Tetrahedron Letters 57 (2016) 2506–2510

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A chemoselective *ipso*-hydroxylation of arylboronic acids using urea-hydrogen peroxide under catalyst free condition

Surabhi Gupta, Priyanka Chaudhary, Vandana Srivastava, Jeyakumar Kandasamy *

Department of Chemistry, Indian Institute of Technology (BHU), Varanasi, Uttar Pradesh 221005, India

ARTICLE INFO

Article history:
Received 16 March 2016
Revised 25 April 2016
Accepted 26 April 2016
Available online 29 April 2016

Keywords:
Oxidation
Arylboronic acid
Phenols
Urea-hydrogen peroxide

ABSTRACT

An efficient and practical method for the chemoselective *ipso*-hydroxylation of arylboronic acids is demonstrated using urea-hydrogen peroxide under catalyst free condition at room temperature. Remarkably, oxidation sensitive functional groups such as olefin, aldehyde, alcohol, ketone, and sulfide as well as heterocycles such as pyridine and thiophene were tolerated under the standard reaction condition. In addition to the solution phase, a solid phase *ipso*-hydroxylation of arylboronic acids has been investigated with urea hydrogen peroxide. The scope and limitations of the solid phase protocol is discussed.

From both synthetic as well as environmental perspectives, solvent, catalyst, and metal free reactions have received considerable attention in organic synthesis.[1] Such reactions are clean (reduced pollution) and cost effective in which execution, work-up, and isolation procedures are relatively simple. Therefore, several methodologies are being developed under solvent, catalyst, and metal free conditions for the synthesis of various fine chemicals and pharmaceuticals.[1a,b,d]

Phenolic compounds play an important role in the prevention as well as treatment of various diseases (Fig. 1).[2] Natural phenolic compounds isolated from herbs and dietary plants (e.g., phenolic acids, flavonoids, tannins, curcuminoids, coumarins, lignans, etc.) exhibit a wide range of biological activities including antimicrobial, anti-inflammatory, anticancer, antithrombotic, anti-allergenic, and antioxidant activities.[3] Besides the biological importance, phenols serve as key intermediates for the preparation of various natural products, pharmaceuticals, agrochemicals, materials, polymers, etc.[4]

Phenols are typically synthesized from aryl halides via nucleophilic substitution with metal hydroxides under harsh reaction conditions.[4b] On the other hand, diazotization of aryl amines, CH-oxidation of aryl rings, and oxidative hydrolysis of arylboronic acids are the alternative routes used for preparation of phenols. Among them, synthesis of phenols from arylboronic acids has received significant attention in organic synthesis, because, arylboronic acids are less toxic, highly stable under air and moisture, commercially available and cost effective.[5] Therefore, numerous methods have been developed recently for the oxidative *ipso*-hydroxylation of arylboronic acids using transition metal catalysts, hydroperoxides, hypervalent iodine reagents, *N*-oxides, photo-catalysts, and electrochemical techniques.[6] The major limitations of some of these existing protocols are the use of strong acidic or basic reaction conditions,[6a,d,o] high reaction temperature,[6f] excess oxidants,[6d,h,j] longer reaction time,[6b] commercially unavailable catalysts or oxidants,[6i,l,m] etc. Moreover, compatibility of oxidation sensitive functional groups during the *ipso*-hydroxylation was not well explored in these existing reports. Therefore, establishing a mild and efficient method for the preparation of phenols from arylboronic acids via oxidative *ipso*-hydroxylation, especially in the presence of oxidation sensitive functional groups, is of great interest.

Aqueous hydrogen peroxide is a green oxidant widely used for the oxidation of various functional groups in organic synthesis.[7] On the other hand, hydrogen peroxide–solid adducts have also received considerable attention in oxidation chemistry due to many advantages including stability, easy handling and storing, high safety, existing in anhydrous form, etc.[7] One of such solid adducts is urea-hydrogen peroxide (UHP) which has been explored in a several solution as well as solid phase oxidation reactions.[8] Being an anhydrous neutral complex, UHP adduct is considered to be a safer alternative to the high concentrated hydrogen peroxide.[8a] Commercial availability, inexpensiveness, odorless, and nontoxic nature are the additional advantages of urea-hydrogen peroxide. Therefore, UHP has been used not only in organic synthesis but also in cosmetics and pharmaceuticals as a

* Corresponding author. Tel.: +91 0542 6702879; fax: +91 0542 6702876.
E-mail address: jeyakumar.chy@iitbhu.ac.in (J. Kandasamy).

http://dx.doi.org/10.1016/j.tetlet.2016.04.099
0040-4039/

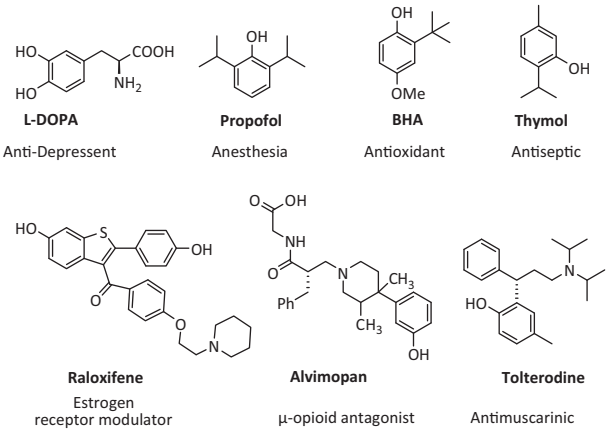
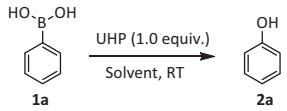


Figure 1. Phenolic compounds in clinical applications.

disinfectant and bleaching agent.[9] Our research group is mainly focused on the development of efficient and eco-friendly methods for organic synthesis.[10] In this context, here we report an efficient and practical method for the conversion of arylboronic acids into corresponding phenols using urea-hydrogen peroxide at room temperature under catalyst and metal free conditions.

At the outset, commercially available phenylboronic acid (**1a**) was chosen as a model substrate and subjected for *ipso*-hydroxylation with UHP in various solvents and solvent free condition (Table 1). All the reactions were performed at room temperature with 1.0 equiv of urea-hydrogen peroxide under catalyst free condition. Among the aprotic solvents, only acetonitrile provided the desired product in a quantitative yield (97%) within 15 min (Table 1, entry 5) while tetrahydrofuran (THF), toluene, diethyl ether and chloroform did not lead to completion even after prolonged reaction time (Table 1, entries 1–4). It is also important to note that by replacing UHP with 30% aqueous hydrogen peroxide in acetonitrile the reaction did not lead to completion even after 60 min (Table 1, entry 6).[6j] The low yields in this reaction may be attributed to the formation of peroxyimidic acid. In the case of protic solvents, methanol was found to be very efficient to provide 97% of the desired product within 5 min while ethanol, *t*-butanol and water took slightly longer reaction time (Table 1, entries 7–10). It is interesting to note that the reactivity of 30% aqueous hydrogen peroxide in methanol is found to be relatively efficient when compared with acetonitrile which provides 69% of the desired product after 60 min at room temperature (Table 1, entry 11). Nevertheless, the oxidative *ipso*-hydroxylation of phenylboronic acid was achieved in a high yield under solid-state condition (i.e., solvent free) with UHP, however the reaction requires an external heat (45 °C) for melting the substrates (Table 1, entry 12). Based on the optimization study, methanol was found to be an efficient medium for the *ipso*-hydroxylation reaction with UHP at room temperature under catalyst free condition (Table 1, entry 7).

Table 1
Oxidation of phenylboronic acid using urea-hydrogen peroxide (UHP)[a]



Entry	Solvent	Time (min)	Yield[b] (%)
1	THF	120	40
2	Toluene	120	30
3	Diethyl ether	120	68
4	$CHCl_3$	120	20
5	CH_3CN	15	97
6	CH_3CN	60	07[c]
7	CH_3OH	5	97
8	C_2H_5OH	35	90
9	*t*-BuOH	40	80
10	H_2O	90	65
11	CH_3OH	60	69[c]
12	Solvent free	30	95[d]

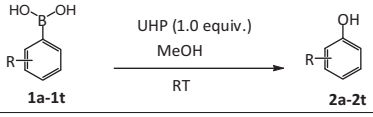
[a] Reaction conditions: Substrate (1.0 mmol) and UHP (1.0 equiv) was stirred in 3 mL of solvents at room temperature.
[b] Isolated yield.
[c] Instead of UHP, 30% aqueous hydrogen peroxide was used.
[d] Reaction was carried out at 45 °C.

As optimized condition in the hand, a general applicability of the method was further explored by subjecting various substituted arylboronic acids for the *ipso*-hydroxylation and the results are summarized in Table 2. Similar to phenylboronic acid, α- and β-naphthylboronic acids were converted into corresponding naphthols in 96% yields (Table 2, **2b**–**2c**). In addition, the electron rich, i.e., ethyl, methoxy and phenyl substituted arylboronic acids underwent *ipso*-hydroxylation in excellent yields (>95%) within the period of 15 min at room temperature (Table 2, **2d**–**2f**). On the other hand, deactivated arylboronic acids such as nitro, fluoro, chloro, and bromo substituted arylboronic acids have also undergone *ipso*-hydroxylation smoothly to provide the desired products in a comparable yield (>95%) to those of activated arylboronic acids (Table 2, **2g**–**2k**). Also, aryl diboronic compound such as 1,4-phenylenediboronic acid was successfully converted to hydroquinone in a quantitative yield with 2.0 equiv of urea-hydrogen peroxide at room temperature (Table 2, **2l**).

It has been widely observed that urea-hydrogen peroxide (UHP) cannot oxidize the organic functional groups (e.g., sulfides, thiols, amines, olefins, alcohols, aldehydes, etc.) efficiently in the absence of catalyst.[8a–c] However, the current study reveals that *ipso*-hydroxylation of arylboronic acids can be achieved very efficiently under catalyst free condition at room temperature. By considering these facts, we have anticipated that UHP can be used as a chemo-selective oxidant for the *ipso*-hydroxylation of arylboronic acids which contain oxidation susceptible functional groups. To test the hypothesis, olefin, aldehyde, alcohol, and sulfide functionalized arylboronic acids (**1m**–**1r**) as well as heteroaryl boronic acids (**1s**–**1t**) were subjected for the *ipso*-hydroxylation reactions under optimized condition. However, during the course of *ipso*-hydroxylation in methanol, we have observed a formation of minor amount of undesired products (~10–15%), particularly in the case of substrates with aldehyde (**1n**, **1o**) and sulfide (**1r**) functional groups.[11] Therefore, the reactions of sensitive group functionalized arylboronic acids were performed in acetonitrile which took slightly longer time for completion, however with high chemoselectivity (Table 2, **2m**–**2t**).

In general, olefins are prone to epoxidation or dihydroxylation in the presence of oxidizing agents (e.g., MCPBA, *t*BuOOH, Oxone, etc.).[12] Interestingly, olefin was found to be remained intact during the *ipso*-hydroxylation with UHP and gave the desired product in 95% yield (Table 2, **2m**). Similarly, aryl aldehydes and ketones are known to undergo different oxidation reactions including Dakin oxidation, Baeyer–Villiger oxidation, etc.[12] In addition, aryl alcohols can get easily oxidized to corresponding aldehydes or carboxylic acids in the presence of oxidizing agents. Interestingly, all these functionalities were well tolerated during the *ipso*-hydroxylation and gave the desired phenols in >92% yields (Table 2, **2n**–**2q**). It is well known that sulfides are highly oxophilic in nature which readily undergo oxidation to sulfoxide or sulfone with most of the oxidizing agents (e.g., MCPBA, H_2O_2 with different catalysts, oxone, etc.).[12,13] Therefore a sulfide containing arylboronic acid (i.e., 4-(thiomethyl)phenylboronic acid, **1r**) was tested for *ipso*-

Table 2
Oxidation of substituted arylboronic acids to corresponding phenols using UHP[a,b]



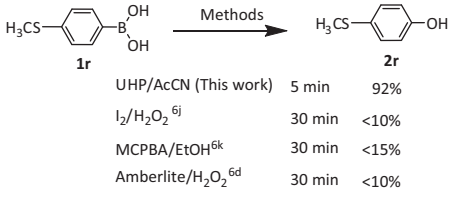
1a-1t 2a-2t

2a (5 mins, 97%)	**2b** (10 mins, 96%)	**2c** (5 mins, 96%)	**2d** (2 mins, 97%)	**2e** (15 mins, 96%)
2f (15 mins, 96%)	**2g** (5 mins, 95%)	**2h** (15 mins, 96%)	**2i** (10 mins, 96%)	**2j** (5 mins, 95%)
2k (5 mins, 95%)	**2l** (5 mins, 96%)[c]	**2m** (45 mins, 95%)[d]	**2n** (45 mins, 92%)[d]	**2o** (45 mins, 92%)[d]
2p (30 mins, 95%)[d]	**2q** (30 mins, 96%)[d]	**2r** (5 mins, 92%)[d]	**2s** (2h, 87%)[d]	**2t** (6 h, 91%)[c]

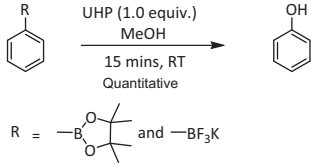
[a] Reaction condition: Substrate (1.0 mmol) and UHP (1.0 equiv) was stirred in 3 mL of methanol at room temperature.
[b] Isolated yield.
[c] 2.0 equiv of UHP was used.
[d] Acetonitrile was used as the solvent.

hydroxylation reaction with UHP in acetonitrile. Remarkably, sulfide group was found to be stable while chemoselective oxidation of boronic acid was observed in 92% yield (Table 2, **2r**). In contrast, other reagents which are reported for *ipso*-hydroxylation such as MCPBA,[6k] I_2/H_2O_2,[6j] and Amberlite/H_2O_2[6d] gave only a minor amount of desired product (<15%) along with a mixture of undesired products (Scheme 1). It is also worthy to note that heterocyclic boronic acids such as 2-formyl-3-thienylboronic acid and 3-pyridylboronic acid were successfully converted to corresponding alcohols (Table 2, **2s** and **2t**) in good yields at room temperature, which shows the broad synthetic utility of this method.

Similar to arylboronic acids, other surrogates such as phenylboronic acid pinacol ester and potassium phenyltrifluoroborate were hydroxylated in quantitative yields (Scheme 2). In addition, alkyl boronic acids such as 2-phenylethyl-, *n*-butyl- and cyclohexyl



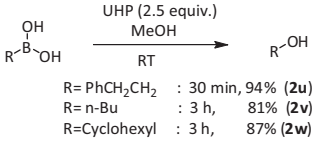
Scheme 1. Oxidation of 4-(thiomethyl)phenylboronic acid in different conditions.



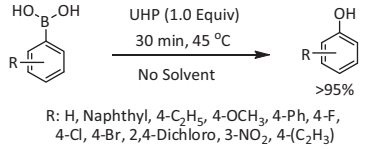
Scheme 2. Oxidation of phenyl boronic acid pinacol ester and potassium phenyltrifluoroborate.

boronic acids were also efficiently converted to corresponding alcohols in high yields (Scheme 3).

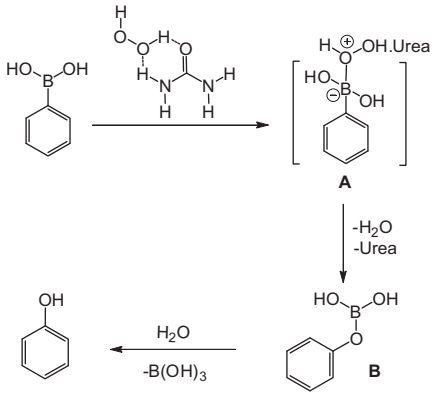
It is interesting to note that a large number of reactions can occur very efficiently under solid state condition (i.e., solvent free) when compared to the reactions carried out in solvents.[1a] During the optimization, we have observed that phenylboronic acid undergoes *ipso*-hydroxylation efficiently under solvent free condition with 1.0 equiv of UHP at 45 °C (Table 1, entry 12). To



Scheme 3. Oxidation of alkyl boronic acids with urea-hydrogen peroxide.



Scheme 4. Oxidation of arylboronic acids under solvent-free condition.



Scheme 5. Proposed mechanism of *ipso*-hydroxylation reaction.

understand the scope and limitation of this protocol, other substituted arylboronic acids were subjected for *ipso*-hydroxylation under solid state condition.[14] The substrates without sensitive functional groups gave the desired products (**2a–21**) in high yields (>95%) within 30 min (Scheme 4) while a mixture of undesired products were observed in the case of substrates with oxidation sensitive functional groups (**1n–1t**) except **1m**.[15] We presume that high reaction temperature as well as uneven mixing of substrates with oxidant (while melting), perhaps the reason for this poor selectivity. Therefore, we believe that solvent would be essential for performing a chemoselective oxidation of functionalized arylboronic acids with UHP at room temperature.

A proposed mechanism for the oxidative *ipso*-hydroxylation reaction was shown in Scheme 5. An electrophilic attack of urea-hydrogen peroxide on the boron (**A**) followed by migration of the aryl group from boron to oxygen generates the boronate ester **B**.[6k] This unstable ester is further hydrolyzed into phenol and boric acid in the presence of water. The strong hydrogen bonding between the urea and hydrogen peroxide probably enhances the stability of UHP and releases the hydrogen peroxide in a controlled manner which results in high selectivity and reactivity.[8c] On the other hand, high peroxide concentration (~97%) present in the urea-hydrogen peroxide may be an another reason for the better reactivity over simple 30% aqueous hydrogen peroxide.

In conclusion, we have demonstrated an efficient and practical method for the oxidative *ipso*-hydroxylation of arylboronic acids with urea hydrogen peroxide under catalyst and metal free condition at room temperature. The electron donating and withdrawing functional group substituted arylboronic acids as well as alkylboronic acids underwent *ipso*-hydroxylation smoothly at room temperature. Remarkably, oxidation susceptible functional groups such as olefin, aldehyde, alcohol, ketone and sulfide were tolerated under the standard reaction condition which shows the broad scope of this methodology. In addition, heterocyclic moieties such as pyridine and thiophene were found to be very stable during the *ipso*-hydroxylation to give the desired alcohols in good yields. A solid state *ipso*-hydroxylation of arylboronic acids with urea hydrogen peroxide has been investigated and observed that substrates having no sensitive functional groups undergo *ipso*-hydroxylation smoothly while a poor chemo-selectivity was observed in the case of substrates containing oxidation sensitive groups.

Acknowledgements

J.K. gratefully acknowledges IIT (BHU) for the start-up research grant and DST – India for young scientist start-up research grant (YSS/2014/000236). P.C. and S.G. acknowledge IIT (BHU) for a research fellowship. J.K. thanks Dr. K. Murugan (Yung Shin, Taiwan) and Dr. S. Sabiah (Pondicherry University) for a helpful discussion during the manuscript preparation. J.K. acknowledges Central Instrumentation Facility Center (CIFC)-IIT BHU for the NMR facilities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.099.

References and notes

1. (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025; (b) Gawande, M. B.; Bonifacio, V. D.; Luque, R.; Branco, P. S.; Varma, R. S. *ChemSusChem* **2014**, *7*, 24; (c) Ghosh, R.; Olofsson, B. *Org. Lett.* **2014**, *16*, 1830; (d) Sun, C. L.; Shi, Z. J. *Chem. Rev.* **2014**, *114*, 9219; (e) Nagaraju, A.; Ramulu, B. J.; Shukla, G.; Srivastava, A.; Verma, G. K.; Raghuvanshi, K.; Singh, M. S. *Green Chem.* **2015**, *17*, 950; (f) Lu, G. P.; Zeng, L. Y.; Cai, C. *Green Chem.* **2011**, *13*, 998; (g) Qu, G. R.; Mao, Z. J.; Niu, H. Y.; Wang, D. C.; Xia, C.; Guo, H. M. *Org. Lett.* **2009**, *11*, 1745.
2. (a) James, R.; Glen, J. B. *J. Med. Chem.* **1980**, *23*, 1350; (b) Mishra, B. B.; Tiwari, V. K. *Eur. J. Med. Chem.* **2011**, *46*, 4769; (c) Amorati, R.; Valgimigli, L. *Org. Biomol. Chem.* **2012**, *10*, 4147; (d) Nicholson, R. L.; Hammerschmidt, R. *Annu. Rev. Phytopathol.* **1992**, *30*, 369.
3. (a) O'Connell, J. E.; Fox, P. F. *Int. Dairy J.* **2001**, *11*, 103; (b) Balasundram, N.; Sundram, K.; Samman, S. *Food Chem.* **2006**, *99*, 191; (c) Choudhary, R. K.; Swarnkar, P. L. *Nat. Prod. Res.* **2011**, *25*, 1101; (d) Ranilla, L. G.; Kwon, Y. I.; Apostolidis, E.; Shetty, K. *Bioresource Technol.* **2010**, *101*, 4676.
4. (a) Tyman, J. H. P. *Synthetic and Natural Phenols*; Elsevier: New York, 1996; (b) Rappoport, Z. *The Chemistry of Phenols*; John Wiley & Sons, 2013; (c) Pilato, L. *React. Funct. Polym.* **2013**, *73*, 270.
5. Hall, D. G. *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*; Wiley-VCH, 2006.
6. (a) Xu, J. M.; Wang, X. Y.; Shao, C. W.; Su, D. Y.; Cheng, G. L.; Hu, Y. F. *Org. Lett.* **2010**, *12*, 1964; (b) Chowdhury, A. D.; Mobin, S. M.; Mukherjee, S.; Bhaduri, S.; Lahiri, G. K. *Eur. J. Inorg. Chem.* **2011**, 3232; (c) Paul, A.; Chatterjee, D.; Rajkamal; Haider, T.; Banerjee, S.; Yadav, S. *Tetrahedron Lett.* **2015**, *56*, 2496; (d) Mulakayala, N.; Ismail; Kumar, K. M.; Rapolu, R. K.; Kandagatla, B.; Rao, P.; Oruganti, S.; Pal, M. *Tetrahedron Lett.* **2012**, *53*, 6004; (e) Yang, D. S.; An, B. J.; Wei, W.; Jiang, M.; You, J. M.; Wang, H. *Tetrahedron* **2014**, *70*, 3630; (f) Chatterjee, N.; Goswami, A. *Tetrahedron Lett.* **2015**, *56*, 1524; (g) Begum, T.; Gogoi, A.; Gogoi, P. K.; Bora, U. *Tetrahedron Lett.* **2015**, *56*, 95; (h) Mahanta, A.; Adhikari, P.; Bora, U.; Thakur, A. J. *Tetrahedron Lett.* **2015**, *56*, 1780; (i) Hosoi, K.; Kuriyama, Y.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2010**, 1284; (j) Gogoi, A. *Synlett* **2012**; (k) Chen, D. S.; Huang, J. M. *Synlett* **2013**, 499; (l) Zhu, C.; Wang, R.; Falck, J. R. *Org. Lett.* **2012**, *14*, 3494; (m) Prakash, G. K. S.; Chacko, S.; Panja, C.; Thomas, T. E.; Gurung, L.; Rasul, G.; Mathew, T.; Olah, G. A. *Adv. Synth. Catal.* **2009**, *351*, 1567; (n) Qj, H. L.; Chen, D. S.; Ye, J. S.; Huang, J. M. *J. Org. Chem.* **2013**, *78*, 7482; (o) Gupta, S.; Chaudhary, P.; Seva, L.; Sabiah, S.; Kandasamy, J. *RSC Adv.* **2015**, *5*, 89133; (p) Zou, Y. Q.; Chen, J. R.; Liu, X. P.; Lu, L. Q.; Davis, R. L.; Jorgensen, K. A.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 784; (q) Molloy, J. J.; Law, R. P.; Fyfe, J. W. B.; Seath, C. P.; Hirst, D. J.; Watson, A. J. B. *Org. Biomol. Chem.* **2015**, *13*, 3093.
7. Jones, C. W. *Applications of Hydrogen Peroxide and Derivatives*; RSC Royal Society of Chemistry: Cambridge, 1999.
8. (a) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533. and references cited therein; (b) Taliansky, S. *Synlett* **2005**, 1962. and references cited therein; (c) Ankudey, E. G.; Olivo, H. F.; Peeplesa, T. L. *Green Chem.* **2006**, *8*, 923; (d) Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *1*, 189.
9. Mokhlis, G. R.; Matis, B. A.; Cochran, M. A.; Eckert, G. J. *J. Am. Dent. Assoc.* **2000**, *131*, 1269.
10. Chaudhary, P.; Gupta, S.; Muniyappan, N.; Sabiah, S.; Kandasamy, J. *Green Chem.* **2016**, *18*, 2323.
11. In the case of substrates with aldehyde group, a minor amount of methyl esters were observed. On the other hand, more than one product was observed in the case of sulfide functionalized boronic acid which may corresponds to 4-(methylsulfinyl)phenylboronic acid and 4-(methylsulfinyl)phenol).

12. *Modern Oxidation Methods*; Bäckvall, J.-E., Ed., 2nd ed.; Wiley-VCH: Weinheim, 2010.
13. Chakravarthy, R. D.; Ramkumar, V.; Chand, D. K. *Green Chem.* **2014**, *16*, 2190.
14. In most of the cases, we have observed exothermicity (heat generation) while mixing UHP with arylboronic acids under solvent free condition at room temperature (we have attempted all the reactions in 1 mmol scale). For a gram scale reaction, the flask containing arylboronic acids should be cooled (~0–5 °C) before adding UHP and appropriate precautions should be taken.
15. It has been reported previously that oxidation of sulfide, pyridine, aldehyde, etc., can be achieved using UHP under solid state condition in higher temperature without any catalysts. See Ref. 8d.