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Potassium *tert*-Butoxide Mediated Aerobic Hydroxylation of Arylboronic Acids: An Application towards the Synthesis of (*E*)-Phenoxy Acrylates

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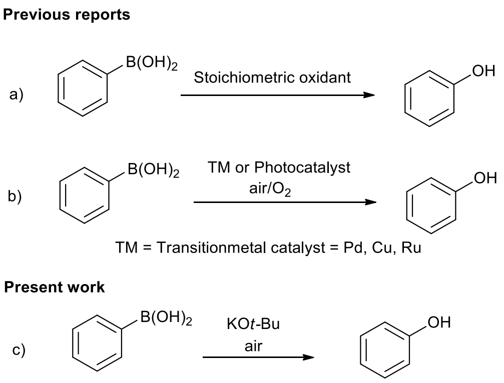
The first example of potassium *tert*-butoxide mediated aerobic hydroxylation of arylboronic acids is described. A variety of arylboronic acids bearing both electron donating and withdrawing substituents successfully participated in the reaction and furnished phenols in good yields. This strategy also provides access for one pot synthesis of (*E*)-3-phenoxy acrylates from arylboronic acids and propiolates. The solvent plays an important role and a binary solvent system comprising CH_3CN/THF is appeared to be the best.

Phenols are important scaffolds found in many biological systems, pharmaceuticals and polymers.[1] Besides, they also serve as versatile intermediates in organic synthesis.[2] Therefore, several methods have been developed towards the synthesis of phenols.[3] Among them, oxidative hydroxylation of arylboronic acids represents a straight forward method to access phenols in an effective manner. Previously, stoichiometric amount of oxidants such as peroxides[4], Oxone[5], benzoquinones[6], *N*-oxides[7] and hypervalent iodine[8] compounds were commonly used reagents to achieve such transformation. However, nowadays, environmentally friendly and inexpensive molecular oxygen (O_2 and air) is found to be an effective oxidant in the presence of transition-metal catalysts[9], and photoredox catalysts[10]. Recently, photoredox oxidative hydroxylation of boronic acids in the absence of metal catalyst is also well described[11]. Notably under photochemical conditions, the formation of superoxide radical anion, the key intermediate, is proposed to act as the highly active terminal oxidant. Nevertheless, to perform this transformation, in most cases, use of stoichiometric amount of amines, as electron donor is always necessary. Despite these significant developments, the aerobic hydroxylation of arylboronic acids mediated by base in the absence of metal- and photocatalyst is relatively unknown.[12] Alternatively, synthesis of phenols from aryl halides has also been recognized as one of the valuable approaches.[3] However, to achieve such transformations, use of metal catalyst is inevitable. Thus, there is always a demand in developing new and convenient protocols, particularly metal free approach, toward the synthesis of phenols under mild reaction conditions.



Scheme 1: Hydroxylation of arylboronic acids

Potassium *tert*-butoxide (KO*t*Bu) is one of the commercially available and most commonly used alkoxide base, which has been reported to promote a number of organic transformations including C-C and C-N bond formation reactions.[13] Beside to its role as a strong base, KO*t*Bu may also act as a single electron donor to initiate the radical reactions.[13] Extensive studies have been devoted to KO*t*Bu mediated/catalyzed coupling reactions involving aryl halides that are believed to proceed via radical intermediate.[13] In 2013, Li and co-workers reported an interesting study describing a KO*t*Bu mediated alkenylation of quinazolines with terminal alkynes.[14] In the reaction, they proposed that a superoxide radical anion could be formed via direct reduction of O_2 by KO*t*Bu. Inspired by this report on

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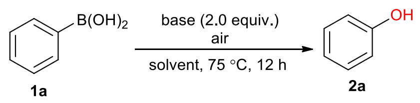
superoxide radical anion formation and our continued interest in the chemistry of organoboronic acids[15], we set out to perform an oxidative hydroxylation of organoboronic acids using KO*t*Bu. Herein we report a potassium *tert*-butoxide mediated aerobic oxidative hydroxylation of aryl boronic acids that can give phenols. In addition, one pot phenoxylation involving propiolates and aryl boronic acids forming substituted (*E*)-phenoxy acrylates is also described. The present method allows us to use commercially available and air stable arylboronic acids. Importantly, it avoids the use of transition metal catalyst and photocatalyst. Moreover, the reaction is performed under air which makes the reaction operationally simple.

The reaction of phenylboronic acid (**1a**) with KO*t*Bu (2.0 equiv.) in the presence of air at 75 ^{o}C using CH$_3$CN/THF as a binary solvent in a ratio of 4:1 for 12 h afforded phenol (**2a**) in 79% isolated yield (Table 1). Control experiments revealed that **2a** was not observed in the absence of either air or KO*t*Bu (entries 2 and 3). The solvent plays an important role and a binary solvent system comprising CH$_3$CN/THF is appeared to be the best. When the reaction was carried out in THF, **2a** was obtained in 49% yield whereas in CH$_3$CN, only 55% yield was observed. Other solvents such as DMF and toluene were not suitable (entries 6 to 7). When the reaction was carried out with 1.0 equivalent of KO*t*Bu phenol (**2a**) was obtained in 60% yield (entry 8). Likewise, changing the base from KO*t*Bu to KOH, Et$_3$N and K$_2$CO$_3$ also gave the desired product in low yields (entries 9 to 11). Similarly, lowering the reaction temperature to 50 ^{o}C afforded the desired product only in 44% yield after 12 h (entry 12).

Table 1: Results of Aerobic Oxidative Hydroxylation Organoboronic Acids[a,b]

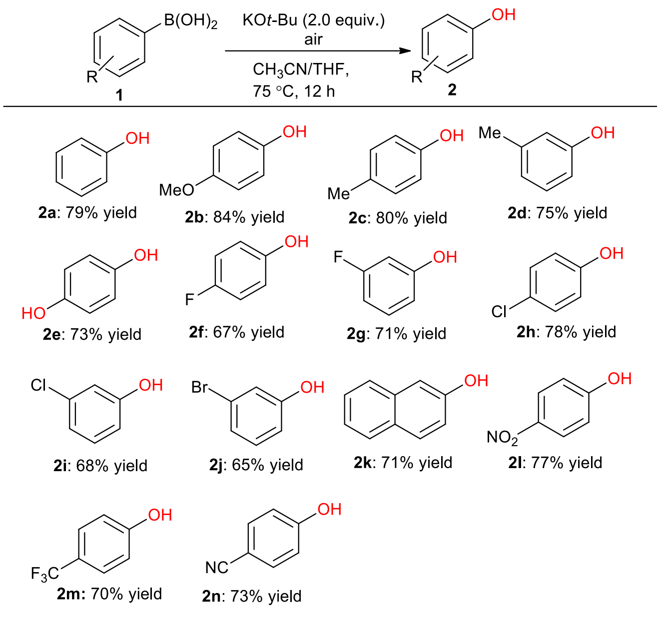


Entry	Base	Solvents	Temperature	yield
1	KO*t*Bu	CH$_3$CN /THF	75	79
2	-	CH$_3$CN /THF	75	0
3	KO*t*Bu	CH$_3$CN /THF	75	0^c
4	KO*t*Bu	THF	75	49
5	KO*t*Bu	CH$_3$CN	75	55
6	KO*t*Bu	DMF	75	0
7	KO*t*Bu	toluene	75	0
8	KO*t*Bu^d	CH$_3$CN /THF	75	60
9	KOH	CH$_3$CN /THF	75	11
10	Et$_3$N	CH$_3$CN /THF	75	18
11	K$_2$CO$_3$	CH$_3$CN /THF	75	12
12	KO*t*Bu	CH$_3$CN /THF	50	44
13	KO*t*Bu	CH$_3$CN /THF	100	77
14	NaO*t*Bu	CH$_3$CN /THF	75	40

a) All reactions were carried out using phenyl boronic acid (**1a**) (1.0 mmol) and KO*t*Bu (2.0 mmol) in the presence of air for 24 h. b) Isolated Yield. c) The reaction was carried in inert atmosphere. d) 1.0 mmol of KO*t*Bu was used

With the optimized reaction conditions in hand, the scope of the organoboronic acids was examined (Table 2). In general, aryl boronic acids are compatible for the reaction whereas alkyl boronic acids did not yield the desired product. As shown in Table 2, aryl boronic acids bearing both electron-donating and electro withdrawing substituents furnished the products in good yields. For instance, the reaction of *p*-methoxy (**1b**), *p*-tolyl- (**1c**) and *m*-tolylboronic (**1d**) acids afforded their corresponding phenols **2b-d** in 75-84 yields. Importantly, *p*-aryl diboronic acid (**1e**) also gave **2e** in 73% yield. Similarly, arylboronic acids (**1f-j**) bearing fluoro-, chloro- and bromo-substituents furnished the products **2f-j** in 65-78% yield. Likewise, 2-naphthol (**2k**) was also obtained in 71% yield. Arylboronic acids (**1l-m**) bearing electron withdrawing substituents also participated well in the reaction and afforded the respective products in 70-77% yield. It is noteworthy to mention that under present reaction conditions, heteroaryl- and styrylboronic acids did not furnish the hydroxylated product.

Table 2: Results of Aerobic Oxidative Hydroxylation Organoboronic Acids[a,b]



a) All reactions were carried out using aryl boronic acid (**1**) (1.00 mmol) and KO*t*Bu (2.0 mmol) in the presence of air using CH$_3$CN/THF (4:1) solvent at 75 ^{o}C for 12 h. b) Isolated Yields.

After successfully establishing the scope of aryl boronic acid, we also studied the one pot hydrophenoxylation of propiolates (Table 3). Unlike hydroxylation reaction, this transformation requires a higher reaction temperature of 100 ^{o}C to furnish the desired product in high yields. The scope of the reaction was examined by treating various arylboronic acids with ethyl propiolate (**3a**). As expected, aryl boronic acids bearing both electron-donating and electro withdrawing substituents successfully participated in the reaction and furnished (*E*)-ethyl 3-phenoxyacrylates (**4a-j**) in 55-95% yield in a highly regio- and stereoselective manner. Likewise, methyl hex-2-ynoate (**3b**) and ethyl pent-2-ynoate (**3c**) gave the desired product in good yield. It is noteworthy to mention that no reaction was observed with 3-aryl propiolates.

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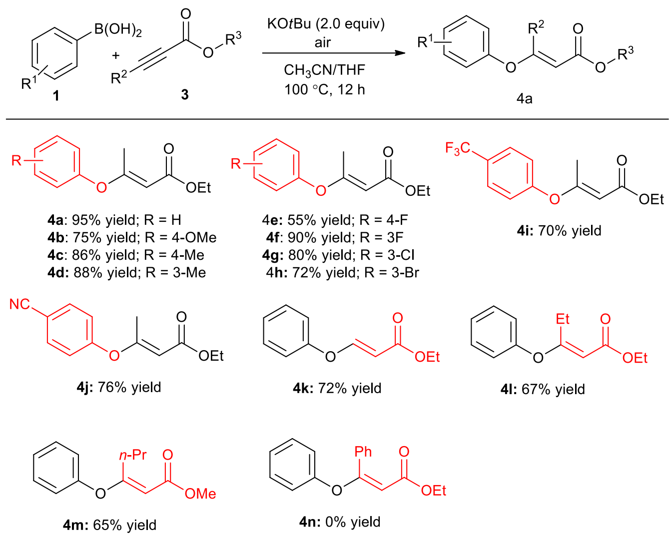
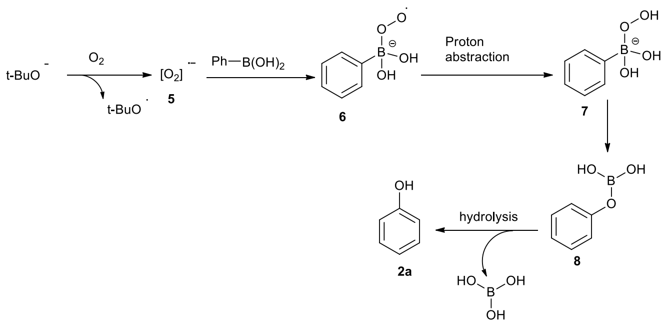
Table 3: Results of Phenoxylation of Propiolates[a,b]



a) All reactions were carried out using aryl boronic acid (**1**) (1.00 mmol), propiolates (**3**) (0.50 mmol) and KO*t*Bu (2.00 mmol) in the presence of air using CH$_3$CN/THF (4:1) solvent at 100 °C for 12 h. b) Isolated Yields

The reaction mechanism for the present reaction remains uncertain. However, a plausible mechanism is proposed based on the available literature report.[13,14] The reaction may be initiated by forming superoxide radical ion **5** via single electron transfer from KO*t*Bu to O$_2$. Then, superoxide radical anion may react with **1a** to give the intermediate **6**. Subsequent protonation of intermediate **6** and further 1,2-aryl shift gives the final phenol product. An alternative mechanism that proceeds through PhB(OH)$_2$-O$_2$ adduct, which was then reduced by KO*t*Bu to form the intermediate cannot be ruled out completely. To realize the radical pathway mechanism, a radical trapping experiment was performed using TEMPO as the radical inhibitor. Under standard reaction conditions, the reaction of phenyl boronic acid **1a** with 1 equivalent of TEMPO gave phenol **2a** in 27% yields, however, with 2.5 equivalent of TEMPO, no **2a** was observed. The results depict that the reaction may proceed through a radical pathway in the presence of KO*t*Bu.



Scheme 2: Proposed mechanistic pathway

In conclusion, we have successfully described a practical and efficient method for the synthesis of phenols from arylboronic acids using stoichiometric amount of KO*t*Bu in the presence of air. A variety of arylboronic acids bearing both electron donating and withdrawing substituents successfully participated in the reaction and furnished phenols in good yields. To further, one pot synthesis of (*E*)-3-phenoxy acrylates from arylboronic acids and propiolates is also demonstrated. Advantageously, this method avoids the use of any noble metal catalyst or photocatalyst. Thus, this operationally simple protocol can be very useful in academic and possibly may be extended to industrial applications as well.. Extension of the scope of the reaction and the detailed mechanistic study are currently under study.

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Conflicts of interest

There are no conflicts to declare

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