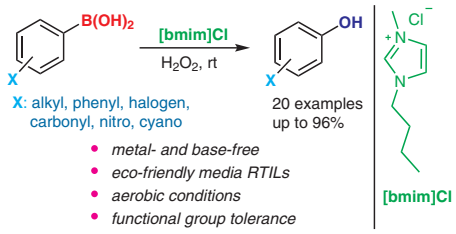
Synlett E.-J. Shin et al. Letter

Room-Temperature Ionic Liquids (RTILs) as Green Media for Metal- and Base-Free *ipso*-Hydroxylation of Arylboronic Acids

Eun-Jae Shin
Gyu-Tae Kwon
Seung-Hoi Kim*

Department of Chemistry, Dankook University, 119 Dandaero, Cheonan 31116, Republic of Korea
kimsemail@dankook.ac.kr



Received: 26.06.2019
Accepted after revision: 03.07.2019
Published online: 17.07.2019
DOI: 10.1055/s-0037-1611894; Art ID: st-2019-k0331-l

Abstract The oxidative hydroxylation of arylboronic acids to the corresponding phenolic compounds under metal- and base-free aerobic conditions is successfully demonstrated on a greener media. Hydrogen peroxide, as an eco-friendly oxidant, is compatible with green mediates room-temperature ionic liquids (RTIL)s, providing hydroxylation products of arylboronic acids in an efficient manner. The RTIL support is particularly interesting for its reusability.

Key words room-temperature ionic liquid, *ipso*-hydroxylation, arylboronic acid, phenol, hydrogen peroxide

The functional group transformation of organic compounds is one of the fundamental pathways used to introduce novel functionality into organic derivatives, and this approach has been frequently utilized to obtain valuable target materials in both academic and industrial chemical processes. Several strategies have been developed to determine more efficient protocols providing various functional groups in organic compounds that play significant roles in synthetic organic chemistry. Among the many organic compounds prepared using this functional group conversion, phenols have been considered and used as one of the most important organic materials.[1] Therefore, the synthesis of phenols continues to attract the attention of organic chemists. To obtain phenol derivatives through chemical synthetic routes, the *ipso*-hydroxylation of phenylboronic acid has been intensively and widely used under various reaction conditions.[2]

For the success of this method, the use of an oxidant such as anhydrous trimethylamine *N*-oxide[3], OXONE,[4] hypervalent iodine,[5] hydroxylamine[6] or peroxides,[7] photocatalyzed hydroxylation,[8] and metal-complex-mediated transformations[9] have been developed. In addition, metal-free biocatalysts have been efficiently applied to the *ipso*-hydroxylation of arylboronic acids.[10] It is of interest that this transformation has been intensively carried out using hydrogen peroxide as an oxidant because it is a well-known high-efficiency-per-weight, and environmentally benign, oxidant. Numerous investigations have been performed to improve the efficiency and convenience of the process under diverse systems utilizing H_2O_2 and various supports. Urea,[11] biosilica[12] PEG-400,[13] H_3BO_3,[14] Al_2O_3,[15] WERSE,[16] PVD/PVP,[17] iodine,[18] Amberlite IR-120,[19] Mont K-10@Ag-NPs,[20] and silica chloride[21] have been used as supports for the successful conversion of boronic acids into the desired phenolic derivatives.

Notwithstanding the good results obtained through the protocols, continuous efforts have been 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 suitable approaches to reducing the economic and environmental burden of various chemical processes. In our search for more environmentally friendly routes, we sought potentially greener reaction conditions, such as the use of a benign oxidant and a sustainable support under aerobic conditions, to promote the hydroxylation of arylboronic acid. Thus, we postulated that the combination of hydrogen peroxide and room-temperature ionic liquids (RTILs) would be a greener reaction system for the *ipso*-hydroxylation of arylboronic acid, furnishing the corresponding phenols.

To date, the development of green and sustainable chemical processes with no waste production, maximum material recycling, and lower financial burden is the biggest challenge in chemical industries. To address this issue, chemists began looking for more versatile solvents, eventually using ionic liquids (ILs) consisting of a substituted heterocyclic cation with an organic or inorganic anion.[22] It is

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

well known that RTILs exist in liquid state at room temperature and have unique properties such as nonvolatility, thermal stability, solvation ability, and easy recyclability. These unique characteristic properties render RTILs as more versatile materials, not only as chemical mediates but also as precious substances in organic synthetic catalysis, solid support, and nanoparticle formation.[23]

Regarding the application of RTILs as a reaction media in oxidative hydroxylation, an interesting study on the preparation of a task-specific IL, acid-functionalized magnetic ionic liquid ([AcMAIL]), and its application was recently reported by Banerjee et al.[24] The prepared [AcMAIL]s were successfully employed in the *ipso*-hydroxylation of arylboronic acids in addition to the regioselective Friedel–Crafts acylation in the presence of hydrogen peroxide.

Initially, building on the previous work of others[24] and of our own[25] on achieving the *ipso*-hydroxylation of arylboronic acids, we postulated that a combination of hydrogen peroxide and simple RTILs could be used for the preparation of phenols through the hydroxylation of arylboronic acids.

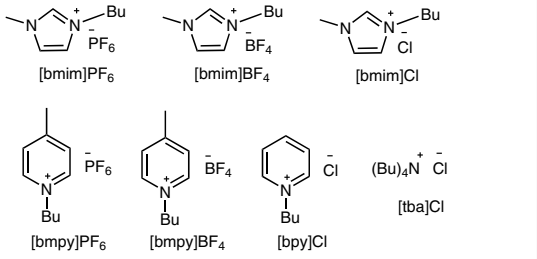
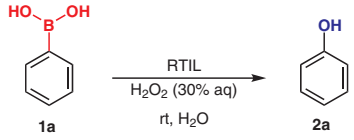


Figure 1 RTILs used in the reaction optimization

For developing such a reaction system, we have undertaken the *ipso*-hydroxylation of phenylboronic acids using acid- and metal-free RTILs along with hydrogen peroxide. As described in Table 1, all of the RTILs used in this study are commercially and readily available. Moreover, one characteristic nature of RTILs is water-miscibility, which depends on the anion species of the IL.[26] Since our reaction system consists of aqueous H_2O_2 and water, the initial objective is to elucidate the effect of the anions. Thus, several RTILs (Figure 1) possessing different anions, [bmim]PF_6, [bmim]BF_4, and [bmim]Cl, were tested first under the conditions described in Table 1. In general, a satisfactory outcome forming the desired product **2a** was obtained regardless of the anion species presented in the RTILs. However, it is of interest that a relatively longer reaction time was required for the conversion into **2a** when less hydrophilic RTILs were employed (Table 1, entries 1 and 2). Of the RTILs tested, the most water-miscible media, [bmim]Cl, turned out to be very effective in our system in terms of the reaction time and isolated yield of desired product **2a** (Table 1, entry 3). To verify the effect of the cationic part of the RTILs, slightly different types of RTILs possessing either 1-butyl-4-methylpyridium or 1-butylpyridium as a cationic component were also examined for the hydroxylation of **1a** under the same conditions. As depicted in Table 1, the results were nearly identical to those of the previous tests (Table 1, entries 4–6). The characteristic reactivity of the anion of the IL was further confirmed using another hydrophilic RTIL, [tba]Cl (Table 1, entry 7).

Table 1 Screening the RTILs for Hydroxylation of Phenylboronic Acid (**1a**)

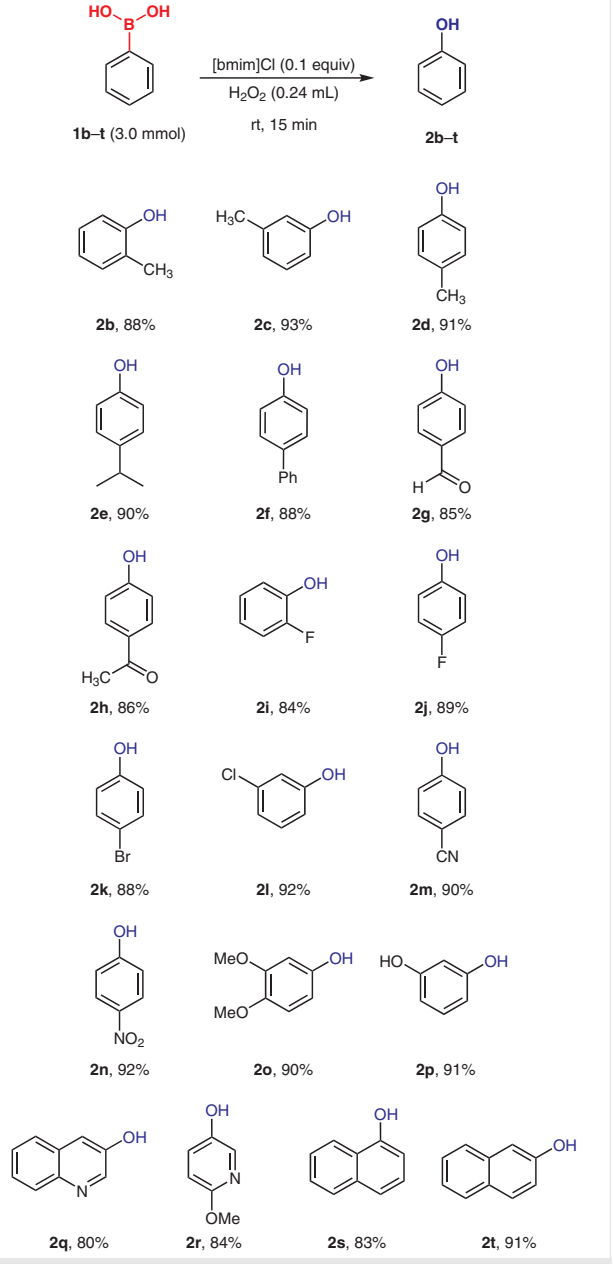


Entry[a]	RTIL (equiv)	Time	Yield (%)[b]
1	[bmim]PF_6 (0.1)	6 h	92
2	[bmim]BF_4 (0.1)	4 h	97
3	[bmim]Cl (0.1)	10 min	96
4	[bmpy]PF_6 (0.1)	6 h	90
5	[bmpy]BF_4 (0.1)	4 h	95
6	[bpy]Cl (0.1)	10 min	95
7	[tba]Cl (0.1)	10 min	96
8	[bmim]Cl (1.0)	10 min	95
9	[bmim]Cl (0.05)	12 h	68
10	[bmim]Cl (0.01)	24 h	64
11	none	48 h	40

[a] Reaction conditions: 1.0 equiv of **1a** and 1.0 equiv of H_2O_2.
[b] Isolated yield based on **1a**.

Our following experiments focused on the effect of the amount of the [bmim]Cl media used. To evaluate this, variable amounts of [bmim]Cl were employed, and the results are described in Table 1. No significant outcome was observed from increasing the amount of [bmim]Cl up to 1.0 equivalent (Table 1, entry 8). In contrast, when the reaction was performed with decreased amounts of reaction media, the reduced isolated yield of **2a** and prolonged reaction times for conversion were observed (Table 1, entries 9 and 10). To verify the role of the IL, the conversion of **1a** into **2a** was tested in the absence of IL. Unfortunately, the reaction did not reach completion even when the reaction time was prolonged (Table 1, entry 11).

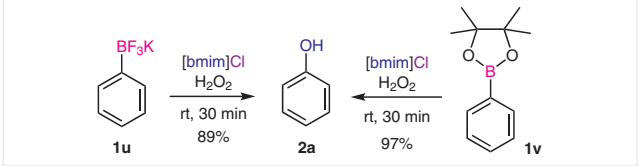
Based on the results obtained thus far, we inferred that the cooperation between RTILs and the H_2O_2 oxidant would be a versatile route for the *ipso*-hydroxylation of arylboronic acids for producing the corresponding hydroxylation products. Having established the optimum conditions (Table 1, entry 3), we further explored the versatility and applicability of our system by using various arylboronic acids for the *ipso*-hydroxylation. The results are presented in Scheme 1.



Scheme 1 Substrate screening

Irrespective of the electronic properties of the arylboronic acids, the transformation was successful, resulting in the moderate to high yields of the corresponding phenolic compounds. Notably, the present catalytic system displayed a considerable tolerance toward various functional groups such as carbonyl (**2g** and **2h**), halogens (**2i–l**), cyano (**2m**), nitro (**2n**), and alkoxy (**2o** and **2p**) functionalities. Although their products were obtained in relatively low yields, heteroaryl boronic acids were also amenable to this protocol. Quinoline-3-boronic acid and 6-methoxy-3-pyridinylboronic acid were examined under the same conditions, leading to the desired products **2q** and **2r**, respectively. However, hydroxylation of 2-furanyl and 3-thienylboronic acids resulted in negligible yields under identical conditions. The conversions of both naphthalene-1-boronic acid and naphthalene-2-boronic acid also occurred, producing the corresponding products 1-naphthol (**2s**) and 2-naphthol (**2t**) at 83% and 91% isolated yields, respectively. Furthermore, we explored this method for the alkylboronic acid, octylboronic acid, showing a mixture of unidentified products.

Even though diverse boronic acids are readily available and highly cooperative in our system, the tendency of boronic acids to rapidly decompose and other drawbacks have limited their applications in organic synthesis.[27] To overcome the shortcomings and expand the scope of our system, potassium phenyltrifluoroborate (**1u**) and phenyl boronic acid ester (**1v**) were employed as boronic acid surrogates under the same conditions used earlier in this study. As depicted in Scheme 2, the transformation was uneventful, producing the desired product **2a** in good to excellent yields. The completion of the conversion of these surrogates into phenol required a slightly prolonged reaction time.



Scheme 2 Expansion to boronic acid surrogates

From the viewpoint of sustainability, recycling and reuse of reaction media should be investigated to increase the value of the presented protocol. Accordingly, we turned our attention to recycling and reuse of the reaction media RTIL. Since the RTILs are insoluble in organic solvent, the reaction mixture was extracted with diethyl ether after the initial reaction was completed. Then, the recycled [bmim]Cl was directly employed in the consecutive conversion of phenylboronic acid (**1a**) into phenol (**2a**) under the same conditions used before. As described in Figure 2, the transformation proceeded well, as expected, in a fashion similar to the case of using fresh [bmim]Cl. The conversion was completed within 10 min in each run to afford **2a** in satisfactory yield from the 1st, 2nd, and 3rd runs together with the slightly diminished yields of **2a** from both the 4th and 5th runs (Figure 2). The effect of the residents that could be cumulated from the previous runs in the IL has not yet been fully investigated.

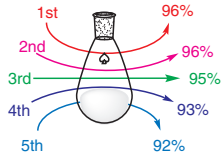
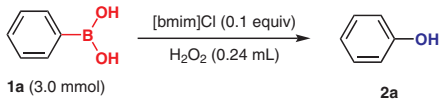


Figure 2 Reusability test

At this point, as was stated above, the successful transformation of arylboronic acids to phenolic compounds using [AcMAIL]s, which contain an iron metal and an acidic moiety has been revealed.[24] Therefore, it would be important to investigate whether or not the presence of these substance affect our system. To elucidate the influence, we set up the hydroxylation of phenylboronic acid utilizing our reaction system along with $FeCl_3$ or acetic acid, and the results are summarized in Table 2. As depicted, the reaction with $FeCl_3$ at room temperature was initialized vigorously, which rendered monitoring the progress impossible (Table 2, entry 1) whereas the hydroxylation starting up in an ice-bath did not occur and low conversion into **2a** was observed even when the temperature was allowed to warm up to room temperature (Table 2, entry 2). No further investigations to elucidate this observation were performed in this study. In contrary, transformation to **2a** proceeded smoothly in the presence of acetic acid, but little disappointed outcome was revealed (Table 2, entry 3). These two experiments clearly indicated that the simple addition of iron salts or acetic acid was not compatible with our newly developed system.

Table 2 The Effect of Metal or Acid on the Reaction



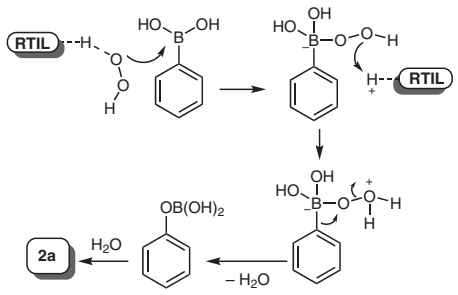
1a (3.0 mmol) **2a**

Entry	Additive (equiv[a])	Conditions	Result
1	$FeCl_3$ (1.0)	rt	too vigorous
2	$FeCl_3$ (1.0)	0 °C to rt	low conversion
3	AcOH (1.0)	rt, 10 min	**2a** (85%)[b]

[a] Based on **1a**.
[b] Isolated yield based on **1a**.

For a more practical use of our protocol, we investigated a gram-scale test using 5 grams of **1a** under the conditions used before. The conversion proceeded in a similar fashion, resulted in **2a** in 95% isolated yield.

In consideration of a plausible mechanistic aspect, the successful metal- and base-free hydroxylation of arylboronic acids to the corresponding alcohols can be attributed to the enhanced nucleophilicity of hydrogen peroxide through hydrogen bonding with the RTIL which is consisted of cationic and anionic components (Scheme 3).



Scheme 3 Plausible mechanism for the *ipso*-hydroxylation of **1a**

In conclusion, we have developed a simpler and greener protocol for the *ipso*-hydroxylation of boronic acids that produces the corresponding alcoholic derivatives in a satisfactory manner.[28] The combination of eco-friendly oxidant H_2O_2 and ready availability of RTILs were sufficient enough to convert arylboronic acids into phenols under mild aerobic conditions at excellent yields.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611894.

References and Notes

(1) (a) Tyman, J. H. P. In *Synthetic and Natural Phenols*; Elsevier: New York, **1996**. (b) Rappoport, Z. In *The Chemistry of Phenols*; Wiley-VCH: Weinheim, **2003**.
(2) (a) Ainley, A. D.; Challenger, F. *J. Chem. Soc.* **1930**, 2171. (b) Zhu, C.; Falck, J. R. *Adv. Synth. Catal.* **2014**, *356*, 2395. Alternative typical protocols for the nucleophilic substitution of activated aryl halides and transition-metal-catalyzed conversion into phenols: (c) Fyfe, C. A. *The Chemistry of the Hydroxyl Group, Part 1, Vol. 1*; Wiley Interscience: New York, **1971**.
(3) Zhu, C.; Wang, R.; Falck, J. R. *Org. Lett.* **2012**, *14*, 3497.
(4) (a) Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2011**, *76*, 623. (b) Maleczka, R. E. Jr; Shi, F.; Holmes, D.; Smith, M. R. III *J. Am. Chem. Soc.* **2003**, *125*, 7792. (c) Travis, B. R.; Ciaramitaro, B. P.; Borhan, B. *Eur. J. Org. Chem.* **2002**, 3429. (d) Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117.
(5) Chatterjee, N.; Goswami, A. *Tetrahedron Lett.* **2013**, *56*, 1524.
(6) Kianmehr, E.; Yahyaee, M.; Tabatabai, K. *Tetrahedron Lett.* **2007**, *48*, 2713.
(7) (a) Guo, S.; Lu, L.; Cai, H. *Synlett* **2014**, *25*, 1712. (b) Chen, D.-S.; Huang, J.-M. *Synlett* **2013**, *24*, 499.
(8) (a) Toyao, T.; Ueno, N.; Miyahara, K.; Matsui, Y.; Kim, T.-H.; Horiuchi, Y.; Ikeda, H.; Matsuoka, M. *Chem. Commun.* **2015**, *51*, 16103. (b) Zhang, M. J.; Li, H. X.; Li, H. Y.; Lang, J. P. *Dalton Trans.* **2016**, *45*, 17759. (c) Yu, X.; Cohen, S. M. *Chem. Commun.* **2015**, *51*, 9880. (d) Luo, J.; Zhang, X.; Zhang, J. *ACS Catal.* **2015**, *5*, 2250. (e) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 13286. (f) Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jørgensen, K. A.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2012**, *51*, 784. (g) Johnson, J. A.; Luo, J.; Zhang, X.; Chen, Y. S.; Morton, M. D.; Echeverría, E.; Torres, F. E.; Zhang, J. *ACS*

Catal. **2015**, *5*, 5283. (h) Wang, Z. J.; Li, R.; Landfester, K.; Zhang, K. A. I. *Polymer* **2017**, *126*, 291. (i) Xie, H. Y.; Han, L. S.; Hung, S.; Lei, X.; Cheng, Y.; Zhao, W.; Sun, H.; Wen, X.; Xu, Q. L. *J. Org. Chem.* **2017**, *82*, 5236. (j) Sawant, S. D.; Hudwekar, A. D.; Kumar, K. A. A.; Venkateswarlu, V.; Singh, P. P.; Vishwakarma, R. A. *Tetrahedron Lett.* **2014**, *55*, 811. (k) Matsui, K.; Ishigami, T.; Yamaguchi, T.; Yamaguchi, E.; Tada, N.; Miura, T.; Itoh, A. *Synlett* **2014**, *25*, 2613.

(9) (a) Dar, B. A.; Bhatti, P.; Singh, A. P.; Lazar, A.; Sharma, P. R.; Sharma, M.; Singh, B. *Appl. Catal. A* **2013**, *466*, 60. (b) Yang, D.; An, B.; Wei, W.; Jiang, M.; You, J.; Wang, H. *Tetrahedron* **2014**, *70*, 3630. (c) Yang, H.; Li, Y.; Jiang, M.; Wang, J.; Fu, H. *Chem. Eur. J.* **2011**, *17*, 5652. (d) Affrose, A.; Azath, I. A.; Dhakshinamoorthy, A.; Pitchumani, K. *J. Mol. Catal. A: Chem.* **2014**, *395*, 500. (e) Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett.* **2010**, *12*, 1964. (f) Inamoto, K.; Nozawa, K.; Yonemoto, M.; Kondo, Y. *Chem. Commun.* **2011**, *47*, 11775. (g) Zheng, J.; Lin, S.; Zhu, X.; Jiang, B.; Yang, Z.; Pan, Z. *Chem. Commun.* **2012**, *48*, 6235. (h) Gogoi, N.; Gogoi, P. K.; Borah, G.; Bora, U. *Tetrahedron Lett.* **2016**, *57*, 4050.

(10) (a) Silveria-Dorta, G.; Monzon, D. M.; Crisostomo, F. P.; Martin, T.; Martin, V. S.; Carrillo, R. *Chem. Commun.* **2015**, *51*, 7027. (b) Kotoucova, H.; Strnadova, I.; Kovandova, M.; Chudoba, J.; Dvorakova, H.; Cibulka, R. *Org. Biomol. Chem.* **2014**, *12*, 2137.

(11) Gupta, S.; Chaudhary, P.; Srivastava, V.; Kandasamy, J. *Tetrahedron Lett.* **2016**, *57*, 2506.

(12) Mahanta, A.; Adhikari, P.; Bora, U.; Thakur, A. J. *Tetrahedron Lett.* **2015**, *56*, 1780.

(13) Gohain, M.; du Plessis, M.; van Tonder, J. H.; Bezuidenhoudt, B. C. B. *Tetrahedron Lett.* **2014**, *55*, 2081.

(14) Gogoi, K.; Dewan, A.; Gogoi, A.; Borah, G.; Bora, U. *Heteroat. Chem.* **2014**, *25*, 127.

(15) Gogoi, A.; Bora, U. *Tetrahedron Lett.* **2013**, *54*, 1821.

(16) Saikia, E.; Bora, S. J.; Chetia, B. *RSC Adv.* **2015**, *5*, 102723.

(17) 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.

(18) Gogoi, A.; Bora, U. *Synlett* **2012**, *23*, 1079.

(19) Mulakayala, N. ; Ismail; Kumar, K. M.; Rapolu, R. K.; Kandagatla, B.; Rao, P.; Oruganti, S.; Pal, M. *Tetrahedron Lett.* **2012**, *53*, 6004.

(20) Begum, T.; Gogoi, A.; Gogoi, P. K.; Bora, U. *Tetrahedron Lett.* **2015**, *56*, 95.

(21) Wagh, R. B.; Nagarkar, J. N. *Tetrahedron Lett.* **2017**, *58*, 3323.

(22) (a) Wasserscheid, P.; Welton, T. In *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, **2002**. (b) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3773.

(23) For a recent review, see: Vekariya, R. L. *J. Mol. Liquids* **2017**, *227*, 44; and references cited therein for the applications of ILs.

(24) Saha, A.; Payra, S.; Dutta, D.; Banerjee, S. *ChemPlusChem* **2017**, *82*, 1129.

(25) (a) Shin, E.-J.; Kim, H.-S.; Joo, S.-R.; Shin, U. S.; Kim, S.-H. *Catal. Lett.* **2019**, *149*, 1560. (b) Joo, S.-R.; Kwon, G.-T.; Park, S.-Y.; Kim, S.-H. *Bull. Korean Chem. Soc.* **2019**, *40*, 465. (c) Shin, E.-J.; Joo, S.-R.; Kim, S.-H. *Tetrahedron Lett.* **2019**, *55*, 1509.

(26) Kim, K.-S.; Shin, B.-K.; Lee, H. *Korean J. Chem. Eng.* **2004**, *21*, 1010.

(27) (a) Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P.-S.; Kenndy, L. E. *J. Org. Chem.* **2009**, *74*, 7364. (b) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716.

(28) **Typical Procedure for the *ipso*-Hydroxylation**

A flask was charged with phenylboronic acid (3.0 mmol), [bmim]Cl (52.0 mg), and H_2O_2 (aq 30 wt%, 0.24 mL). Then, the mixture was stirred at room temperature in open air for 15 min. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water, then dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (hexanes/EtOAc).

Phenol (2a)

96%, colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 8.4 Hz, 2 H), 6.99–6.95 (m, 1 H), 6.89–6.85 (m, 2 H), 4.80 (br s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 129.7, 120.9, 115.3 ppm.