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Cellulose as recyclable organocatalyst for *ipso*-hydroxylation of arylboronic acids

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ABSTRACT

Cellulose catalyzed oxidative hydroxylation of aryl and hetero-arylboronic acids to the corresponding phenols under metal and base free strategy has been demonstrated. The sustainable *ipso*-hydroxylation takes place using hydrogen peroxide as an oxidant in water under mild condition in shorter period of time. Interestingly, easy recovery and reusability of heterogeneous catalyst without significant loss in catalytic yield makes the protocol environmentally benign.

Introduction

Phenols and their derivatives have been found to an integral part of numerous natural products [1].

They act as vital intermediates and building blocks for the synthesis of pharmaceuticals, polymers and naturally occurring compounds [2–4]. Natural phenolic compounds exhibit a broad range of biological activities [4]. Phenolic compounds have privileged scaffold in prevention as well as treatment of various diseases (Fig. 1) [5–8]. The direct hydroxylation to establish mild and efficient access of aromatic motif to corresponding phenols is of great significance in synthetic chemistry. The traditional method for the preparation of phenol involves Dow's process and Hock's process but results low yield [9]. Besides, this using aryl halide as precursor for the phenol synthesis have also suffered from harsh condition and additional purification steps [10,11]. In this context researchers have found arylboronic acid a new avenue for substituting the existing inactive synthetic precursors. The significant attention gained by arylboronic acid in various organic transformations due to their versatile nature, structural diversity, low toxicity, easy availability, greater stability, and reactivity [12–14].

Investigation showed that arylboronic acids can be easily converted into corresponding phenols by oxidative hydroxylation [15,16], upon careful control on the amount of oxidants and reaction time and it is worth mentioning from previous years that efforts have been made to obtain phenols through *ipso*-hydroxylation. Various protocols for *ipso*-hydroxylation of arylboronic acids were put forwarded using different catalysts such as mont K-10 supported AgNPs-H_2O_2 [17], biosilica-H_2O_2 [18], mont-KSF encapsulated $Co(OH)_x$ catalyzed [19], I_2-H_2O_2 [16], Al_2O_3-H_2O_2 [20], $CuSO_4$-phenanthroline [21], CuNP [22], TBHP [23] amberlite IR-120 resin [24], lactic acid-H_2O_2 [25], Polymer supported Pd-Ag hybrid [26] etc. Although majority of these protocols found to be effective in conversion of phenol through *ipso*-hydroxylation of arylboronic acid but mostly lacking "Greener"' procedure otherwise uses excess oxidizing agent, volatile organic solvents, higher temperature, base, metal catalysts etc. Thus, the development of a metal and base free and environmentally benign procedure for the *ipso*-hydroxylation is more viable alternative to be explored [27]. However, the use of organocatalyst for transformations has carried the attention of the researchers from the point of view of green catalyst, easily available, less expensive and economically sustainable.

In recent years, "Green Chemistry" has emerged as major concern for the development of new synthetic methodologies in modern chemistry perspective. The design of new route with green procedure has attracted especially in the areas of organic synthesis, drug discovery and material sciences [28–31]. Cellulose, an inexhaustible natural polymeric material, endowed with a polyfunctional macromolecular structure and an environmentally benign nature, has attracted wide attention in various branches of chemistry, remarkably in the development of new sustainable heterogeneous catalyst [32–34]. Cellulose has an unusual structure in which every other monomer subunit is upside down. This gives it some extraordinary physical and chemical properties, because

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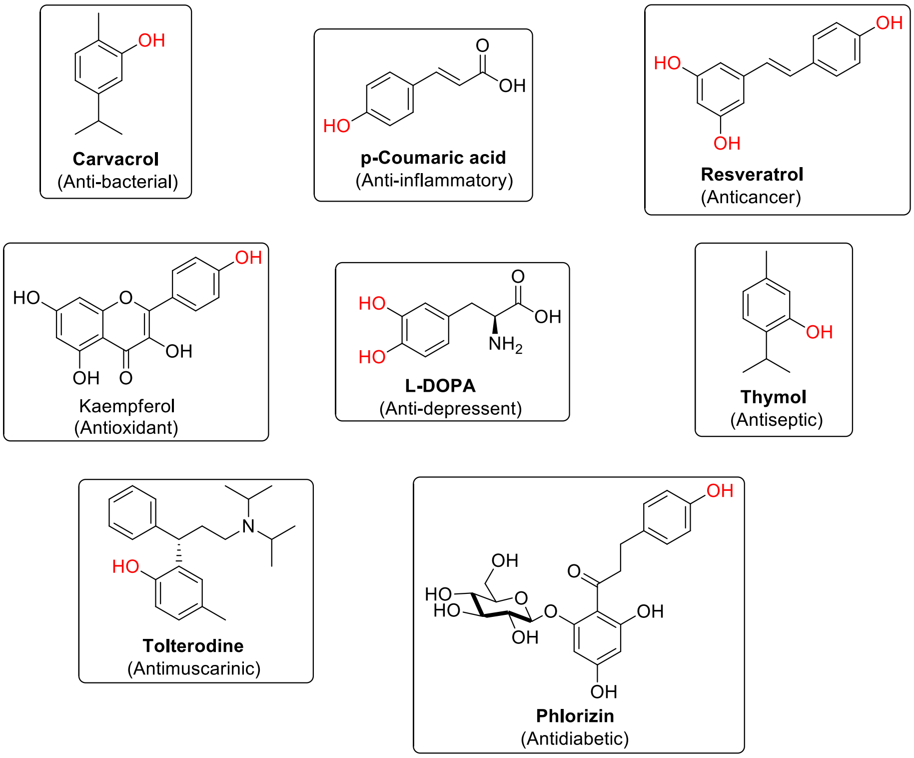


Fig. 1. Structure of phenolic compound used in late clinical research.

adjacent cellulose molecules bind readily into sheets and fibres. The lack of solubility in most organic solvents emanate from its supramolecular architecture and the natural abundance of this biopolymer makes it a promising supporting catalyst in various organic transformations [35]. Very recently, Kim *et al.* had reported chitosan as a biopolymer catalyst for *ipso*-hydroxylation of arylboronic acids to corresponding phenols [36]. However, chitosan production warrants its derivation from its natural source chitin [37]. In contrast, cellulose being nature's most abundant polymer offers greater abundance and direct utilization without any necessary pre-production from natural sources. Therefore, use of cellulose as a biopolymer holds significance in terms of availability and applicability. In view of aforementioned facts and with the concept of sustainable development, here we used cellulose as a biopolymer catalyst for the hydroxylation of arylboronic acids under benign reaction condition.

Experimental

Materials

All the chemicals were purchased from Sigma Aldrich, India and are of analytical grades. The details of characterization techniques are discussed in Supplementary Information (SI).

General procedure for ipso-hydroxylation of arylboronic acids

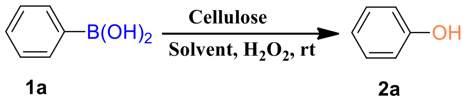
A mixture of arylboronic acid (0.5 mmol), 10 mg cellulose (15 wt%) and 2 mL distilled H_2O were taken in an oven dried 10 mL round bottomed flask. To this 30% aq·H_2O_2 (0.5 mL) was added dropwise and stirred at room temperature for 5 min. After completion of the reaction (monitored by TLC), aqueous layer was centrifuged to recover the catalyst for further use. The products were extracted with EtOAc (3 × 10 mL), dried with anhydrous Na_2SO_4 and then vacuum dried. The crude product was purified by column chromatography on silica gel (EtOAc/ hexane) to obtain the desired product.

Results and discussion

To understand/examine the catalytic applicability of cellulose in *ipso*-hydroxylation, phenylboronic acid (**1a**) was choosen as a model for screening the suitable reaction conditions, and the results are summarized in Table 1. All the reactions were performed at room temperature with cellulose (10 mg) and H_2O_2 (0.5 mL) using various solvents. Initially, the investigation was done without using any oxidant and no conversion was observed even after prolonged stirring (entry 1, Table 1). However, when reaction was performed in the absence of cellulose the corresponding product (**2a**) was obtained in low yield (entry 2 and 3, Table 1) [17,24]. Moreover, excellent results were obtained with the reaction involving a combination of H_2O_2 and cellulose under the same conditions (entry 4, Table 1). The effect of amount of H_2O_2 used in the present protocol was also investigated (entry 5, Table 1). Then we examined the impact of the cellulose catalyst used in the reaction by decreasing the amount to 5 mg shows a slight decrease in the yield of phenol suggesting more amount of catalyst was required for the reaction (entry 6, Table 1). However, increase in the amount of biopolymer catalyst does not improve the yield of phenol (entry 7, Table 1). Encouraged by the interesting results, we then screen the effect of various solvents (2 mL) on the reaction using 10 mg of catalyst. Among the solvents screened, in polar solvents such as methanol, ethanol, isopropyl alcohol, hydroxylation takes place smoothly with good yield (entries 8–12, Table 1). On the other hand to understand the role of solvents towards cellulose catalysed *ipso*-hydroxylation, experiments were performed with aprotic solvents (CH_3CN, CH_2Cl_2 and THF) results 65–72% yield (entries 13–15, Table 1).

With standard reaction condition, it can be understand that the assistance of cellulose with H_2O_2 as oxidant as an adaptable

Table 1
Optimization of cellulose catalysed *ipso*-hydroxylation.[a]



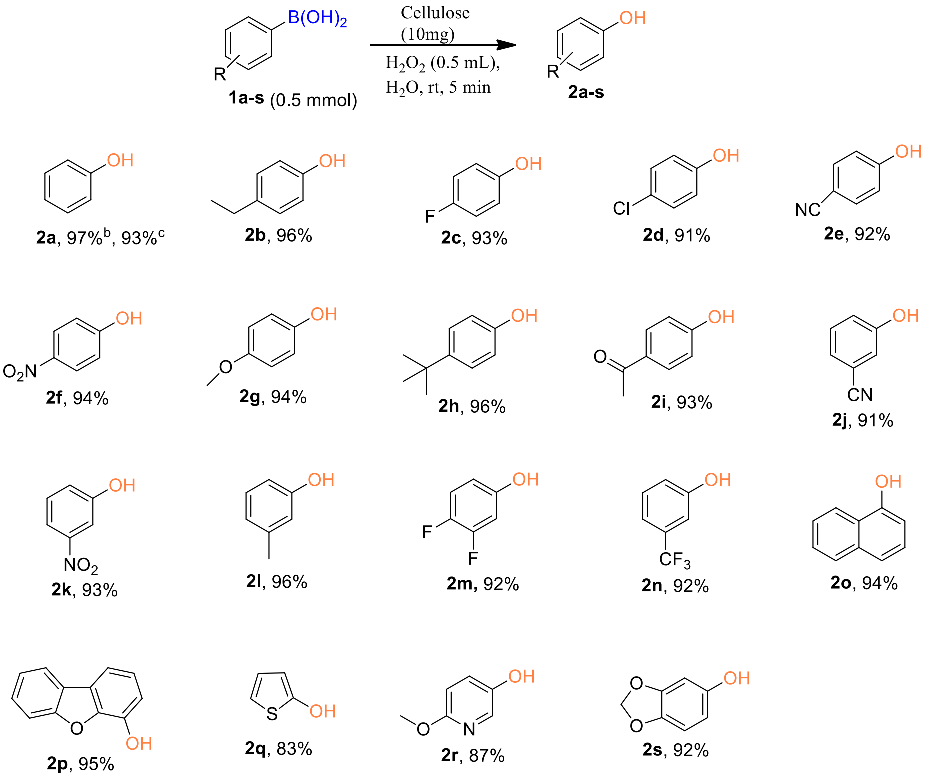
1a **2a**

Entry	Cellulose (mg)	H_2O_2	Solvent (2 mL)	Time (min)	Yield (%)[b]
1	10.0	–	H_2O	60	–
2	–	0.5 mL	–	60	8
3	–	0.5 mL	H_2O	60	15
4	10.0	0.5 mL	H_2O	5	97
5	10.0	0.25 mL	H_2O	5	89
6	5.0	0.5 mL	H_2O	5	93
7	15.0	0.5 mL	H_2O	5	97
8	10.0	0.5 mL	MeOH	5	88
9	10.0	0.5 mL	EtOH	5	83
10	10.0	0.5 mL	*i*PrOH	5	79
11	10.0	0.5 mL	MeOH: H_2O (1:1)	5	84
12	10.0	0.5 mL	EtOH: H_2O (1:1)	5	80
13	10.0	0.5 mL	CH_3CN	5	72
14	10.0	0.5 mL	CH_2Cl_2	5	65
15	10.0	0.5 mL	THF	5	70

[a] Reaction condition: Phenylboronic acid (0.5 mmol), H_2O_2 (30% aq), 15 wt% of cellulose catalyst.
[b] Isolated yield.

alternative course for *ipso*-hydroxylation of arylboronic acids. Next to evaluate the scope and limitation of current procedure, we investigated the scope of our protocol with a series of electronically diverse arylboronic acids subjected to the oxidative hydroxylation and the results are summarized in Table 2. It has been observed that both electron-rich and electron-deficient arylboronic acids resulted corresponding *ipso*-hydroxylated product in good to excellent yield which suggests that the electronic nature of attached substituent has little influence on reaction process. Arylboronic acid with substituent such as Et, OMe, F, Cl, CN, NO_2, *t*-Butyl, COMe at *para* position afford excellent yield (**2b-i,** Table 2) of substituted phenol irrespective of their electronic nature. Meta substituted arylboronic acid also gives the product in excellent yield under the current reaction conditions (**2j-n**, Table 2). It is

Table 2
Cellulose catalysed *ipso*-hydroxylation of boronic acids[a]



1a-s (0.5 mmol) **2a-s**

2a, 97%[b], 93%[c]
2b, 96%
2c, 93%
2d, 91%
2e, 92%
2f, 94%
2g, 94%
2h, 96%
2i, 93%
2j, 91%
2k, 93%
2l, 96%
2m, 92%
2n, 92%
2o, 94%
2p, 95%
2q, 83%
2r, 87%
2s, 92%

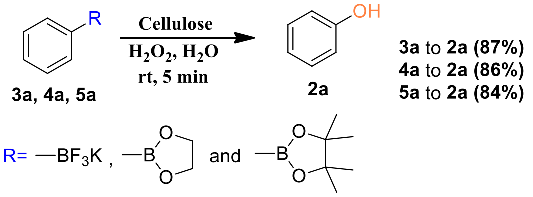
[a] Reaction conditions: arylboronic acid (0.5 mmol), 30% aq·H_2O_2 and 10 mg of cellulose in 2 mL of water at room temperature; [b]Isolated yield; [c]Isolated yield when the reaction was carried with 1 g of **1a**.

Table 3
Comparison of recent catalyst with cellulose for *ipso*-hydroxylation utilizing H_2O_2 as an oxidant

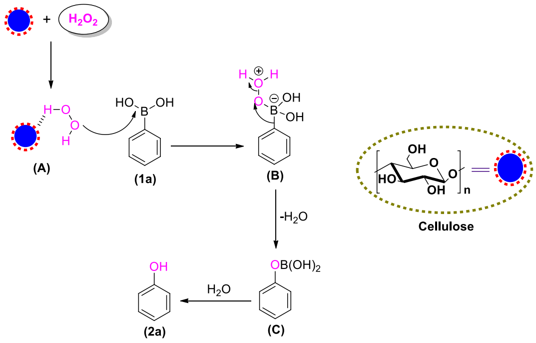
Sl. no	Catalyst	Solvent	Time (min)	Temp (°C)	Yield (%)	Refs.
1	Biosilica	H_2O	5	rt	93	[18]
2	Iodine	–	45	rt	93	[16]
3	WERSA	H_2O	5	rt	98	[38]
4	Mont K-10@AgNPs	–	15	rt	92	[17]
5	PEG-400	–	10	rt	97	[39]
6	Cu_2O NP	–	10	rt	96	[40]
7	Chitosan	H_2O	10	rt	98	[36]
8	Silica chloride	MeCN	5	35	100	[41]
9	Pd-Chit-CNT	–	15	rt	95	[42]
10	Cellulose	H_2O	5	rt	97	This work

noteworthy to observe that heteroaryl boronic acid such as thiophene-2-boronic acid and 6-methoxypyridyl boronic acid were successfully underwent *ipso*-hydroxylation with good yield (83% and 87%) respectively (**2q** and **2r**, Table 2), although excellent yield were observed for hetero-boronic acid to their corresponding alcohols (**2o**, **2p** and **2 s**, Table 2). Thus the developed protocol is highly tolerant towards wide range of substituted arylboronic acid functionalities at room temperature, which shows the wide synthetic utility.

In order to investigate whether our protocol could be upscale to the gram-level, we performed gram-scale reaction of **1a** (1.0 g, 8.19 mmol) under the optimized reaction conditions and results showed reaction proceeded without any significant loss in efficiency affording 0.717 g of **2a** (93%) (Table 2). Thus, the results showed the potential effectiveness of this process for the high-yielding synthesis of phenols.



Scheme 1. Oxidation of phenylboronic acid ester and phenyltrifluoroborate.



Scheme 2. Plausible mechanism for *ipso*-hydroxylation of phenylboronic acid.

The comparison of cellulose catalyzed *ipso*-hydroxylation of arylboronic acid with the existing catalytic systems are well illustrated in Table 3, which reveals the advantage of nature friendly cellulose polymer for the presented hydroxylation reaction.

To expand the scope of our system, similar to arylboronic acids other surrogates such as potassium phenyltrifluoroborate and phenylboronic acid ester (**3a, 4a** and **5a**) were hydroxylated smoothly affording the desired product (**2a**) in good yield (Scheme 1).

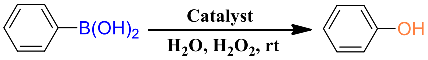
Reaction mechanism

A plausible mechanistic pathway has been proposed based on reported literature [18,36]. Cellulose being a polysaccharide, consists of linearly linked α-D-glucose units containing primary and secondary hydroxyl groups. These hydroxyl groups of cellulose form hydrogen bonds with hydrogen peroxide to enhance its nucleophilicity, which is mainly responsible for the catalytic activity of cellulose [36]. It is assumed that initially cellulose react with H_2O_2 (30% aqueous) to form cellulose-peroxide adduct **A** via hydrogen bonding (Scheme 2). Consequently **A** interacts with phenylboronic acid (**1a**) resulting formation of adduct **B**, which rearranged and subsequent water loss gave adduct **C.** Hydrolysis of **C** afford the phenol (**2a**).

Catalyst reusability

Reusability of any catalyst makes it even more attractive [43]. Although cellulose catalysed efficiently *ipso*-hydroxylation, the heterogenesity and sustainability have been proved by its reusability. Cellulose catalyzed *ipso*-hydroxylation of **1a** under optimal condition. After 1st cycle, the catalyst was filtered and washed several times with Et_2O followed by H_2O. The recovered bio-catalyst was dried in oven at 80 °C for overnight and was further used as catalyst for the *ipso*-hydroxylation of arylboronic acids. It was found that the catalyst maintained good activity for a minimum of five cycles (Table 4). FT-IR spectra and P-XRD analysis (Figs. S1 and S2) further revealed that the structure of the catalyst does not alter during the course of the reaction.

Table 4
Reusability test for cellulose for the synthesis of phenol.



Run	1st	2nd	3rd	4th	5th
Yield (%)	97	96	93	93	88

[a]Reaction condition: Phenylboronic acid (0.5 mmol), H_2O_2 (30% aq), cellulose (10 mg), H_2O (2 mL); [b]Isolated yield

Conclusion

This work represents a simple, efficient and reusable biopolymer catalyst for the *ipso*-hydroxylation of arylboronic acid using readily available hydrogen peroxide as an oxidant under metal and base free greener condition at room temperature in shorter period. The use of cellulose, the most abundant polymer on earth makes the protocol open up with a clean benign method of synthesizing wide variety of phenols and hetero-aryl phenols. Additionally, the environmental advantages of using this new catalytic system in substituting conventional reagents makes the protocol as a scope for transformation of functional group in synthetic chemistry.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151044.

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