Chemically Modified Chitosan as a Biopolymer Support in Copper-catalyzed *ipso*-Hydroxylation of Arylboronic Acids in Water

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In the past decade, copper complexes have been extensively studied and employed in organic transformations.[1] Among these applications, the copper-catalyzed hydroxylation of boronic acids is considered a facile protocol for the preparation of alcohols.[2]

Noting the significant usefulness of copper-catalyzed transformation in organic synthesis, we sought to design an alternative greener pathway utilizing biopolymers and environmentally friendly reaction conditions.

To achieve this aim, we were interested in utilizing chitosan generated by the deacetylation of chitin, the second-most abundant natural polysaccaharide after cellulose. Owing to its combination of unique characteristics, chitosan is used in the form of an unmodified polymer or as modified derivatives in various applications. This is especially true in the presence of readily functionalizable primary amino groups that enable easy and effective chemical modification of the material, thereby imparting several desirable chemical and biological properties.[3]

In general, the polymer-surface modification through the introduction of new complexation groups may result in the formation of different chelating sites. These sites yield considerable changes in the adsorption capacity and the chemical reactivity of the complexed metal ion in solution.

Numerous protocols have been used for chemical modification of chitosan over the last decades. However, the introduction of pyridine derivatives into the chitosan backbone (resulting in Schiff base formation) has recently gained significant attention. One reason for such attention is that this protocol can be applied to metal absorption, antimicrobial activity, gene delivery, sensor applications, and biomedical applications.[4] Presumably, the capacity characterizing imine functionality of chitosan can enhance the metal chelating ability, thereby promoting the catalytic activity of the metal.

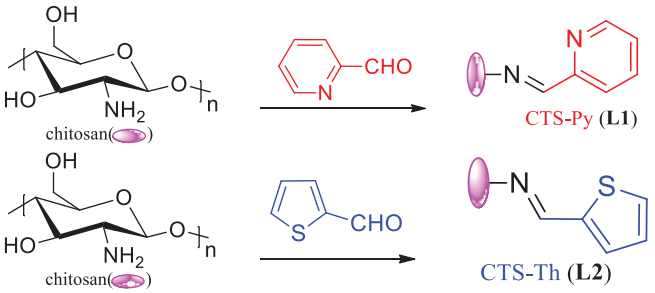
Considering these aspects, we decided to prepare a modified-chitosan platform with pyridine (**L1**), and then investigate its applicability in the most robust and useful reaction called *ipso*-hydroxylation of boronic acids, in conjunction with copper catalyst. In addition, to compare the active role of the pyridine moiety in the chitosan backbone, an alternative chitosan platform (**L2**) modified with thiophene rings was also prepared and applied to the *ipso*-hydroxylation of boronic acids.

A straightforward method for the synthesis of pyridine- or thiophene-modified chitosan supports (CTS-Py, **L1**, and CTS—Th, **L2**, respectively, hereafter) is shown in Scheme 1. Quantifiable yields of modified chitosan derivatives (**L1** and **L2**) were obtained upon the treatment of chitosan with 2-pyridinecarboxaldehyde or 2-thiophenecarboxaldehyde in ethanol at a refluxing temperature.[5] Results of ^{1}H, ^{13}C NMR spectra, and IR spectra corresponded closely to the literature values.[6]

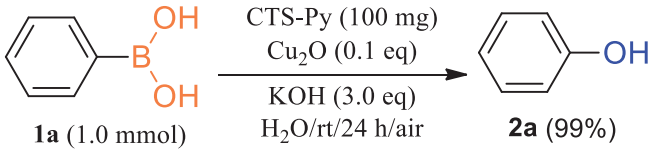
Strong and broad OH absorption bands observed at 3435 and 3300 cm^{-1} in the IR spectra of **L1** and **L2**, respectively. The diagnostic peak occurring at 1649 cm^{-1} corresponded to the condensation of pyridine (or thiophene)-aldehyde with the amino group of the chitosan, suggesting the formation of the imine unit.

On the basis of the ligand-acceleration effect, we hypothesized that anchoring an appropriate copper salt onto the modified-chitosan (**L1**) surface would enhance the catalytic activity of the chelating copper-metal. We evaluated the putative catalytic activity of **L1** by applying this platform to the *ipso*-hydroxylation of arylboronic acids in cooperation with copper salts.

As shown in Table 1, several copper salts along with an appropriate ligand or support in the absence of the most popular oxidant (*i.e.*, H_2O_2) have been frequently employed in the *ipso*-hydroxylation of boronic acids. Notwithstanding the good results obtained via the aforementioned protocols, tremendous efforts continue to be devoted to improving the efficiency of the process, with particular focus on greener reaction conditions. Given the aspects of sustainable chemistry, bio-friendly and eco-friendly reaction platforms could be a suitable approach to reducing the economic and environmental burden of various chemical processes. To address this issue, we sought potential greener reaction conditions, such as the use of a natural bio-support under



Scheme 1. Preparation of CTS-Py (**L1**) and CTS-Th (**L2**).



Scheme 2. Optimized reaction conditions for **L1** promoted *ipso*-hydroxylation of **1a.**

aerobic conditions to promote the hydroxylation of arylboronic acid.

Our first investigation was aimed at hydroxylation of phenylboronic acid (**1a**) under the various conditions (see Supporting Information for details) to identify a suitable copper salt that generating the optimal isolated yield of phenol (**2a**). As depicted, the general reaction conditions were as follows; 1.0 mmol of **1a**, variable amount of **L1**, 3.0 equiv of base, water as a solvent, and 24 h of stirring at room temperature (Scheme 2).

Under the conditions employed (entry 1), no reaction occurred in the absence of the copper catalyst, whereas the addition of copper catalyst was quite effective in producing phenol (entry 2). Based on these results, various copper salts were immediately examined to identify the copper catalyst most suitable for efficient conversion. The use of $CuSO_4{\cdot}5H_2O$, $CuCl_2{\cdot}2H_2O$, and CuBr generated moderate yields (entries 2–5) of the hydroxylation product, but using CuI (entry 6) produced significantly higher yield. The highest yield was achieved when the reaction was executed with Cu_2O (entry 7). Using this copper salt (Cu_2O), further examinations were performed to identify other variables of our catalytic system. The level of hydroxylation achieved was strongly affected by the amount of **L1** (entries 3, 8–10). A subsequent screening test revealed that using a suitable amount of Cu_2O was also relatively critical for achieving effective transformation (entries 11 and 12). Next investigations were focused on the base effect. Several bases such as NaOH, K_2CO_3, Na_2CO_3, $NaHCO_3$, and Cs_2CO_3 were employed under the aforementioned conditions. These bases had a significant effect on the isolated yield of **2a** (entries 13–17). Additional examinations with organic bases such as pyridine and triethylamine provided no considerable improvement (entries 18 and 19). The effect of the pyridine ring was verified by exploring the possibility of a chitosan-induced ligand effect on our system. The result obtained from using pristine chitosan clearly revealed the essential role of pyridine moiety on the chitosan back bone (entry 20). Finally, it was also clarified that appropriate amounts of base (3.0 equiv) are required for achieving satisfactory result (entry 21).

Having identified the optimal conditions, we then explored the versatility and applicability of our platform, **L1** and **L2**, to the synthesis of hydroxy compounds utilizing various boronic acids (Table 2). Regardless of the electronic properties characterizing the arylboronic acids, the transformation was successful, resulting in the corresponding phenolic compounds in moderate to high yields. Of significant, the present catalytic system exhibited considerable tolerance to various functional groups such as alkoxy (**2f–2 h**), amino (**2i**), carbonyl (**2j-2k**), cyano (**2 L**), nitro (**2 m**), chloro (**2n**), and phenyl (**2o**) functionalities. However, the conversion of 1-naphthalene boronic acid was inefficient, as evidenced by an extremely low isolated yield of **2p**. The reason for this inefficiency remains unclear. Although occurring in relatively low yields, heteroaryl boronic acids were also amenable to this protocol. A couple of heteroaryl boronic acids were examined under the same conditions, leading to the desired products (**2q** and **2r**). Unfortunately, using our system, the hydroxylation of phenyl-1,4-diboronic acid providing hydroquinone was unsuccessful.

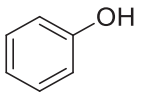
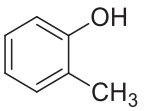
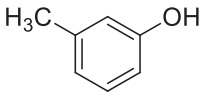
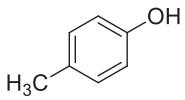
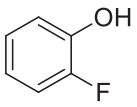
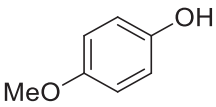
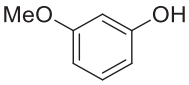
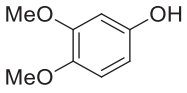
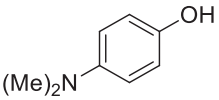
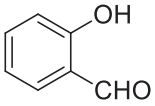
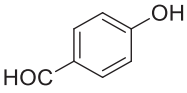
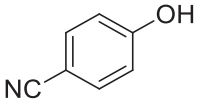
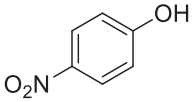
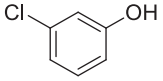
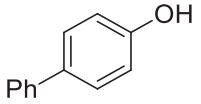
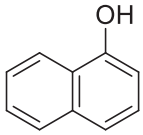
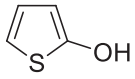
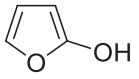
Our next set of experiments focused on exploring the role of the organic moiety bonded to the chitosan backbone. As previously mentioned, we assumed that the catalytic activity of copper could be affected by the chelating sites. This hypothesis was investigated by introducing a

Table 1. Previous works for copper-catalyzed *ipso*-hydroxylation of boronic acids.

Entry	Copper	Support	Conditions	Yield (%)[a]	Reference
1	$CuSO_4$	Phenanthroline	KOH/H_2O/rt./3 h	90	Ref. 2h
2	$CuCl_2$	Brij S-100	Surfactant/H_2O/rt./6 h	95	Ref. 2g
3	Cu(OH)x	Clay	H_2O/rt./20 min	98	Ref. 2e
4	$CuSO_4$	Ellagic acid NP	MeOH/60°C/8 h	91	Ref. 2d
5	Cu	@Fe_2O_4	KOH/H_2O/40°C/24 h	98	Ref. 2c
6	$CuCl_2$	Cryptand	H_2O/rt./20 min	96	Ref. 2b
7	Cu_2O	CTS-Py (**L1**)/CTS-Th (**L2**)	KOH/H_2O/rt./24 h	99	*This study*

[a]Isolated yields obtained from the reaction of phenylboronic acid.

Table 2. Substrate scope of arylboronic acids.[a]

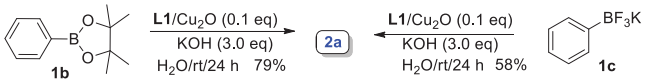
		
2a, 99% (50%)[b]	**2b**, 61% (54%)	**2c**, 48% (34%)
		
2d, 62% (60%)	**2e**, 59% (50%)	**2f**, 69% (60%)
		
2 g, 47% (45%)	**2 h**, 49% (41%)	**2i**, 34% (11%)
		
2j, 64% (45%)	**2 k**, 49% (37%)	**2 L**, 41% (33%)
		
2 m, 66% (50%)	**2n**, 98% (85%)	**2o**, 71% (65%)
		
2p, 10%	**2q**, 44% (35%)	**2r**, 23% (20%)

[a] Conditions: 1.0 mmol of $ArB(OH)_2$, 100 mg of **L1** (or **L2**), 3.0 equiv of KOH, H_2O at rt. for 24 h.

[b] Numbers in parentheses are the isolated yields obtained using **L2** under optimized conditions.

moderate different ligand moiety into the chitosan backbone. As described in Schemes 1 and 2-thiophenecarboxaldehyde was reacted with chitosan, yielding the thiophene-modified platform **L2**, possessing a sulfur atom (rather than a nitrogen atom) as a chelating site. We have now undertaken a systematic study considering the effect of chelating sites on *ipso*-hydroxylation. The resulting **L2** was then employed in the hydroxylation of various boronic acid substrates, which were used in the hydroxylation reaction employing **L1** under the same optimized reaction conditions. The isolated yields of the corresponding alcohols are shown in parentheses in Table 2. The results revealed that, in most cases, the desired products were obtained in slightly lower isolated yields than those realized through the use **L1**. The trends describing the isolated yields indicated that the catalytic activity of chelated-copper was partially affected by the chelating sites of the complex in the platform.

To expand the scope of boronic acids, the new platform (**L1**) was then examined with phenylboronic acid



Scheme 3. Expansion to boronic acid surrogates.

Scheme 4. Brief mechanistic study.

surrogates. The transformation of both a phenyl boronic acid pinacol ester (**1b**) and potassium phenyltrifluoroborate (**1c**) to phenol was explored under previously employed conditions. The conversion proceeded in a similar fashion, yielding **2a** in moderate to good isolated yields (Scheme 3).

Brief mechanistic tests were also conducted to gain insight into the mechanism. In the first stage of testing, to evaluate a potential radical process, 1.0 equiv of a free radical scavenger (TEMPO) was added to the standard reaction conditions. As depicted in Scheme 4, the reaction proceed well to give phenol in a satisfactory result (95% isolated yield), indicating that the radical process could be ruled out in this system. Next try was to carry out the reaction under an Ar atmosphere, leading to a considerable reduction in the conversion (7% isolated yield). This suggested that the molecular oxygen plays a crucial role in realizing an efficient conversion process.[7]

According to previous report,4f chitosan and modified-chitosan derivatives can easily bind with copper (I) ions to form a complex in an aqueous solution. This suggested that sorption of copper-metal in **L1** can occur in our system, and supplementary experiments were carried out to identify the potential copper-complexation. Surprisingly, the complexation manifested as a color change of pristine **L1** from off-white to dark gray after the reaction was easily confirmed by eye.

With the recovered platform (hereafter referred to as **Cu@L1**) from the initial experiment,[8] subsequent *ipso*-hydroxylation of **1a** without additional copper salt under the optimization conditions above was carried out. As expected, the conversion took place to give the corresponding phenol (**2a**) in a satisfactory result (89%) as described in Scheme 5. However, a continuative reuse of **Cu@L1** displayed a profoundly reduced activity. The second run proceed sluggishly and the conversion was incompleted, affording only 17% isolated yield of **2a** even after relatively long reaction time.[9] Despite the paucity of

1a	**Cu@L1**/optimized conditions →	**2a**
Recycle run[a]	First	Second
Isolated yield	89%	17%

[a] Carried out under the conditions: 1.0 mmol of **1a**, 0.10 g of **Cu@L1**, 3.0 eq. of KOH at room temperature for 24 h. The 2nd run was performed over 48 h.

Scheme 5. Sorption and reusability test.

comprehensive investigations on copper absorption and recyclability, the results suggested that Cu-complexation occurred partially *in situ* (*i.e.*, during the reaction). The resulting complex could be reused for the transformation of boronic acids to the corresponding alcohols.

The IR spectrum corresponding to the resulting copper complex of **L1** hanged only slightly indicating that most of the imine sites were unaltered. And, comparison of TGA analyses of **L1** and **Cu@L1** also verified the copper-complexation (see Supporting Information).

In conclusion, we have developed a versatile eco-friendly protocol for the synthesis of substituted phenols via the copper-catalyzed *ipso*-hydroxylation of arylboronic acids.[10] Use of a biopolymer, modified-chitosan platforms in conjunction with readily available copper salts under aerobic conditions rendered the protocol economical and environmentally friendly. The corresponding transformation occurred smoothly affording the corresponding phenols in moderate to high yields, regardless of whether the boronic acid substrates bear electron-withdrawing or electron-donating groups. A chelating effect depending on the chelating atom, nitrogen *versus* sulfur, and copper-complexation with a modified-chitosan backbone were both observed during the conversion. In addition, thus-formed copper complex seemed to be a promising a catalyst for the successive hydroxylation of boronic acid with or without the addition of a copper catalyst.

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Supporting Information. Additional supporting information is available in the online version of this article.

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5. Various protocols were also available. See: Ref. 4g for a representative procedure.
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7. For the crucial role of the molecular oxygen. See: Refs. 2b, 2g, and 2h.
8. Approximately 50% recovery of the support by weight as **Cu@L1**.
9. It could be attributed to the deformation of the platform (**Cu@L1**) and/or leaching of copper-metal into the solution. A scrutinized study is currently undertaken in our laboratory and the results will be reported in due course.
10. Representative procedure of the *ipso*-hydroxylation: preparation of **2d**: preparation of *p*-cresol; a flask was charged with 4-methylphenylboronic acid (1.0 mmol), Cu_2O (0.008 g, 0.1 mmol), CTS-Py (100.0 mg), KOH (0.17 g, 3.0 mmol), and H_2O (5.00 mL). Then, the flask was stirred at room temperature in open air for 24 h. At the end of the reaction, the reaction mixture was filtered and washed with water. Then, the filtrate was acidified with dilute aqueous HCl and extracted with diethyl ether (3 × 10 mL). The organic phases were combined. Combined organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The volatile components were evaporated under reduced pressure. Filtering through short pad of silica (80% hexanes/ 20% ethyl acetate) afforded 0.0671 g of *p*-cresol (**2d**) in 62% isolated yield as a colorless oily liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.05 (d, J = 8.0 Hz, 2H), 6.75 (dd, J = 6.5, 2.0 Hz, 2H), 4.95 (br s, 1H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 153.1, 130.1, 130.0, 115.0, 20.5; HRMS calcd for C_7H_8O: 108.0575, found: 108.0550.

