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Organic hypervalent iodine(III) catalyzed *ipso*-hydroxylation of aryl- and alkylboronic acids/esters

Nachiketa Chatterjee, Avijit Goswami *

Department of Chemistry, Indian Institute of Technology, Ropar (IIT Ropar), Nangal Road, Rupnagar, Punjab 140001, India

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ABSTRACT

An organo-hypervalent iodine(III) catalyzed highly efficient methodology for *ipso*-hydroxylation of diversely functionalized aryl- and alkylboronic acids/esters has been developed using $NaIO_4$ as a co-oxidant. This protocol is also applicable to *N*-heterocyclic boronic acids and esters. Further mechanistic studies revealed that the organoboronic acid (an electron demanding moiety) is acting as a nucleophile in the presence of hypervalent iodine for hydroxylation reactions. In summary, this is the first Letter of a generalized route for organic hypervalent iodine(III) catalyzed hydroxylation of organoboronic compounds.

Phenol is an important class of structural unit found in a wide range of natural products, pharmaceuticals, and polymers.[1] Furthermore, phenols and their derivatives play a significant role in the construction of more complex *O*-heterocycles and aryl ethers.[2] Phenolic compounds have potential therapeutic uses as antitumor, antiviral, antibacterial, cardio-protective, pro-oxidative, and antimutagenic agents (Fig. 1).[3] Therefore, endowing efficient access to phenols through an atom economic way, especially in the presence of multi-functional groups is of a significant research interest.

The classical phenolation methods predominantly comprise activated nucleophilic substitution of aryl halides, benzyne protocols, and Cu-catalyzed transformation of diazoarenes. However, use of harsh conditions, incompatibility toward various functional groups and poor regio-selectivity limit the scope of these protocols.[4] Alternatively, Okamoto et al. reported a unique low-valent titanium (LVT) catalyzed protocol for hydroxylation of sulfonates and allyl or propargylic ethers[5] and Chakraborti et al. described a novel methodology for organocatalytic generation of phenols from *O*-*t*-Boc derivatives.[6] Moreover, during the last few decades, organoboronic species have drawn immense attention for various functional group transformation reactions including hydroxylations.[7] The traditional system for hydroxylation of arylboronic acids consists of hydrogen peroxide as oxidant in the presence of a base.[8]

Excepting hydrogen peroxide, oxone serves as an efficient oxidant for hydroxylation of organoboronic compounds and can react in the absence of a base.[9] Besides, other oxidants such as *N*-oxide,[10] *m*CPBA,[11] $NaClO_2$,[12] and HOF[13] have also been employed for hydroxylation of organoboronic compounds. However, all these methodologies employ the active oxidizing species in stoichiometric amount.

On the other hand, there are very few catalytic protocols, based on Cu and Pd-catalyzed methodologies for the hydroxylation of arylboronic compounds, reported in the literature (Scheme 1).[2,14a–e] Although from the pharmaceutical point of view, metal-free systems are more favored over metal-mediated methods, fewer methods for metal-free catalytic hydroxylation of organoboronic acids have been reported.[4,15]

However, these methodologies too, use hydrogen peroxide as the active oxidizing species in stoichiometric amount. In this context, it is mention worthy that organic hypervalent iodine has established itself as a versatile and unique oxidant with no environmental issues.[16] However, reports regarding the use of this reagent for the hydroxylation of the organoboronic compounds are rare.[17]

To the best of our knowledge, no organo-hypervalent iodine(III) catalyzed hydroxylation of aryl/alkylboronic compounds has been reported so far.[18] Herein, we report the first generalized route for organic hypervalent iodine(III) catalyzed hydroxylation of aromatic and aliphatic boronic acids/esters using $NaIO_4$ as a co-oxidant.

Table 1 summarizes the optimization results of reaction conditions for hypervalent iodine-catalyzed hydroxylation of aryl- and alkylboronic acids at 80 °C with $NaIO_4$ as a co-oxidant. As expected,[19] an initial optimization exhibited no transformation of

* Corresponding author. Tel.: +91 1881 242121.
E-mail address: agoswami@iitrpr.ac.in (A. Goswami).

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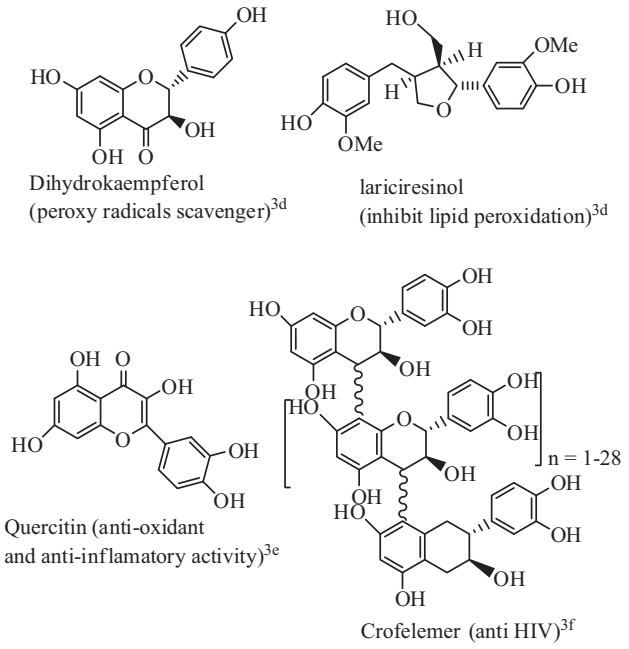
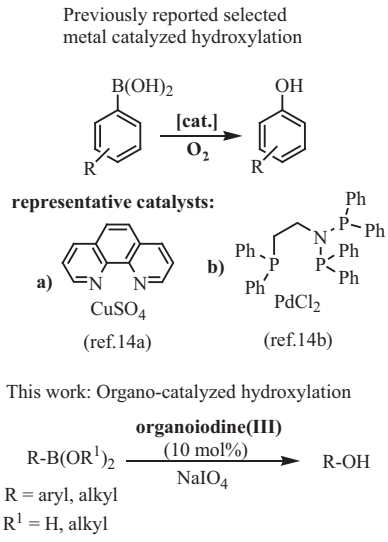


Figure 1. Selected biologically active aromatic alcohols.



Scheme 1. *ipso*-Hydroxylation of organoboronic acids/esters under different reaction conditions.

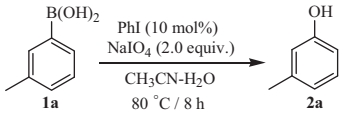
the organoboronic species, in the absence of iodobenzene, either at room temperature or at 80 °C for 14 h with $NaIO_4$ as an oxidant (entries 1 and 2). It is necessary to mention that the hydroxylation reaction of organoboronic acids could not be performed at ambient temperature (entry 3).

Increasing the temperature from 25 °C to 80 °C resulted into a gradual enhancement in product formation (entries 3–9). However, further increase in temperature and reaction time in DMF did not significantly improve the reaction outcome (entry 10). The conversion of the arylboronic acid was observed to go to its optimal completion in 8 h at 80 °C with 10 mol % of PhI and 2.0 equiv of $NaIO_4$ (entry 7).

It is worth mentioning that the reaction proceeded in an inert environment also (entry 8), thus demonstrating no participation of molecular oxygen in the hydroxylation process.

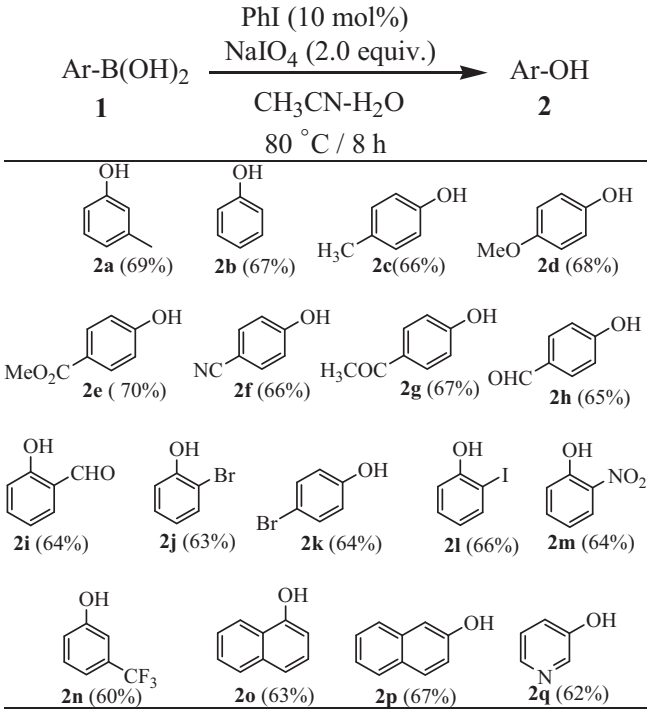
With the optimal reaction conditions in hand, the investigations were extended to additional substrates in order to outline the

Table 1
Optimization of reaction conditions[a]



Entry	PhI (mol %)	Solvent	Temp (°C)	Time (h)	Yield[b] (%) **2a**
1	—	$CH_3CN–H_2O$	25	24	n.r[c]
2	—	$CH_3CN–H_2O$	80	14	n.r[c]
3	40	$CH_3CN–H_2O$	25	14	Trace
4	40	$CH_3CN–H_2O$	50	8	47
5	40	$CH_3CN–H_2O$	80	8	68
6	20	$CH_3CN–H_2O$	80	8	67
7	**10**	**$CH_3CN–H_2O$**	**80**	**8**	**69**[d]
8	10	$CH_3CN–H_2O$	80	8	68[e]
9	10	DMF–H_2O	80	8	65
10	10	DMF–H_2O	95	14	66

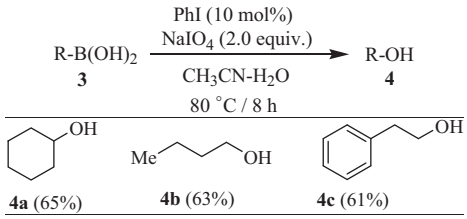
[a] Reaction conditions: **1a** (1.0 mmol), PhI (0.1 mmol, 10 mol %), $NaIO_4$ (2.0 mmol), $CH_3CN–H_2O$ (8 mL, 3:1), 80 °C, 8 h, open air.
[b] Isolated yield.
[c] No reaction and no hydroxylation took place either by stirring the reaction mixture for 24 h at 25 °C or on heating at 80 °C for 14 h.
[d] These reaction conditions are taken as standard reaction conditions (Shown in bold).
[e] The reaction was performed under argon atmosphere; $CH_3CN–H_2O$ was degassed before use.



Scheme 2. Organic hypervalent iodine(III) catalyzed *ipso*-hydroxylation of aromatic boronic acids.

substrate scope of the iodine(III)-catalyzed hydroxylation methodology and the results are summarized in Scheme 2.

Successful hydroxylations of halide-, nitro-, aldehyde-, keto-, nitrile-, and ester-substituted arylboronic acids demonstrated the excellent functional group tolerance of the protocol developed in the present work. The hydroxylations of the *ortho*-substituted arylboronic acids to their corresponding aromatic alcohols (**2i**, **2j**, **2l**, and **2m**) indicated that the steric effect has a negligible role in the reaction outcome. It is noteworthy that the hydroxylation



Scheme 3. Organic hypervalent iodine(III) catalyzed *ipso*-hydroxylation of alkylboronic acids. Reaction conditions: **3** (2.0 mmol), PhI (0.2 mmol, 10 mol %), $NaIO_4$ (4.0 mmol), $CH_3CN–H_2O$ (8 mL, 3:1), 80 °C, 8 h, open air.

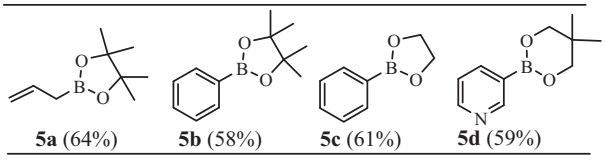


Figure 2. Organic hypervalent iodine(III) catalyzed *ipso*-hydroxylation of organoboronates. Reaction conditions: **5** (1.0 mmol), PhI (0.1 mmol, 10 mol %), $NaIO_4$ (2.0 mmol), $CH_3CN–H_2O$ (8 mL, 3:1), 80 °C, 8 h, open air; the reaction was performed with **5a** in a 3.0 mmol scale.

reactions developed herein works equally well with arylboronic acids having either an electron donating or withdrawing group.

Equally stimulating was the observation that the arylboronic acids with oxidation-sensitive functional group such as aldehydes (**2h** and **2i**) also endured the reaction conditions employed, without undergoing over-oxidation.

The smooth transformation of halide-substituted arylboronic acids to their corresponding halo substituted aromatic alcohols (**2j**, **2k**, and **2l**) makes this protocol further versatile. Hydroxylation of *N*-heterocyclic boronic acid to 3-hydroxy pyridine (**2q**) was also performed successfully, using this method.

Next, alkylboronic acids were also employed for hydroxylation reactions to explore the extent of this methodology (Scheme 3). In general, aliphatic alcohols, especially primary alcohols, are difficult to access through oxidative methods, as they are prone to get over-oxidized easily.[20]

To our delight, the newly developed organocatalytic method did not reveal such difficulties, and both primary (**4b** and **4c**) and secondary alcohols were (**4a**) obtained with moderate yields.

Not only the aromatic/aliphatic boronic acids but other aryl/alkylboronates are also found to be suitable substrates for hydroxylation reaction developed in the present work (Fig. 2). The protocol is found to be reconcilable with the olefin moiety, as it did not cause oxidation of C–C double bond in compound **5a**.

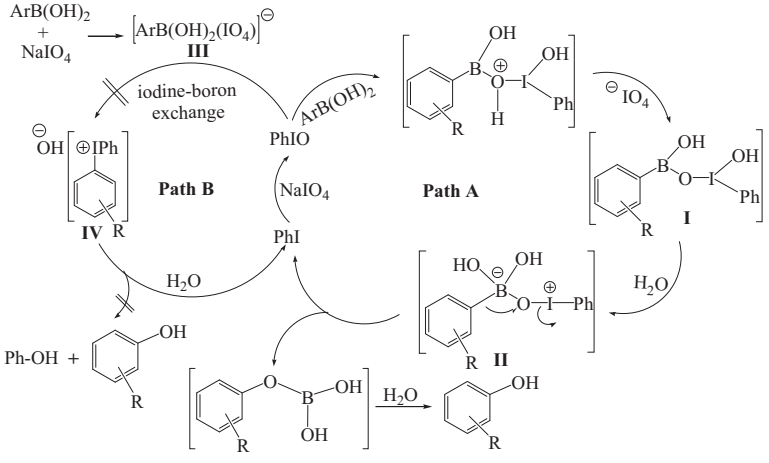
Plausible mechanistic pathways for the organo-hypervalent iodine(III)-catalyzed hydroxylation reaction are depicted in Scheme 4. Successful hydroxylation of the arylboronic acid under inert environment obviates the involvement of molecular oxygen in the oxidation procedure. It is anticipated that iodobenzene in the presence of $NaIO_4$ is first oxidized to iodosobenzene, an organo iodine(III) species, which accounts for the hydroxylation.

Two catalytic cycles can be proposed for this type of hydroxylation reaction: pathways A and B. In pathway A, nucleophilic attack of the organoboron acid to the iodosobenzene produces another meta-stable hypervalent iodine species (**I**), which in the presence of H_2O leads to the tetra coordinated boron intermediate (**II**). The subsequent intra-molecular [1,2] aryl shift of the species (**II**) results in the formation of desired phenol. In this process, iodosobenzene eventually gets reduced to iodobenzene, which undergoes further oxidation to iodine(III) by $NaIO_4$ to initiate a repetitive oxidation-reduction cycle. Similarly, in case of organoboronic esters, in the presence of $NaIO_4$, they are first converted to their corresponding boronic acids,[19] which then undergo hydroxylation following the above mentioned pathway.

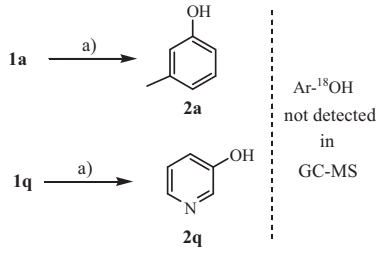
In pathway B, the arylboronic acid is first transformed to tetra coordinated species (**III**) that undergoes iodine-boron exchange[21] to produce iodonium salt (**IV**), which on further reaction with water is supposed to provide phenol and expected aromatic alcohol along with the iodobenzene to commence a new catalytic cycle. It should be mentioned that under no circumstance phenol was detected along with the desired aromatic alcohol.

Two separate reactions were performed with *m*-tolylboronic acid (**1a**) and pyridine-3-boronic acid (**1q**) in anhydrous acetonitrile in the presence of H_2O^{18} in order to establish, more accurately, the pathway by which iodine(III)-catalyzed hydroxylation reaction is operating (Scheme 5). No instance of formation of aromatic alcohol containing isotopic oxygen (Ar-^{18}OH), which would definitely be obtained if the reaction would proceed through path B, was detected in GC–MS. Therefore, it could be inferred that the hydroxylation reaction proceeds through the oxidation of organoiodine(I) to organoiodine(III), which is followed by the nucleophilic attack of the organoboronic species to the organoiodine(III) agent and then intra-molecular [1,2] aryl migration (path A, Scheme 4).

In conclusion, we have developed a novel methodology for organo hypervalent iodine(III) catalyzed *ipso* hydroxylation of aryl- and alkylboronic acids/esters to access diversely functionalized aromatic and aliphatic alcohols. Another notable feature of this protocol is that among the two electron-demanding species (arylboronic acid and PhIO) involved in the reaction, arylboronic acid acts as a nucleophile[22] in spite of being an electron deficient compound. To the best of our knowledge, it is a unique study in the



Scheme 4. Plausible mechanistic pathway.



Scheme 5. H_2O^{18}-isotope labeling experiment. (a) Reaction conditions: **1a** or **1q** (1.0 mmol), PhI (0.1 mmol, 10 mol %), $NaIO_4$ (2.0 mmol), CH_3CN–H_2O^{18} (12 mL, 2:1), 80 °C, 8 h, open air.

field of hydroxylation of aryl/alkylboronic acids and their other surrogates. Further investigations regarding the use of organohypervalent iodine(III)-catalyzed reactions for functional group transformations (other than hydroxylation reaction) of organoboronic compounds are currently ongoing.

Acknowledgments

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Supplementary data

Supplementary data (general procedure for synthesis, characterization data and copies of ^1H and ^{13}C NMR spectra of all the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.118.

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