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#### Short communication

# A green and recyclable chitosan supported catalyst for the borylation of $\alpha$ , $\beta$ -unsaturated acceptors in water



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#### ABSTRACT

We herein report a green and recyclable chitosan supported copper catalyst which is capable of catalyzing the borylation of  $\alpha$ , $\beta$ -unsaturated acceptors in water at room temperature. A broad substrate scope including chalcone derivatives, esters and nitriles have been explored. In all the cases, desired products were obtained in good to excellent yields. Remarkably, this chitosan supported catalyst could be recovered and reused for five times without any significant decrease of reactivity.

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#### 1. Introduction

Organoboron derivatives are one of the most important intermediates because the C-B linkages can be transferred to C-O, C-N and C—C bonds [1]. In contrast to the classical methods, transition metalcatalyzed boron conjugate additions to  $\alpha$ , $\beta$ -unsaturated carbonyl and related compounds provide most efficient and straightforward pathway to form functionalized organoboron reagents [2]. After Hosomi [3] and Miyaura's [4] exploration of this area, borylation of  $\alpha_{\beta}$ -unsaturated acceptors have been successfully achieved by using various transition metal catalysts, such as Rh [5], Ni [6], Pt [7], Pd [8], Zn [9] etc. Among the other reported catalysts, Cu-based catalyst has drawn substantial attention for this transformation because of its inexpensiveness, lower toxicity and abundance. Although Cu<sup>1</sup>-based catalyst [10] effectively catalyzes boron conjugate addition reaction still, it particularly involves complicated experimental procedures, requires strong base and is mainly limited to homogeneous systems. On the other hand, Cu<sup>II</sup>catalyzed borylation [11,12] which was recently developed, exhibited a more green and convenient pathway by using only water as solvent. In order to further fulfill the requirements of sustainability, development of alternative highly active and low cost heterogeneous Cu<sup>II</sup> based catalyst for recycle and reuse is still highly desirable.

Immobilization of metal catalysts on heterogeneous support is one of the best solutions to overcome the problems associated with recovery and reuse of expensive homogeneous catalysts and to avoid product contamination [13]. Also, recovery and recyclability of immobilized metal catalysts makes the whole protocol green and sustainable both economically and environmentally. Magnetic materials [14], silica [15], zeolites [16] and polymers [17] were successfully employed as the support in the past. Recently, chitosan (CS) has attracted significant interest due to its green property, stability and ability of chelation [18]. Several examples have been reported by using chitosan-supported metal catalvst for C—C [19], C—N [20], C—S [21] and C—O [22] bond formation. However, to best of our knowledge, no such example of C-B bond formation has yet been reported before and it still remains a challenge. In 2013, Časar et al. [23] disclosed that D-glucosamine could be used as ligand for the borylation in the presence of basic CuCO<sub>3</sub>. This result indicated the possibility of applying chitosan as support towards similar transformation. In this work, we describe a new strategy towards the borylation of  $\alpha$ , $\beta$ -unsaturated acceptors by utilizing a heterogeneous, green and recyclable chitosan supported copper catalyst.

#### 2. Methods

#### 2.1. Materials

<sup>1</sup> These authors contributed equally.

Reagents were commercially supplied and used as received. Chitosan was purchased from Aldrich (medium molecular weight, CAS

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9012-76-4). CS@Cu(OH)<sub>2</sub>, CS@CuO [24] and other CS@Cu catalysts [21] were prepared following the procedures reported.

#### 2.2. Analytical methods

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance 500 or 600 MHz spectrometers at ambient temperature. Data for <sup>1</sup>H NMR are reported as follows: chemical shift (ppm, scale), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiplet resonances, br = broad), coupling constant (Hz), and integration. Data for <sup>13</sup>C NMR are reported in terms of chemical shift (ppm, scale), multiplicity, and coupling constant (Hz). Flash column chromatographic purification of products was accomplished using forced-flow chromatography on Silica Gel (200–300 mesh). High Resolution Mass Spectra (HRMS) were recorded using a JEOL JMS-700 spectrometer. The weight percentage and metal leaching of copper were determined by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis. The copper loading of CS@Cu(OH)<sub>2</sub> was found to be 1.50 mmol/g.

Procedure for the preparation of sample for ICP analysis to determine the catalyst loading: Catalyst (~20 mg) was placed in a clean test tube and heated with  $H_2SO_4$  (1 mL) at 200 °C. After 30 min, several drops of concentrated HNO<sub>3</sub> were added carefully and the tube was shaken occasionally. HNO<sub>3</sub> was continuously added until a clear solution was obtained and excess amount of HNO<sub>3</sub> was allowed to evaporate under heating. After the solution was cooled to room temperature, 1 mL of aqua regia was added carefully. Effervescence of gas was observed and the solution becomes clearer. The solution was then transferred to a volumetric flask and made up to 50 mL with water which was submitted for ICP analysis.

Procedure for the preparation of ICP analysis to determine the metal leaching: After the reaction was finished, the reaction mixture was filtered. The filtrate obtained was concentrated and diluted with 10 mL of THF. Then 50% v/v of the crude THF solution (5 mL) was then passed through a membrane filter (0.25 or 0.45  $\mu$ m) into a clean test tube. After evaporation of solvent, the solid obtained in the test tube was heated to 200 °C and 1.0 mL of concentrated H<sub>2</sub>SO<sub>4</sub> was added. Following similar procedure described above, concentrated HNO<sub>3</sub> were added at regular

#### Table 1

Optimization of reaction conditions<sup>a</sup>.

 $\begin{array}{c|c} O & Support@Cu (5 mol% Cu) \\ \hline \\ 1a & + B_2(pin)_2 & H_2O, rt, 12 h \end{array} \begin{array}{c} O & B(pin) \\ \hline \\ H_2O, rt, 12 h & 2a \end{array}$ 

intervals until the resulting solution was clear. After the solution was cooled to room temperature, 1 mL of aqua regia was added carefully. Effervescence of gas was observed and the solution becomes clearer. The solution was then transferred to a volumetric flask and made up to 50 mL with water which was submitted for ICP analysis.

## 2.3. General procedure for CS@Cu catalyzed borylation of $\alpha_i\beta$ -unsaturated acceptors in water

CS@Cu(OH)<sub>2</sub> (6.7 mg, 5 mol% Cu loading) and **L4** (2.4 mg, 6 mol%) were mixed in water (2 mL). The mixture was stirred for 1 h at room temperature, followed by successive addition of chalcone **1a** (41.0 mg, 0.2 mmol) and B<sub>2</sub>(pin)<sub>2</sub> (60.9 mg, 0.24 mmol). After stirring for 12 h at room temperature, the reaction mixture was filtered and washed with THF (3 mL). Excess amount of NaBO<sub>3</sub>·4H<sub>2</sub>O (244 mg) was then added to filtrate and the mixture was stirred at room temperature for 4 h. The aqueous layer was extracted with EtOAc (20 mL) three times, and the combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After concentrated under reduced pressure, the crude mixture was purified by preparative TLC (<sup>*n*</sup>hexane/EtOAc = 4/1) to afford the desired product **3a** (45.3 mg, quant.).

#### 3. Results and discussion

We conducted the reaction of bis(pinacolato)diboron  $(B_2(pin)_2)$  with chalcone **1a** in water by using  $Cu(OH)_2$  as catalyst, 2,2'-bipyridine ligand **L1** as additive. The desired 1,4-addition product **2a** was obtained in 93% yield with 1.6% leaching (Table 1, entry 1). Since  $Cu(OH)_2$  is almost insoluble in water, metal leaching could probably be ascribed to the generation of pinBOH by-product [12] during the reaction process. Based on the catalytic cycle [11], stoichiometric amount of pinBOH was generated as by-product which presumably might be absorbed on the surface of CS@Cu catalyst and caused the metal leaching. When we tried to immobilize  $Cu(OH)_2$  on series of different supports, the yield decreased in all cases (Table 1, entries 2–4). However, chitosan (CS) could give comparable results with non-immobilized  $Cu(OH)_2$  (Table 1, entry 5). To be mentioned, this reaction could also proceed

Entry	Metal salts		Support	Ligand	Yield (%) <sup>b</sup>	Leaching (%) <sup>c</sup>
1	Cu(OH) <sub>2</sub>		-	L1	93	1.6
2	Cu(OH) <sub>2</sub>		TiO <sub>2</sub>	L1	64	0.7
3	$Cu(OH)_2$		Fe <sub>3</sub> O <sub>4</sub>	L1	52	16.5
4	$Cu(OH)_2$		SiO <sub>2</sub>	L1	69	1.2
5	$Cu(OH)_2$		Chitosan	L1	90	0.7
6	Cu(OH) <sub>2</sub>		Chitosan	-	47	1.1
7	CuCN		Chitosan	L1	NR	No leaching <sup>d</sup>
8	CuSO <sub>4</sub>		Chitosan	L1	46	65.7
9	CuCl <sub>2</sub>		Chitosan	L1	37	59.0
10	CuF <sub>2</sub>		Chitosan	L1	71	25.6
11	CuBr <sub>2</sub>		Chitosan	L1	39	72.1
12	CuO		Chitosan	L1	17	3.9
13	Cu(OH) <sub>2</sub>		Chitosan	L2	83	1.4
14	Cu(OH) <sub>2</sub>		Chitosan	L3	91	No leaching <sup>d</sup>
15	Cu(OH) <sub>2</sub>		Chitosan	L4	Quant.	No leaching <sup>d</sup>
	N Si	N N H	H N O			
L1	L2	L3	L4			

<sup>a</sup> Reaction conditions: substrate 1 (0.2 mmol), B<sub>2</sub>(pin)<sub>2</sub> (1.2 equiv), Support@Cu (5 mol% Cu loading), L (6 mol%), H<sub>2</sub>O (2 mL), rt, 12 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by ICP analysis.

<sup>d</sup> Under detection limit.





<sup>a</sup> Reaction conditions: substrate **1** (0.2 mmol), B<sub>2</sub>(pin)<sub>2</sub> (1.2 equiv), CS@Cu(OH)<sub>2</sub> (5 mol% Cu loading),

L4 (6 mol%), H2O (2 mL), rt, 12 h

<sup>b</sup> Isolated yields were shown.

without any external ligand, but significant decrease of reactivity accompany with metal leaching was observed (Table 1, entry 6). Ligand was known to be crucial for the improved reactivity of borylation by coordination to metal center [10,23].

Next, we examined various chitosan supported copper (CS@Cu) catalysts obtained from different copper salts. It was found CS@CuCN gave no desired products although no metal leaching was observed (Table 1, entry 7). Catalyst derived from soluble copper salts caused serious metal leaching problems (Table 1, entries 8-11). CS@CuO prepared from insoluble CuO resulted in very poor reactivity (Table 1, entry 12). Following, other types of pyridine ligands [25] were tested to avoid the leaching of copper from chitosan support. Silane-type pyridine ligand is known to possess a good affinity towards chitosan. However, the leaching level could not be suppressed and yield decreased when L2 was used (Table 1, entry 13). To our delight, pyridine ligand substituted with aliphatic secondary amine L3 could give the desired product in 91% yield without any metal leaching. Finally, in the presence of amide-type pyridine ligand L4, the desired product 2a was obtained in quantitative yield and no metal leaching was observed (Table 1, entry 15).

Under the optimized conditions, the substrate scope of  $\alpha,\beta$ -unsaturated acceptors was surveyed and the results are summarized in Table 2. Chalcone derivatives bearing mono- or di-substituted functional groups are suitable substrates and the corresponding 1,4-adducts were obtained in good to excellent yields. By successive oxidation of achieved organoboron compounds [26], the  $\beta$ -hydroxy products could be directly synthesized (**3a-3h**). Both electron-withdrawing and electron-donating groups could be applied. Borylation of  $\alpha,\beta$ -unsaturated ketones having aromatic-aliphatic structures all proceeded well under the optimized conditions (**3i**, **3j**, **3l**), even where steric hindrance existed (**3k**). Methyl- and Ethyl- esters were also well tolerated (**3m**, **3n**). It is worth mentioning that  $\beta$ -hydroxy nitriles (**3o**) which have emerged as versatile synthons for several natural products [27] and pharmaceuticals [28] was obtained in 82% yield. The nitrile group can be further transformed to other functional groups such as amides [29], carboxylic acids [30], and so on.

In order to illustrate the practical applications of such heterogeneous catalytic system, the recovery and reuse of catalyst are very important factors. Actually, the  $CS@Cu(OH)_2$  catalyst remained insoluble during the reaction process and after the completion of reaction. It could be easily removed and recovered from the reaction mixture by simple filtration process when reaction was finished. The recovered catalyst was washed slightly by diethyl ether, dried and then directly used for next cycle. Up to five reused cycles, the desired product was all obtained in excellent yields (Fig. 1) and no metal leaching was observed. Although slightly decrease of yield was found in the fifth run, the



Fig. 1. Recovery and reuse of catalyst. Reaction conditions: see Table 1, entry 15. The catalyst was washed with NaHCO<sub>3</sub>(aq) during the sixth run.

catalyst can be activated again by treatment with a queous  $\ensuremath{\mathsf{NaHCO}}_3$  solution.

#### 4. Conclusion

In conclusion, we have demonstrated that borylation of  $\alpha$ , $\beta$ unsaturated acceptors can be achieved by using a chitosan supported Cu(OH)<sub>2</sub> catalyst. Various substituted  $\alpha$ , $\beta$ -unsaturated ketones and esters could be applied under the optimized conditions.  $\beta$ -hydroxy nitriles could also be obtained by this new developed method. Remarkably, this chitosan supported copper catalyst could be easily recovered and reused for five cycles without any significant decrease of reactivity.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.catcom.2016.08.002.

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