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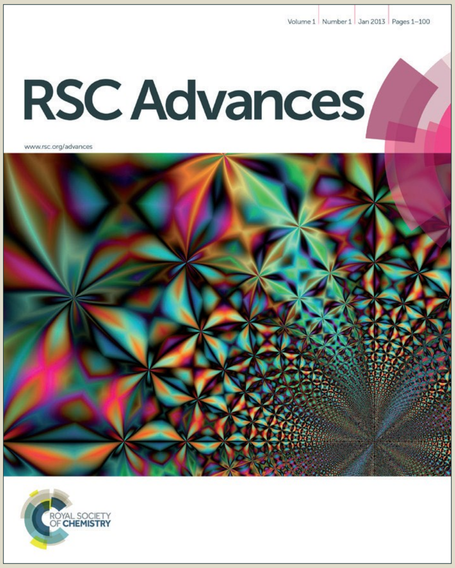
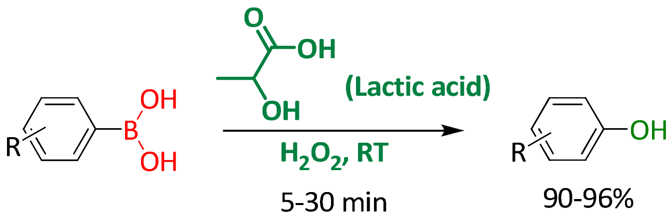


Table of Contents Entry



A bio-based green solvent, lactic acid is found to be an efficient reaction medium for the catalyst free oxidation of aryl boronic acids into phenols with aqueous hydrogen peroxide.

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Bio-based green solvent for the catalyst free oxidation of arylboronic acids into phenols

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A bio-based green solvent, lactic acid is found to be an efficient reaction medium for the catalyst free oxidation of arylboronic acids into phenols with aqueous hydrogen peroxide. Various substituted arylboronic acids have undergone *ipso*-hydroxylation smoothly at room temperature to provide corresponding phenols in excellent yields. Remarkably, the oxidation susceptible functional groups such as sulphide, ketone, aldehyde and olefin are tolerated under the reaction conditions. Over all, lactic acid showed higher efficiency as a solvent medium when compared with conventional acetic acid.

Solvents play an important role in organic synthesis while in some cases solvents itself drive the reaction without any catalysts.[1] Such kind of catalyst free organic reactions offer several advantages like reduced environmental pollutions, uncomplicated experimental and workup procedures, simple purification steps, etc.[2, 3] Therefore, the catalyst free organic transformations have received more attention in recent years. On the other hand, "green solvents" have been focused in the past few decades in order to minimize the environmental pollution resulting from the use of hazardous solvents in chemical production.[4-7] Green solvents have been majorly characterized by their level of toxicity, volatility, reusability, stability, flammability, bio-degradability and renewability.[8, 9] In the past decade, water, supercritical CO_2, ionic liquids, organic carbonates, fluorous compounds and polyethylene glycol (PEG) were identified as green solvents and efficiently used in organic synthesis (Figure 1, **A**).[4-9] Recently, bio-based solvents which are produced from renewable sources have received much attention due to their sustainability and eco-compatibility (Figure 1, **B**).[10] From environmental point of view, bio-based solvents are also considered as green solvents which could be an alternative not only to the conventional petroleum based solvents, but also to the expensive non-bio based green solvents in organic synthesis.[10-12]

Glycerol, a by-product obtained from triglycerides during the biodiesel production, is already explored as a green solvent in many organic reactions.[13,14] Other bio-based solvents such as 2-methyltetrahydrofuran, ethyl lactate, ɣ-valerolactone, D-limonene, *p*-cymene and fatty acid methyl esters (FAMEs) are now significantly replacing the hazardous petroleum solvents in many organic synthesis.[4-12] In addition, eutectic mixture of various biomass derived chemicals or solvents (example: eutectic mixture of glycerol, levulinic acid, carbohydrates, gluconic acid, etc.) have found selective applications in organic synthesis as well as in pharmaceutics.[15-18]

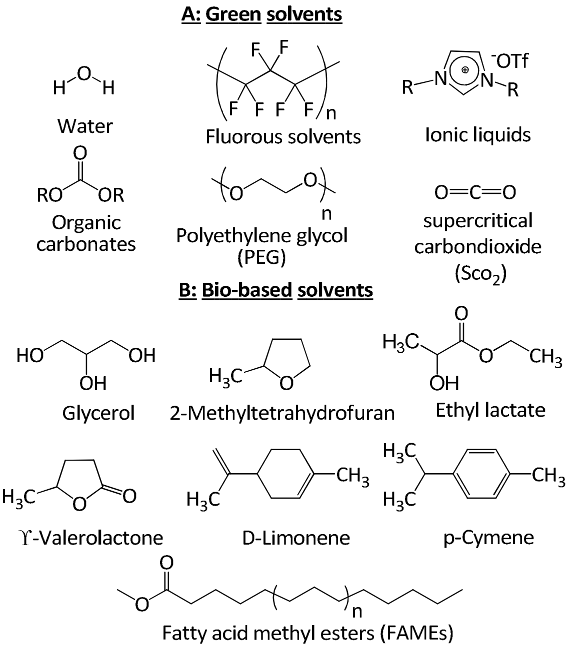

Figure 1. Structures of various green and bio-based solvents used in organic synthesis.

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Phenolic compounds have found wide applications in various fields like medicines, cosmetics, food industry, materials and polymers, etc (Figure 2).[19-24] There are different approaches for the preparation of phenolic compounds which includes i) nucleophilic substitution of aryl halides with hydroxyl nucleophile, ii) diazotization of aromatic amines followed by aqueous hydrolysis, iii) CH-oxidation of aryl rings and iv) oxidative hydrolysis of arylboronic acids.[25] Synthesis of phenols from arylboronic acids is becoming more preferable as compared to other methods due to ready availability, low toxicity and high stability (toward heat, air and moisture) of arylboronic acids.[26] Therefore, recently numerous methods have been developed for the oxidative conversion of arylboronic acids into phenols using transition metals, hydrogen peroxide with different catalysts, hypervalent iodine reagents, N-oxides, photo catalysts and electrochemical techniques.[27-38] The common problems associated with majority of these reports are the use of harsh reaction conditions,[36] non-ecofriendly solvents[34], high reaction temperature,[36] longer reaction time,[33] excess oxidants,[27, 28, 35] non-commercially available catalysts or oxidants,[29, 30, 34] etc. Therefore, the development of simple, efficient and greener method is still in demand and we have directed our studies towards finding a suitable catalyst free system for the oxidative conversion of arylboronic acids into phenols using green oxidant aqueous hydrogen peroxide.

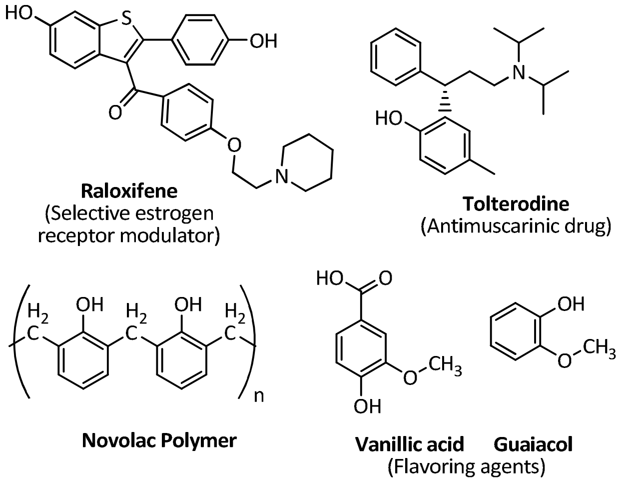
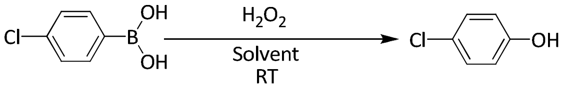


Figure 2. Applications of phenolic compounds in different fields.

At the outset, 4-chlorophenylboronic acid was chosen as a model substrate and oxidized with 1.0 equivalent of 30% aqueous hydrogen peroxide in various solvents such as methanol, ethanol, t-butanol, water, tetrahydrofuran (THF), acetonitrile, toluene, glycerol and acetic acid (Table 1). Among the polar protic solvents, methanol provides the maximum yield of 4-chlorophenol, i.e. 41% after 60 minutes (Table 1, entry 1) while other protic solvents such as ethanol, t-BuOH, glycerol and water gave relatively lower yields (Table 1, entries 2-5). It is also important to note that even after prolonged reaction time (12 h) full conversion of boronic acid into phenol was not observed in methanol (Table 1, entry 6). Further, the oxidation reaction was carried out in polar aprotic solvents such as THF, acetonitrile and toluene (Table 2, entries 7-9). The maximum yield of 42% was observed in acetonitrile while THF and toluene provide less than 40% of the desired product. Finally, we have tested the reaction in acetic acid and fortunately the reaction leads to completion in 15 minutes to yield 95% of 4-chlorophen (Table 1, entry 10). Despite the efficiency, acetic acid (glacial) is corrosive, and its vapor irritates the eyes, produces a burning sensation in the nose, and can lead to a sore throat and lung congestion.[39] Moreover, about 75% of the acetic acid used in the industry is currently produced through chemical methods.[40, 41]

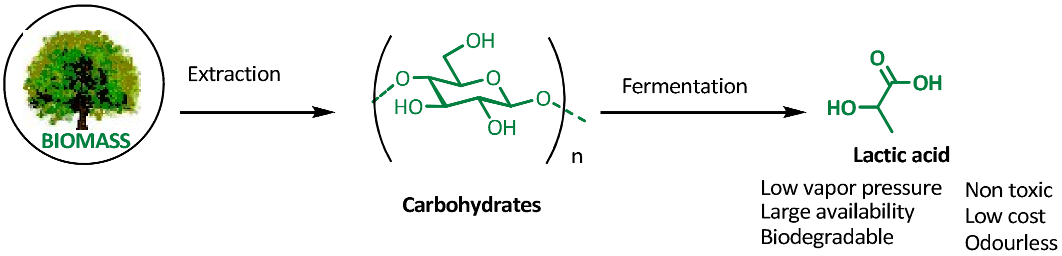
Table 1. Oxidation of 4-chlorophenylboronic acid in various solvents with hydrogen peroxide.[a]



Entry	Solvent	H_2O_2 (equiv.)	Time (min)	Yield (%)[b]
1	CH_3OH	1.0	60	41
2	C_2H_5OH	1.0	60	37
3	t-BuOH	1.0	60	33
4	Glycerol	1.0	60	18
5	H_2O	1.0	60	31
6	CH_3OH	1.0	12 h	84
7	THF	1.0	60	38
8	CH_3CN	1.0	60	42
9	Toluene	1.0	60	35
10	CH_3COOH	1.0	15	95
11	Lactic acid	1.0	5	95

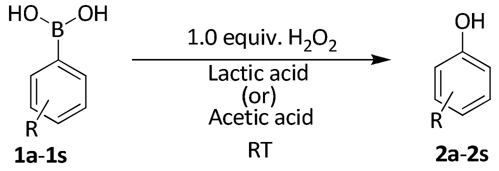
[a]Reaction conditions: Substrate (0.5 mmol), Solvent (1 mL), H_2O_2 (1.0 equiv.), stirred RT. [b] Isolated Yield

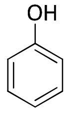
Lactic acid is a biomass derived weak acid widely used in the food, agricultural, textile, pharmaceutical and cosmetic industries.[42, 43] However, lactic acid is less explored as a solvent in organic synthesis while acetic acid have found wide applications. In contrast with acetic acid, lactic acid is a nontoxic and odorless liquid produced through the safer fermentation method from carbohydrates (Scheme 1).[43,44] The pKa, density and boiling point of lactic acid is 3.7, 1.20 g/cm^3 and 120 °C, respectively, which is comparable with acetic acid (pKa. 4.7, d: 1.05g/cm^3 and bp.117 °C) and therefore we anticipate that lactic acid can be a suitable alternative to the acetic acid.[45] Recently, Yanlong Gu group has demonstrated the first application of lactic acid as a green solvent for multi-component reactions (MCR) with several advantages like reusability of the reaction medium, high efficiency, easy isolation of products, etc.[45] Impressed by the above work, we have carried out the oxidation reaction in lactic acid and pleased to see the quick and clean conversion of 4-chlorophenylboronic acid into 4-chlorophenol in good yield (Table 1, entry 11). Encouraged, we have further studied the oxidation of various functionalized arylboronic acids not only in lactic acid, but also in acetic acid in order to compare the efficiency of the reaction mediums. The results obtained are summarized in Table 2.

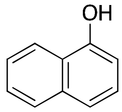


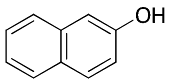
Scheme 1. Lactic acid from biomass.

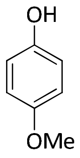
Table 2. Oxidation of various functionalized arylboronic acids in lactic acid and acetic acid.[a]

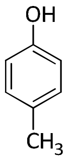


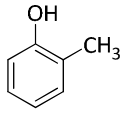

2a (5 min, 95%)[b]
(15 min, 95%)[c]

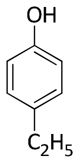

2b (5 min, 93%)[b]
(15 min, 95%)[c]

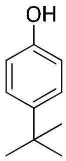

2c (5 min, 94%)[b]
(15 min, 96%)[c]

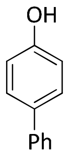

2d (5 min, 90%)[b]
(15 min, 95%)[c]

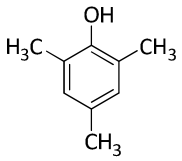

2e (5 min, 95%)[b]
(15 min, 93%)[c]

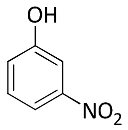

2f (10 min, 95%)[b]
(30 min, 95%)[c]

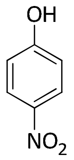

2g (5 min, 93%)[b]
(15 min, 95 %)[c]

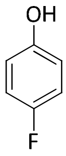

2h (5 min, 96%)[b]
(20 min, 93%)[c]

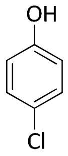

2i (5 min, 93%)[b]
(20 min, 97%)[c]

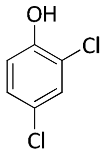

2j (30 min, 94%)[b]
(60 min, 94%)[c]

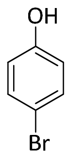

2k (10 min, 91%)[b]
(30 min, 95%)[c]

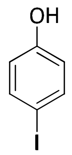

2l (5 min, 92%)[b]
(30 min, 94%)[c]

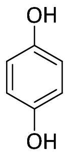

2m (5 min, 92%)[b]
(30 min, 92%)[c]

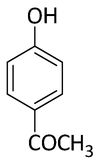

2n (5 min, 95%)[b]
(15 min, 95%)[c]


2o (15 min, 93%)[b]
(30 min, 90%)[c]


2p (10 min, 94%)[b]
(30 min, 96%)[c]

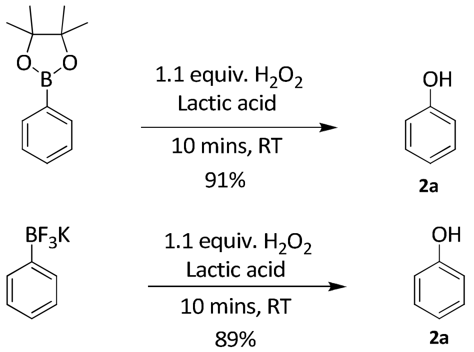

2q (15 min, 94%)[b]
(30 min, 91%)[c]


2r (10 min, 95%)[b,d]
(30 min, 95%)[c,d]


2s (10 min, 95%)[b]
(30 min, 95 %)[c]

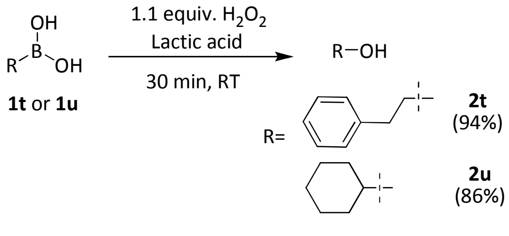
[a] Reaction conditions: Substrate (0.5 mmol), Solvent (1 mL), H_2O_2 (1.0 equiv.), stirred at RT; Isolated yield is shown in the table.
[b] Lactic acid is used as solvent. [c] Acetic acid is used as solvent. [d] 1,4-phenylenediboronic acid is used as a substrate with 2.5 equiv. H_2O_2.

The un-substituted arylboronic acids such as phenylboronic acid, and α, β-naphthylboronic acids were converted into corresponding phenol and naphthols (Table 2, **2a-2c**) within 5 minutes in lactic acid while acetic acid required about 15 minutes. Nevertheless, bo solvents gave the desired products in excellent yiel Subsequently, the oxidation of methoxy, methyl, ethyl, tertia butyl, phenyl, nitro, fluoro, chloro and iodo substituted phenylboronic acids were tested in order to establish a general applicability of this methodology in complex synthesis (Table 2, **1d-1q**). All these substrates underwent *ipso*-hydroxylation smoothly irrespective of electronic properties of the arylboronic acids and desired products were obtained up to 97% yield (Table 2, **2d-2q**). Similarly, 1,4-phenylenediboronic acid was oxidized to hydroquinone in quantitative yield with 2.5 equivalent of hydrogen peroxide (Table 2, **2r**). Further to extend the scope of this methodology, oxidation of 4-acetyl phenylboronic acid (a substrate which can undergo Baeyer-Villiger oxidation) was examined in both lactic acid and acetic acid medium. Remarkably, ketone functional group was found to be very stable during the oxidation and gave 4-acetyl phenol in 95% yield in both solvents (Table 2, **2s**). Over all, lactic acid was found to be very efficient solvent medium for the oxidative *ipso*-hydroxylation reaction when compared with acetic acid.



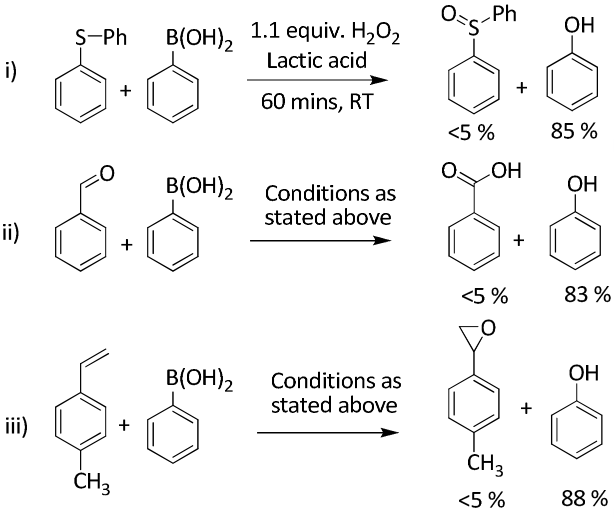
Scheme 2. Oxidation of phenylboronic acid pinacol ester and potassium phenyltrifluoroborate in lactic acid.

Similar to arylboronic acids, other surrogates such as phenylboronic acid pinacol ester and potassium phenyltrifluoroborate were successfully converted to phenol in a short time (Scheme 2). In addition, alkylboronic acids such as 2-phenylethylboronic acid (**1t**) and cyclohexylboronic acid (**1u**) were oxidized to corresponding alcohols in good yields with equal efficiency (Scheme 3).



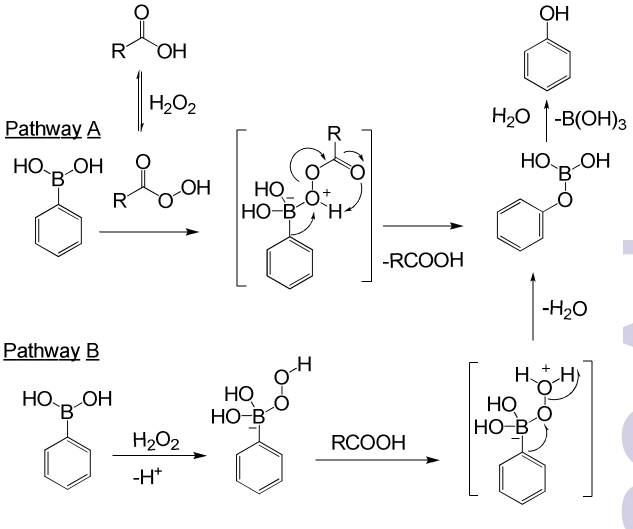
Scheme 3. Oxidation of alkylboronic acids with hydrogen peroxide in lactic acid.

Further, to test the functional group tolerance, a series of competition experiments were conducted between phenylboronic acids and oxidation susceptible functional groups. The study reveals that sulfide, aldehyde and olefin functional groups are tolerated under the reaction condition while phenylboronic acid was selectively converted into phenol (Scheme 4).



Scheme 4. Oxidation of various sensitive functional groups wi lactic acid.

Although the exact mechanism of the reaction is unclear, two possible mechanistic pathways (**A** and **B**) are shown in Scheme 5. According to pathway **A**, the first step would be the formation o peracid (peracetic/perlactic acid) which is generally known as mor reactive species than simple hydrogen peroxide.[46] The resulted peracid reacts with arylboronic acid to provide boronate ester which is further hydrolyzed to phenol and boric acid in the presence of water (Scheme 5, **A**).[37] On the other hand, the oxidation may involve the electrophilic attack of the hydrogen peroxide on boron followed by protonation of the peroxide by the acetic acid or lactic acid.[28] Subsequent migration of the aryl group from boron to oxygen generates boronate ester which is further hydrolyzed to phenol by water (Scheme 5, **B**). However, we believe that th acidity of the reaction medium would play an important role in the oxidation reaction. Because, lactic acid (pKa: 3.7) is relatively more acidic than acetic acid (pKa: 4.7) and it could be a reason for the enhanced activity of lactic acid over acetic acid.



Scheme 5. Two different mechanistic pathways (**A** and **B**) for the oxidation reaction.

By considering the environmental impacts, the use of many traditional organic solvents in chemical production should be avoided or at least should be replaced with greener alternatives. However, so far there is no universal green solvent that can be used in all situations and therefore search for "green solvents" is still ongoing. In this direction, we have demonstrated here the application of lactic acid as a bio based green solvent for the catalyst free oxidation of arylboronic acids into phenols with aqueous hydrogen peroxide. The electron donating and withdrawing functional groups substituted arylboronic acids underwent oxidative *ipso*-hydroxylation smoothly and yielded corresponding phenols in high yield. Remarkably, the oxidation-sensitive functional groups such as sulphide, ketone, aldehyde and olefin are tolerated under the reaction condition which shows the broad scope of the methodology. This study reveals that lactic acid can be used not only for acid catalyzed reactions,[45] but also to the selective oxidation reactions. More importantly, the efficiency of lactic acid is found to be equal or even slightly better than acetic acid and therefore acetic acid can be efficiently replaced by lactic acid in organic synthesis. However, significant research is still needed to assess the complete credentials and short comings of lactic acid in organic synthesis in which our group is currently engaged.

Acknowledgements

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