficient boron conversion.

To develop more effective catalyst systems for this reaction, the effects of various copper salts, bases, solvents and ligands were investigated. The detailed results were listed in Table 1. Marder *et al.* [7] have demonstrated that *t*-BuOK is an effective generator of active nucleophile. When we replaced *t*-BuOLi with other bases, such as Li<sub>2</sub>CO<sub>3</sub> and Na<sub>2</sub>CO<sub>3</sub>, the yields decreased dramatically. To explore the role of *t*-BuOLi in the reaction, the verification experiments were carried out under the same conditions without bromohexane. B<sub>2</sub>pin<sub>2</sub> were completely degraded in the presence of *t*-BuOLi, indicating that *t*-BuOLi is involved in the initial step.

Fixing *t*-BuOLi as base, we explored the reaction with various Cu salts. Cu(CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> gave a better yield (95%) than CuI (85%) and Cu(OAc)<sub>2</sub> (92%) (entries 5 and 6). The reactions in DMF were better than in toluene, maybe due to the solubility of salts (entries 7 and 8). With the addition of KI, the yield was as high as 96%. The various ligands were performed in the presence of CuI/*t*-BuOLi system in DMF, and it was found that ligands played an important role in the reactions. Phosphine ligands of DPEPhos, Johnphos gave much better yields (entries 10 and 11) than the DPPP and DPPB (entries 12 and 13). Notably, the amino acid of dimethylglycine acted as a good ligand as well, and yield was as high as 75%.

The application of amino acids and their derivatives as ligands in synthetic organic chemistry promoted by the ruthenium, rhodium or iridium complexes has attracted more and more attentions [8]. Therefore, we turned our attention to amino acid catalyzed borylation of B<sub>2</sub>pin<sub>2</sub> with bromohexane (Table 2). Cu(CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> was better Cu salt than Cu(OAc)<sub>2</sub> and CuI, and gave the yield as high as 92%. Using the reaction procedure for Cu(CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub>/dimethylglycine, we also examined other amino acids as ligands for the borylation. It is found that in addition to dimethylglycine, one can also use natural amino acids of L-proline, L-α-alanine, L-phenylalanine and L-cystine. They all give quite similar yields regardless of the properties of the side chains. It is worthy to mention that the coupling between bromohexane or

B<sub>2</sub>pin<sub>2</sub> with the amino groups on the amino acid moiety was negligible in all the amino acid catalyzed borylation reaction as tested by GC/MS. Therefore, we conclude the reaction conditions in entry 3, Table 2 were optimal for further investigation on the reaction scope.

With the conditions in entry 3 (Table 2), we set out to carry out the reactions of B<sub>2</sub>pin<sub>2</sub> with various alkyl bromide substrates, as shown in Table 3. The secondary alkyl bromides of cyclopentane and cyclohexane bromides worked fairly well, giving the desired products in good yields of 80% and 75%, respectively (entries 1 and 2). For primary alkyl bromides, it was found that a variety of substituent, such as ether, nitrile and alkene, could be tolerated in the amino acid-mediated amidation reaction. Interestingly, alkene group kept stable (entries 3–5). The reaction also proceeded well with aryl bromide (yield 75%). To our disappointment, alkyl chloride failed to give the corresponding product, due to the low activity of chloro (entry 7).

Furthermore, the reactions between bis(neopentyl glycolato)-diboron (**1b**) with alkyl bromides were also investigated under identical conditions (Table 4). To our delight, most substituted alkyl bromides were well tolerated under the optimized conditions, leading to the desired products in moderate to good yields. Similar as B<sub>2</sub>pin<sub>2</sub>, both of primary and secondary alkyl bromides reacted well (entries 1–3), and many substituents could be tolerated, including

**Table 2**

The reaction of diboron reagent (**1a**) with alkyl electrophile (**1b**) with various amino acids as ligands.<sup>a</sup>

Entry	Catalyze	Ligand	Yield (%) <sup>b</sup>
1	CuI	Dimethylglycine	75
2	Cu(OAc) <sub>2</sub>	Dimethylglycine	83
3	Cu(CF <sub>3</sub> SO <sub>3</sub> ) <sub>2</sub>	Dimethylglycine	92
4	Cu(CF <sub>3</sub> SO <sub>3</sub> ) <sub>2</sub>	L-proline	82
5	Cu(CF <sub>3</sub> SO <sub>3</sub> ) <sub>2</sub>	L-α-alanine	84
6	Cu(CF <sub>3</sub> SO <sub>3</sub> ) <sub>2</sub>	L-phenylalanine	85
7	Cu(CF <sub>3</sub> SO <sub>3</sub> ) <sub>2</sub>	L-cystine	87

<sup>a</sup> Conditions: “Cu” (10 mol% for B<sub>2</sub>pin<sub>2</sub>), ligand (13 mol% for B<sub>2</sub>pin<sub>2</sub>), **1a** (0.25 mmol), **2a** (0.38 mmol), solvent (0.5 mL), Ar, 25 °C, 18 h.

<sup>b</sup> Yield based on alkyl halides and determined by GC-MS.

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