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Synthesis of Benzoxaboroles by *ortho*-Oxalkylation of Arylboronic Acids with Aldehydes/Ketones in the Presence of Brønsted Acids

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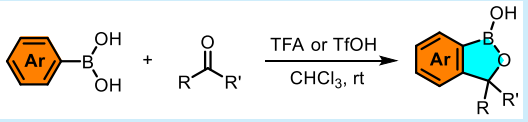
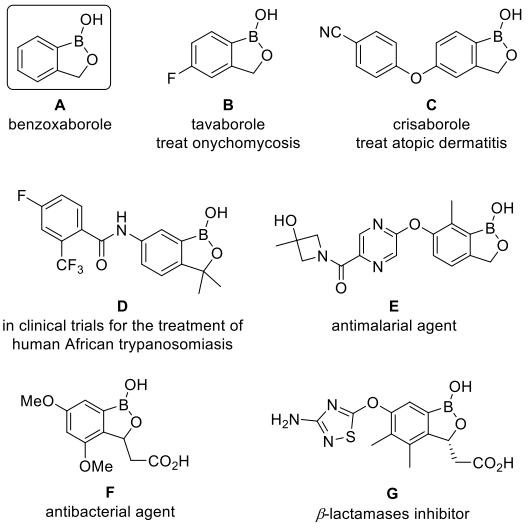
ABSTRACT: Herein we describe a simple and efficient synthesis of benzoxaboroles from arylboronic acids and aldehydes or ketones in the presence of a Brønsted acid. This method greatly simplifies the starting materials and reduces the number of reaction steps. The reaction can also be accomplished with acetals and ketals. The reaction has a wide substrate scope and high practicability.



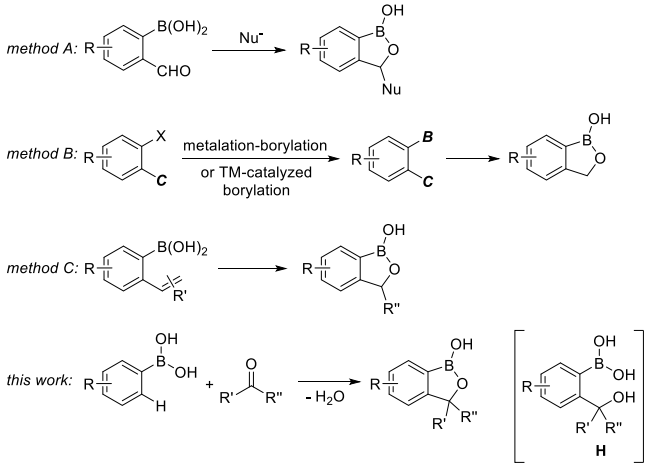
Benzoxaborole is a class of five-membered cyclic arylboronic acid hemiesters. Compound **A**, the simplest example, was first obtained by Torssell in 1957 (Scheme 1);[1] however, this type of compound was underestimated for a long time. The increasing interest in benzoxaboroles was supported by the discovery of the biologically activities of tavaborole (**B**) and crisaborole (**C**) and their FDA approval for the treatment of onychomycosis and atopic dermatitis, respectively.[2] In the past two decades, the vast majority of benzoxaboroles have been synthesized and found to have various biological activities, including antifungal, antibacterial, antiviral, anti-inflammatory, and antiprotozoal properties.[2] For example, AN5568 (**D**) was in clinical trials for the treatment of human African trypanosomiasis. Compounds **E**, **F**, and **G** were found to be an efficient antimalarial agent, antibacterial agent, and β-lactamases inhibitor, respectively. Additionally, Hall and coworkers discovered that benzoxaboroles have exceptional sugar-binding properties under physiological conditions.[3]

Scheme 1. Medicinal Application of Benzoxaboroles



With the expanding role of benzoxaboroles in medicinal chemistry, many methods have been developed for their synthesis (Scheme 2).[2c,d,f−i,4] One of the methods (method A) involves an addition reaction of nucleophiles to *ortho*-formyl arylboronic acid. This strategy is feasible for various types of nucleophiles, including $NaBH_4$, organozinc reagents, indoles, nitroalkanes, amines, *N*-ethyl aniline, carbonyl compounds, α,β-unsaturated carbonyl compounds, acrylonitrile, silyl cyanide, and isocyanide. The second method (method B)

Scheme 2. Methods for Synthesis of Benzoxaboroles



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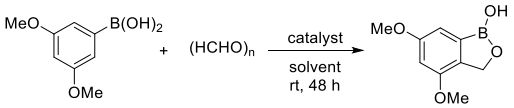
involves the introduction of a boron substituent to the aromatic ring, either by metalation−borylation or by transition-metal-catalyzed borylation. The third method (method C) involves the intramolecular electrophilic or nucleophilic *O*-addition of boronic acid to alkenes of *ortho*-alkenyl-substituted arylboronic acids. Nevertheless, these methods use relatively complex arylboron compounds as the starting substrates or intermediates. Moreover, strict manipulations are essential for some cases involving highly reactive organometallic reagents and metal-catalyzed reactions. Undoubtedly, these requirements will increase the difficulty of the synthesis and decrease the practical utility of the methods. It is clear that benzoxaboroles can be regarded as the intramolecular dehydration product of *ortho*-hydroxyalkyl-substituted arylboronic acids (**H**). In consideration of the atom economy, an ideal method to obtain **H** is the direct *ortho*-hydroxyalkylation of arylboronic acids with aldehydes or ketones; however, arylboronic acids are highly reactive, and only a few types of functionalization of arylboron compounds have been previously reported, and most of them deal with halogenations and nitration.[5]

Previously, we reported an intramolecular arylative ring opening of donor−acceptor cyclopropanes in the presence of triflic acid.[6] We found that the strong Brønsted acid showed exceptional function in the Friedel−Crafts alkylation reaction. In view of the nature of the same reaction type, we first investigated the reaction of 3,5-dimethoxyl phenylboronic acid with paraformaldehyde in the presence of different commonly used Brønsted acids (Table 1). Trifluoroacetic acid (TFA) was shown to be the most efficient catalyst (entry 1). The stronger acids, *p*-toluenesulfonic acid (TsOH), triflic acid (TfOH), and sulfuric acid, gave lower yields (entries 2−4), whereas the weaker acid, acetic acid (AcOH), gave no product (entry 5). We also tested Amberlyst 15, a heterogeneous acid catalyst, but obtained a relatively low yield (entry 6). Increasing or reducing the loading amount of TFA lead to a lower yield due to overhydroxymethylation or the insufficient conversion of **1a** (entries 7 and 8). The optimization of solvents showed that only the reaction carried out in chlorohydrocarbon solvents worked (entries 9−14). When the reaction time was extended, the yield decreased, presumably due to overalkylation (entry 15). A reasonable explanation for this is that product **3a** is somewhat more nucleophilic than substrate **1a** as a result of the electronic effect. In comparison, when 1,3-dimethoxybenzene was applied to the reaction with paraformaldehyde under the optimized conditions, the desired hydroxymethylation product was not observed, with the exception of some polymer-like precipitate.[7] This indicates that in the presence of a strong Brønsted acid, benzoxaborole was more stable than the corresponding benzylic alcohol.

The reaction of various arylboronic acids with paraformaldehyde was examined (Scheme 3). In general, arylboronic acids with electron-donating groups at the *meta* position gave the desired products in moderate to good yield. When the nucleophilicity of the aryl ring was reduced, stronger acids, TfOH or TsOH, were necessary for the reaction to succeed. Compounds **3d** and **3e** were intermediates in the synthesis of bioactive molecules, but three to five steps were needed in the previously reported synthetic route.[8] With this method, starting from simple and commercially available substrates, only one step is required. Thus this methodology greatly simplifies and shortens the preparation of benzoxaboroles.

Table 1. Optimization of the Reaction of Boronic Acid 1a with Paraformaldehyde 2a[a]

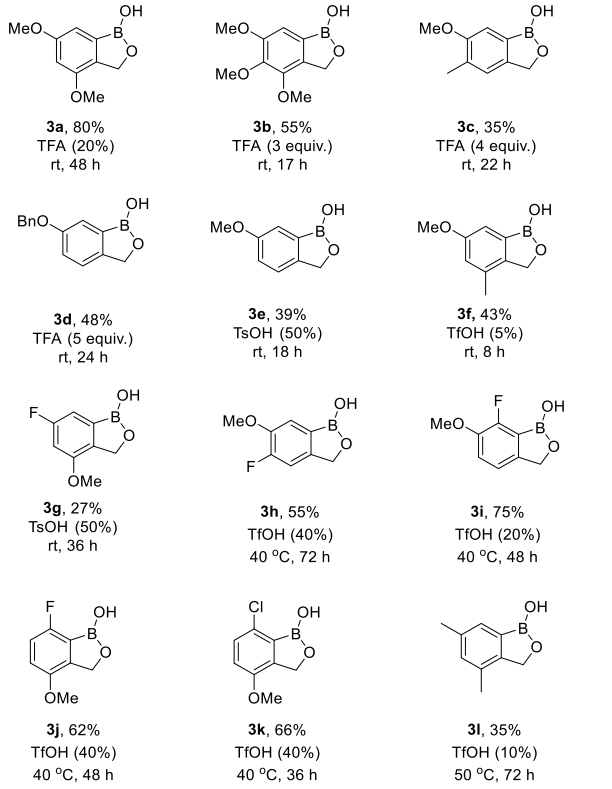


1a 2a 3a

entry	cat. (equiv)	solvent	yield (%)
1	TFA (0.2)	$CHCl_3$	80
2	TsOH (0.05)	$CHCl_3$	27
3	TfOH (0.01)	$CHCl_3$	14
4	H_2SO_4 (0.2)	$CHCl_3$	14
5	AcOH (5)	$CHCl_3$	N.R.
6	Amberlyst 15[b]	$CHCl_3$	34
7	TFA (0.1)	$CHCl_3$	54
8	TFA (0.3)	$CHCl_3$	28
9	TFA (0.2)	DCM	29
10	TFA (0.2)	CCl_4	44
11	TFA (0.2)	DCE	29
12	TFA (0.2)	CH_3CN	trace
13	TFA (0.2)	THF	N.R.
14	TFA (0.2)	*n*-hexane	N.R.
15[c]	TFA (0.2)	$CHCl_3$	49

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst, solvent (5 mL), rt, 48 h. The product was isolated by silica gel chromatography. [b]150 mg of Amberlyst 15 was used. [c]Reaction time was prolonged to 72 h. N.R., no reaction.

Scheme 3. Substrates Scope of Arylboronic Acids[a]



[a]Reaction conditions: arylboronic acid (0.5 to 1 mmol), **2a** (1.2 equiv), catalyst, $CHCl_3$ (0.1 M). The reaction was monitored by TLC analysis, and the product was isolated by silica gel chromatography.

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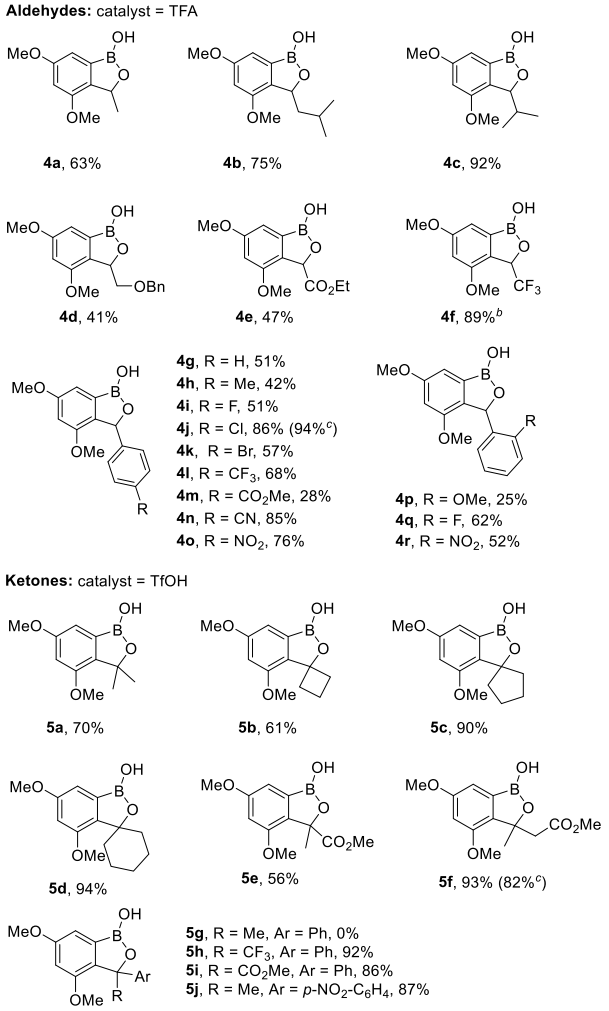
Then, various aldehydes and ketones were applied in the reaction with arylboronic acid **1a** (Scheme 4). For both

Scheme 4. Substrates Scope of Aldehydes and Ketones[a]

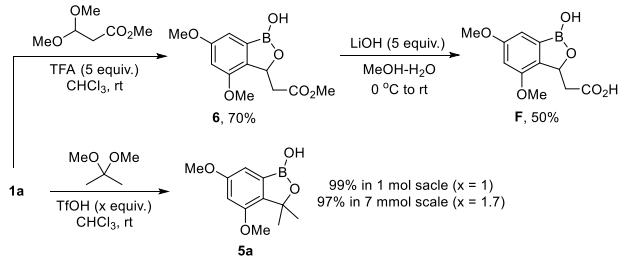


[a]Reaction conditions: **1a** (0.5 to 1 mmol), aldehyde or ketone (1.2 equiv), catalyst (see the SI for details), $CHCl_3$ (0.1 M). The reaction was monitored by TLC analysis, and the product was isolated by silica gel chromatography. [b]75% aqueous solution of trifluoroacetaldehyde monohydrate was used. [c]Reaction was carried out on a 5 mmol scale.

aliphatic and aromatic aldehydes, the yields were moderate to excellent. For **4f**, an aqueous solution of trifluoroacetaldehyde was used, and the yield was satisfactory. For ketones, the stronger acid TfOH must be used due to the diminished electrophilicity of the reactants. For linear or cyclic ketones, the yield was good to excellent; however, it is necessary to point out that the general aryl ketone failed to react (**5g**), except for substrates bearing electron-withdrawing groups (**5h**–**j**). In some cases, the reactions were carried out on a gram scales and produced a satisfactory yield (**4j** and **5f**).

We also noticed that some aldehydes are not stable, but the corresponding acetals are stable. Therefore, it is essential and valuable to test acetals and ketals in the reaction with arylboronic acid (Scheme 5). To our delight, compound **6** could be obtained in moderately high yield from a one-step reaction of **1a** with a commercially available acetal, and **6** could be converted to **F** by subsequent hydrolysis. In comparison, **F** was synthesized in four steps from a commercially available

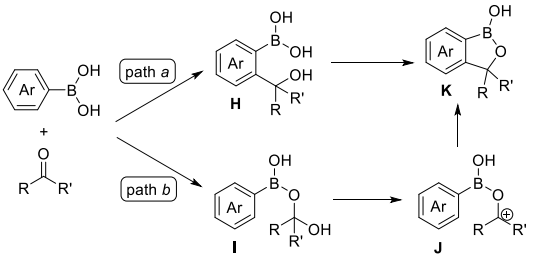
Scheme 5. Reactions of 1a with Acetal and Ketal



compound using the previously reported method.[9] When acetone was replaced by the corresponding dimethyl ketal, the yield of **5a** was greatly improved, even in gram-scale manipulation.

For the formation of benzoxaboroles, we proposed an intermolecular (path a) and an intramolecular (path b) Friedel–Crafts alkylation mechanism (Scheme 6). The arenes

Scheme 6. Proposed Mechanism



with electron-donating groups could react with aldehydes in the presence of Brønsted acids,[7] so path a is possible for similar aryl boronic acids. For the formation of **3j** and **3k**, it was possible for both of the two *ortho* positions of the methoxyl group of the aryl boronic acid substrates to be alkylated. The yields of both **3j** and **3k** were >60%, and this result means that the ortho position near the boronic acid group is more reactive than the other one. A rational explanation is that the boronic acid segment serves as a directing group. Literature reports[10] confirm that some *ortho*-formyl arylboronic acids contain both formyl and acetal forms, and so a similar intermediate **I** might also form. **I** could be converted to a carbon cation **J**, which subsequently undergoes an intramolecular Friedel–Crafts reaction to form the benzoxaborole **K** (path b). A similar effect was also proposed by Hall and coworkers to explain the silver(I)-mediated *ortho*-halogenation of arylboronic acids.[5g]

In summary, we have developed a simple and efficient method for the synthesis of benzoxaboroles. This methodology enriches the range of the functionalization of arylboron compounds. The method has a very broad substrate scope of aldehydes and ketones. With this strategy, benzoxaboroles, especially C3-substituted benzoxaboroles, can be conveniently obtained. Furthermore, metals are not required for this transformation. This method may be very practical and beneficial in the synthesis of pharmaceuticals involving benzoxaboroles. Other types of functionalization of organoboron compounds are currently under investigation in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00032.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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