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An alternative route for boron phenoxide preparation from arylboronic acid and its application for C – O bond formation

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Highlights:

- > Efficient synthetic route to benzyl phenyl ether preparation
- > Development of two C–O bonds formation in a one-pot system
- Versatile combination of arylboronic acids, hydrogen peroxide, and benzyl halides in choline hydroxide
- > Performance under a metal- and base-catalyst-free in an aerobic environment
- > Further applicability to various electrophiles

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An alternative route for boron phenoxide preparation from arylboronic acid and its application for C - O bond formation

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ABSTRACT

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Keywords: arylboronic acids hydrogen peroxide choline hydroxide benzyl phenyl ether one-pot synthesis An efficient synthetic route to benzyl phenyl ether preparation has been successfully developed *via* a one-pot synthetic protocol utilizing a combination of arylboronic acids, hydrogen peroxide (H_2O_2), and benzyl halides. The whole procedure consists of two consecutive reactions, formation of boron phenoxide from arylboronic acids and its nucleophilic attack. A simple operation under mild conditions such as room-temperature ionic liquid (choline hydroxide), aerobic environment, and absence of metal- and base-catalysts has been employed. Expansion to utilize benzyl surrogates was also successfully accomplished.

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bond forming of organic compounds are considered as the fundamentals in construction of numerous organic compounds.¹ Accordingly, these strategies have been frequently utilized to obtain a variety of functional materials in both academic and industrial areas. Along with the facile functional group transformations, one-pot synthesis has also gained considerable and broad range of interests in synthetic organic chemistry owing to the simplicity of their process compared with step-by-step production. One-pot synthesis has special benefits, such as no intermediate isolation, no change of reaction conditions, and no other additives, among the others.

Given the aspects of sustainable chemistry, bio- and ecofriendly reaction platforms could be suitable approaches to reducing the economic and environmental burdens of various chemical processes. As part of our continuous endeavor of searching for more versatile synthetic routes, ² we were able to accomplish oxidative hydroxylation of arylboronic acids to the corresponding phenolic derivatives using a greener conditions: such as combination of hydrogen peroxide and choline, a roomtemperature ionic liquid (RTIL).

With the promising outcomes obtained from the aforementioned our study, we focused intensively on expanding the scope of the reaction system. One of the possibilities is to conduct a consecutive coupling reaction of the reaction intermediate, supposedly a boron phenoxide (IA in Scheme 2), with several suitable electrophiles. Among the electrophiles, benzyl halides would be good candidates for benzyl phenyl ether preparation under the base- and metal-catalyst-free conditions. Furthermore, the whole process could be carried out in a one-pot environment.

To date, as depicted in Scheme 1, several synthetic routes for the preparation of benzyl phenyl ethers have been widely used.



Scheme 1. Representative approaches for benzyl phenyl ether preparation

Phenol benzylation using benzylating reagents, mainly benzyl bromide, under the various conditions is one of the readily available pathways that is assigned as Route [**A**] in Scheme 1.³ Since the first report by McKillop,⁴ although some drawbacks limit the application of this approach, it has been frequently used in benzyl phenyl ether preparation. For most cases, the presence of an appropriate base was mandatory for the successful carbon-oxygen bond formation. In a related development, several improved conditions such as use of deep eutectic solvent,⁵ phase transfer catalyst,⁶ and mild base,⁷ have been recently revealed. In addition to this process, alternative interesting approaches utilizing organoboron derivatives have been explored. As shown in Scheme 1 Route [**B**], Batey *et al.* reported the copper-catalyzed alcohol etherification with potassium aryltrifluoroborates in the presence of 4Å molecular sieves.⁸ More recently, a very

assigned as Route [**C**] in Scheme 1.⁹ In their study, utilizing arylboronic acids and H_2O_2 in the presence of Pd-catalyst has been performed for the preparation of various benzyl phenyl ethers. Inspired by this outcome and our previous results,² we postulated that if the reaction media were able to keep the intermediate alive, then it could act as a readily available nucleophile for subsequent nucleophilic attack to benzyl substrates, furnishing benzyl phenyl ethers in a one-pot system. To verify the efficiency of the proposed strategy, the whole process should consist of a simple catalyst-free, one-pot operation in an aerobic environment.

 Table 1. Optimization for one-pot synthesis of benzyl phenyl ether (2a)

B(C 1a	DH) ₂ 1. 30% 2. Benz	aq. H ₂ O ₂ /C yl bromide/		2a	
Entry	1a (mmol)	H_2O_2 (mL)	BnBr (mmol) ^b	ChOH (mL)	Yield (%)
1	2.0	0.2	1.7	0.5	42
2	2.0	0.2	1.7	1.0	66
3	2.0	0.4	1.7	1.0	67
4	2.0	0.4	2.4	1.0	71
5	2.0	0.4	1.0	1.0	99

^a Isolated yield (based on benzyl bromide)

^b BnBr: benzyl bromide

To elucidate the protocol, a model platform consisting of phenylboronic acid (**1a**) and benzyl bromide was selected. To our delight, formation of two carbon-oxygen bonds resulting in ethereal linkage *via* a consecutive coupling reaction was successfully achieved in satisfactory manner. Optimization of the reaction conditions for achieving best yield of **2a** was carried out, and the results are described in Table 1.

The first attempt was carried out with 2.0 mmol of phenylboronic acid (**1a**) with H_2O_2 (0.20 mL) in choline hydroxide (0.50 mL) at room temperature (Table 1, entry 1). After the mixture of **1a** and H_2O_2 was stirred at room temperature for 5 min, benzyl bromide (1.7 mmol) was subsequently added into the reaction mixture. The GC–MS analysis of the reaction aliquot showed the formation of the corresponding product **2a** (Figure 1).

Building on the initial result, the subsequent experiment was focused on the effect of the amount of the solvent (ChOH). A moderately improved yield of **2a** was obtained using 1.0 mL of ChOH (Table 1, Entry 2). Under the same conditions, increment of the amount of the H_2O_2 also gave **2a** in a similar manner (Table 1, Entry 3). No significant improvement (71%) was observed using increased amount of benzyl bromide up to 2.4 mmol (Table 1, Entry 4). In contrast, when the reaction was performed with 0.5 equivalent of benzyl bromide (1.0 mmol), outstanding outcome (99%) was achieved (Table 1, Entry 5).¹⁰



Figure 1. Reaction progress monitored by GC

Consequently, this condition was regarded as a standard condition throughout the present study.



Table 2. Benzylation using benzyl bromides

^a Isolated yield based on benzyl bromide.

Based on these observations, we could become assured that the combination of arylboronic acids, H_2O_2 , and benzyl bromides in ChOH would be an alternative efficient route for the benzyl

established in Table 1, we further examined the utility of the new protocol using the various arylboronic acids and benzyl bromides. The results are presented in Table 2.

Table 3. Reaction with benzyl chlorides



 $^{\rm a}$ Conditions: 2.0 mmol of boronic acid, 1.0 mmol of benzyl chloride, 0.4 mL of $\rm H_2O_2,$ 1.0 mL of ChOH at room temperature

^b Isolated yield based on benzyl chloride

From the reactions with arylboronic acids bearing functional groups, the ethereal linkage formation was also successful, resulting in the moderate to high yields of the corresponding ethereal compounds (2a - 2i). Notably, the present system displayed a considerable tolerance toward carbonyl and bromine functionalities (2j - 2m). The expected product formation using naphthalene-2-boronic acid also occurred. However, unfortunately, the obtained product was not analytically pure owing to several inseparable by-products.

For better understanding of the reactivity of our approach, we further investigated the substrate scope of the benzylation using benzyl chlorides, and the results are described in Table 3. To address this, 4-fluorobenzyl chloride was selected as a substrate and subjected to react with **1a** under the one-pot preparation conditions used before. Significantly, the corresponding 4-fluorobenzyl phenyl ether (**2n**) was obtained in **an** excellent yield. Slightly disappointing results (**2o** - **2q**) were observed using sterically demanding benzyl chlorides in which it could be attributed to a steric effect.

Taking into account the reactivity obtained thus far, C–O bond formation of IA using somewhat different substrates in place of the benzyl halides would be a more challenging subject. To elucidate the diversity, we have now undertaken substitution reaction with benzyl tosylate, ally bromide, 2bromoacetophenone, and quinoxaline as depicted in Scheme 1. Unfortunately, employing benzyl tosylate led to 2a with severely diminished yield (17%) along with a mixture of unidentified products. It is of interest that both allyl bromide and 2bromoacetophenone turned out to be the suitable substrates yielding the expected products (2r and 2s, respectively) in excellent vield.

Table 4. Coupling reaction of IA with benzyl surrogates

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^a Isolated yield based on benzyl surrogate

^c 0.3 eq. of TCT employed

Quinoxaline possessing sterically demanding reaction sites was employed in our novel protocol under the standard conditions used above. Spectroscopic analyses indicated that disubstituted product (**2t**) was obtained as major one. To demonstrate the practicality and robustness of this approach, we applied it toward the reaction with 2,4,6-trichloro-1,3,5-triazine (TCT) which is an efficient reagent for further transformation in organic synthesis. Under the conditions presented in Table 4, the whole procedure underwent smoothly, and product (**2u**) was exclusively obtained with 23% isolated yield.

 Table 5. Coupling reaction with acid chlorides: Preparation of esters



^a Numbers in parenthesis are isolated yield (based on acid chlorides)

in natural and synthetic products showing a wide range of biological activities, which is utilized as a building block in the synthesis of fine organic compounds. Owing to its versatility, a variety of synthetic methodologies have been reported in which both transesterification and acylation of alcohols have been considered the most accessible protocols. To accomplish these strategies, acid- or base-catalyzed reaction of alcohols with carboxylic acids, anhydrides or acid chlorides has been frequently employed.¹¹ In addition, a metal complex-mediated acylation of alcohols has also been frequently utilized, although some disadvantages such as harsh reaction conditions, toxicity, and tedious workup are still presented.¹²

Considering of these aspects, we, next, focused on the preparation of ester derivatives utilizing the same strategy used above by simply changing the electrophile to acid chlorides under similar conditions. As shown in Table 5, a wide range of acid chlorides were employed, providing the desired esters in moderate to satisfactory manners. Not only aryl acid chlorides but also cyclohexanecarbonyl chloride was suitable electrophiles to produce the corresponding products (3a - 3g). Moreover, heteroaryl acid chlorides were also selected as coupling substrates, yielding 3h and 3i with moderate yields.



Scheme 2. Plausible mechanism for the present protocol

Although there is a paucity of crucial study of reaction mechanism, consecutive reactions, formation of **IA** *via ipso*-hydroxylation of arylboronic acids followed by its nucleophilic reaction, could be attributed to the formation of two C– O bonds of the final products. One-pot system containing a basic RTIL (ChOH) was sufficient to provide a basic environment, leading to an enhanced nucleophilicity of **IA**. The formation of intermediate **(IA)** was indirectly confirmed by the isolation of phenol which is the equivalent of **IA**.¹³ Based on these assumptions and observations mentioned above, we proposed a following mechanistic pathway for the present protocol (Scheme 2). The initial step involves the activation of H₂O₂ by ChOH *via* hydrogen bonding, followed by attack on boronic acid. Migration of phenyl group generates boron phenoxide **(IA)**, which then undergoes coupling reaction to afford the corresponding product.

In conclusion, we have developed a simple and green protocol for producing benzyl phenyl ethers and ester derivatives, which were accomplished using two C– O bond formation in a one-pot system under mild reaction conditions.¹⁴ The combination of ecofriendly oxidant (H₂O₂), sustainable reaction media (choline hydroxide), and readily available reaction substrates was efficiently cooperated in an aerobic environment. In addition, the use of base- and metal-catalyst-free conditions should be highlighted. Further investigations on the scope and limitations

^b 0.5 eq. of quinoxaline employed

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- 13. Under the standard conditions, the reaction mixture using **1a** was quenched with 3 M HCl solution before the addition of benzyl bromide. After an appropriate work-up and purification, we were able to isolate the product, which is identified as phenol by the spectroscopic analyses (¹H & ¹³C NMR and FT-IR).
- 14. Representative one-pot procedure; A flask was charged with phenylboronic acid (4.0 mmol), choline hydroxide (aq. 40-50 wt%, 2.0 mL), and H₂O₂ (aq. 30 wt%, 0.8 mL). Then, the mixture was stirred at room temperature in open air for 1 h. Next, 0.34 g of benzyl bromide (2.0 mmol) was added into the flask at room temperature, then the resulting mixture was allowed to stir at room temperature for 2 h. Quenched with 3 M HCl solution, then extracted with extracted with diethyl ether (3 X 10 mL). The combined organic layers were washed with brine, dried with anhydrous Na₂SO₄, and the volatile solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (hexanes only). Benzyl phenyl ether (2a); colorless oily liquid. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.48 - 7.40 (m, 4H), 7.37 - 7.28 (m, 3H), 7.03 - 6.97 (m, 3H), 5.10 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 158.8, 137.1, 129.5, 128.6, 127.9, 127.5, 120.9, 114.9, 69.9.

Supplementary Material

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