

Scalable, Metal- and Additive-Free, Photoinduced Borylation of Haloarenes and Quaternary Arylammonium Salts

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ABSTRACT: We report herein a simple, metal- and additive-free, photoinduced borylation of haloarenes, including electron-rich fluoroarenes, as well as arylammonium salts directly to boronic acids. This borylation method has a broad scope and functional group tolerance. We show that it can be further extended to boronic esters, and carried out on gram scale as well as under flow conditions.

Aromatic boronic acids find increasingly important roles in the areas of synthetic organic chemistry,¹ catalysis,² molecular self-assembly,³ carbohydrate analysis,⁴ molecular sensing,⁵ materials science⁶ and medicinal chemistry.⁷ While the reaction of organomagnesium and organolithium reagents with trialkyl borates, first described by Khotinsky (RMgX)⁸ and Letsinger (RLi),⁹ remains in use, transition metal-catalyzed C–X-¹⁰ and C–H-borylation¹¹ reactions have recently emerged as efficient alternatives that bypass air- and moisture-sensitive intermediates. In addition, transition metal-free, base-mediated borylation of iodo- and bromoarenes to arylboronic esters,¹² as well as the Sandmeyer-type borylation of anilines¹³ and electrophilic borylation of electron-rich arenes¹⁴ have been recently developed. These methods can be advantageous, since the use of heavy metals, expensive and air-sensitive catalysts and ligands can be avoided. However, the practicality and scalability of these methods may be limited by the narrow substrate scope and high molecular weight of the boron reagents.

Photochemical activation of molecules enables reactivity patterns that can be difficult to achieve from the ground states.¹⁵ A multitude of homolytic and heterolytic pathways that can be accessed from singlet and triplet excited states affords numerous synthetic possibilities. A number of photoinduced processes have been successfully adapted in the chemical industry (e.g. the Toray PNC process,¹⁶ rose oxide¹⁷ and vitamin D¹⁸ syntheses), pointing to the significant potential of photoinduced reactions.¹⁹

Photoinduced Ar–X bond dissociation is a key step in a number of important photochemical carbon–carbon and carbon–heteroatom bond-forming reactions, including nucleophilic substitution,²⁰ arylation,²¹ alkylation,²² and photocyclization²³ reactions.

We report herein that haloarenes, including electron rich fluoroarenes, as well as aryltrimethylammonium salts readily react with tetrahydroxydiboron (first introduced by Molander and Dreher for the Pd-, and later Ni-catalyzed borylations²⁴) and other diboron reagents to give aromatic boronic acids and esters under ultraviolet light in the

absence of catalysts and additives in a scalable and practical manner in common grade solvents and without deoxygenation of the reaction mixtures (Figure 1).

Initial experiments showed that a reaction of bromobenzene with tetrahydroxydiboron in methanol under ultraviolet irradiation ($\lambda = 254$ nm) produced phenylboronic acid (**1**) in 92% yield after 3 h at 15 °C. The optimal temperature was 10–20 °C, with increased amounts of benzene observed at higher temperatures. The reaction did not proceed in the dark (see Table S1 in the SI) and showed a good quantum yield ($\Phi = 0.34$).

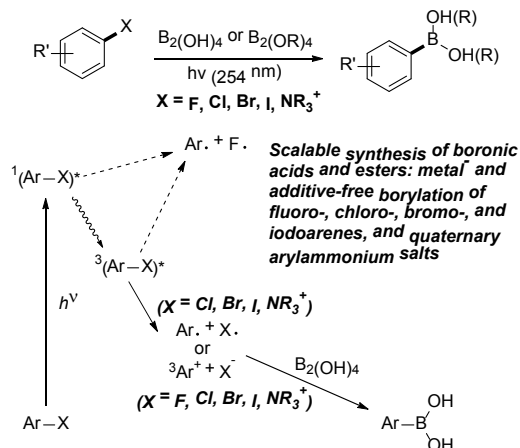


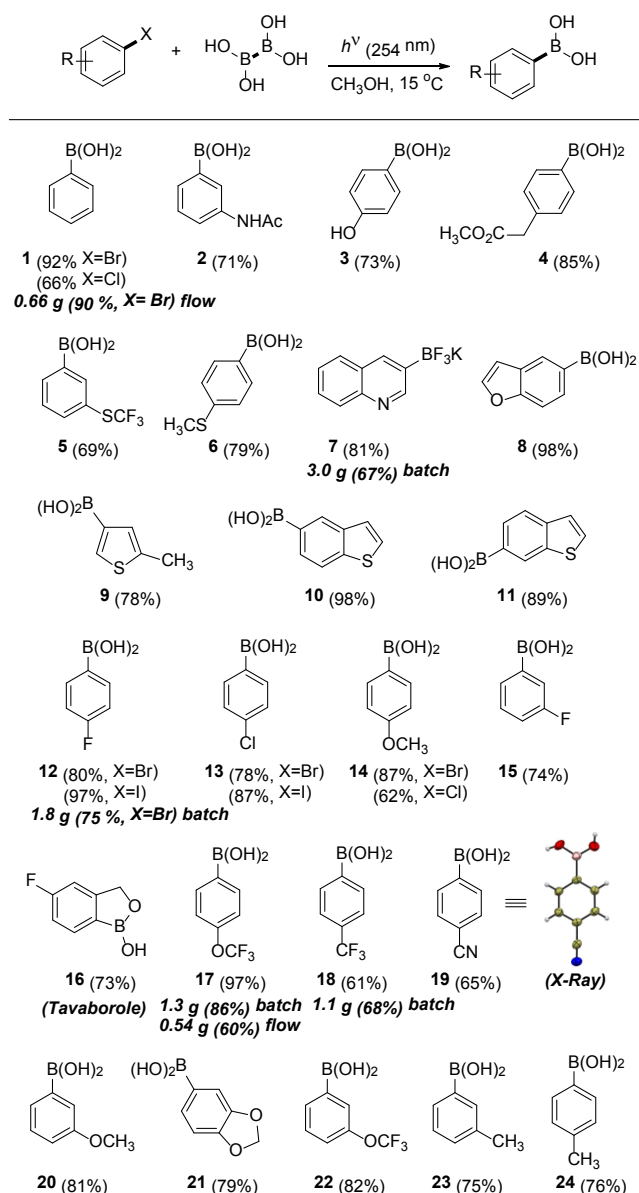
Figure 1. Photoinduced borylation

The preparative scope of the reaction was explored with a series of substituted bromoarenes. A diverse set of functional groups is well tolerated, including amide (**2**, 71%), phenol (**3**, 73%), arylacetate ester (**4**, 85%), thioether (**5**, 79% and **6**, 69%), and other functionalities (**7–25**). Both electron-releasing and electron-withdrawing substituents can be very well accommodated. Nitrogen-, oxygen-, and sulfur-containing heteroarylboronic acids were also prepared in high yields, as shown for products **7–11**. The boronic acids can be directly converted into the corresponding organotrifluoroborates as a part of the isolation procedure. For example, the borylation reaction of 3-bromoquinoline was followed by treatment of the reaction mixture with potassium difluoride²⁵ to give the corresponding trifluoroborate **11** in 81% yield.

Iodoarenes and chloroarenes were also successfully converted to boronic acids. The reactions with iodoarenes were very fast and produced the boronic acids (**12** and **13**) in high yields within 1 h. Chloroarenes reacted slower than bromoarenes (66% of **1** and 62% of **14** after 24 h). These observations are in accord with the increase in the bond dissociation energies (BDE) of the $\text{C}_6\text{H}_5\text{-X}$ bonds (C-I 272, C-Br 336, C-Cl 400 $\text{kJ}\cdot\text{mol}^{-1}$).²⁶ The differential reactivity of C-X bonds can be used for the chemoselective and high-yielding synthesis of haloarylboronic acids, as shown for **12**, **13**, **15** and **16**.

Boronic acids find increasing use in medicine,⁷ as exemplified by the fungal leucyl-tRNA synthetase inhibitor tavaborole (**16**, Table 1) that has recently been approved for treatment of onychomycosis.²⁷ Using the photoinduced borylation, **16** was prepared from the corresponding bromoarene in 73% yield after a simple work-up. Tavaborole was previously prepared using air- and moisture-sensitive reagents (NaH , $n\text{-BuLi}$, and B(OiPr)_3).²⁸ The successful synthesis of **16** also indicates that an ortho-substituent is well-tolerated during the borylation event. Furthermore, good quantum efficiency of the borylation reaction enabled practical gram-scale syntheses of several representative boronic acids (**12**, **17**, **18** on 1.1–1.8 g scales) and trifluoroborate **7** (3 g) using simple quartz test-tubes and low intensity UV sources without deoxygenation of the reaction solutions.

Table 1. Scope of the Photoinduced Reaction of Haloarenes with Tetrahydroxydiboron.^a



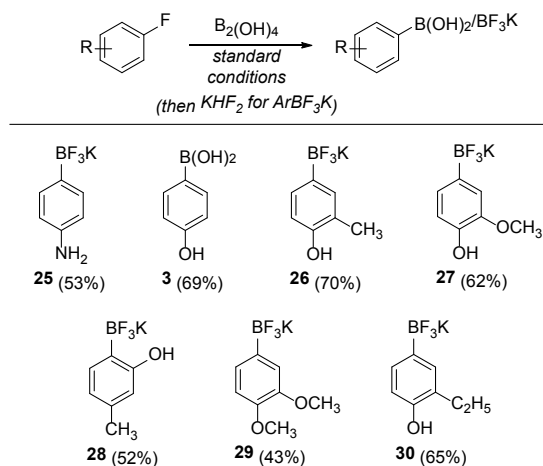
^a Bromoarenes were used unless specified otherwise. Reaction conditions for small scale experiments: haloarene (0.6–1 mmol), tetrahydroxydiboron (1–1.6 mmol), CH₃OH (5–6 mL), 15 °C, 3–24 h, UV lamp (254 nm); then treatment with KHF₂ for ArBF₃K.

Preliminary experiments also show that the reaction can be translated to a continuous flow process (**1**, 90% and **17**, 60%). Reaction mixtures typically remained homogeneous. Monitoring of the borylation reactions by ¹¹B NMR indicated formation of trimethyl borate that may arise from solvolysis of B–X bond-containing inorganic byproducts of the reaction.

Fluorobenzene proved resistant to the borylation in line with the high BDE of the C₆H₅–F bond (526 kJ·mol^{–1})²⁶ that exceeds the energy of absorbed light (469 kJ·mol^{–1}). Remarkably, 4-fluoroaniline readily produced (4-aminophenyl)boronic acid that was isolated as trifluoroborate **25** in 53% yield, indicating that certain Ar–F bonds can be harnessed for the synthesis of boronic acids without the use of transition metals.²⁹ Similarly, 4-

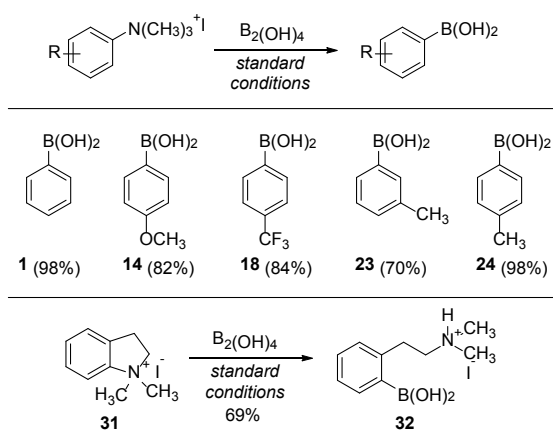
fluorophenol reacted smoothly to give boronic acid **3** in 69% yield (Table 2). Other fluoroarenes bearing electron-releasing substituents are also competent substrates (**26–30**). The procedure is particularly suitable for borylation of unprotected fluoroanilines and fluorophenols that have so far eluded C–F borylation. The reactivity observed for 4-fluoroaniline and other similar fluoroarenes in the photoinduced borylation reaction is consistent with the formation of the triplet aryl cation via the *heterolysis* of the C–F bond. This process is favored for the electron rich haloarenes and, unlike Ar–F homolysis, is greatly facilitated in polar protic solvents, as previously described by Albini, Fagnoni and Protti.³⁰ Indeed, the yield of the reaction of 4-fluorophenol with B₂pin₂ was solvent-dependent. No reaction was observed in hexane after 2 h, and only 5% of the borylation product was formed in acetonitrile, while 20% of the borylation product was produced in methanol. This observation is in line with the experimental and computational data reported for the photoinduced heterolysis of 4-fluorophenol.³⁰ Although B₂(OR)₄ generally behave as electrophiles, complexation with Lewis bases (e.g., fluoride, alkoxides, N-heterocyclic carbenes, 4-methylpyridine, and phosphines)³¹ produces nucleophilic sp²-sp³ Lewis base–diboron adducts that react with organic electrophiles in the absence of transition metal catalysts.³² It is possible that the photoheterolytically-produced fluoride ion forms a transient nucleophilic sp²-sp³ B₂(OR)₄F[−] complex that then reacts with the triplet cation.³³ Interestingly, B₂pin₂F[−] adduct was proposed as an intermediate in the borylation of arenediazonium salts,^{13c} and [NMe₄][B₂pin₂F] was subsequently shown to effect the diazonium borylation.^{31d} The photoinduced borylation of fluoroarenes is the first example of metal-free and direct conversion of fluoroarenes to arylboronic acids.

Table 2. Borylation of Fluoroarenes. ^a

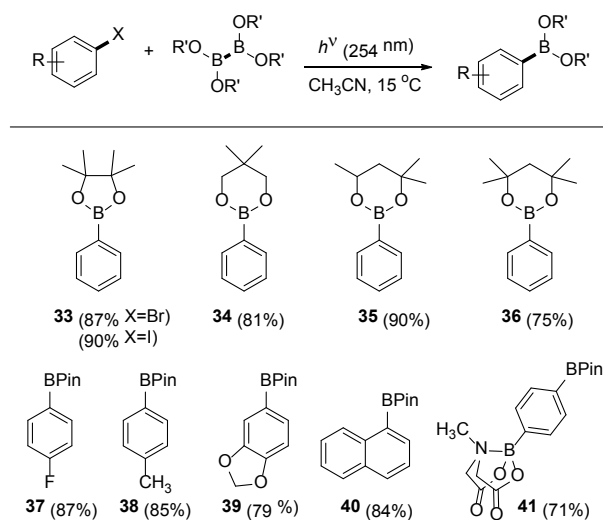


^a Reaction conditions: see footnote for Table 1.

Encouraged by the outcome of the experiments with haloarenes, we turned our attention to the borylation of other carbon–heteroatom bonds. In particular, we focused on the Ar–N-borylation, since few methods are known for this transformation.^{13,34} Interestingly, aryltrimethylammonium iodides reacted rapidly and produced the corresponding boronic acids **1**, **14**, **18**, **23**, and **24** in 70–98% yields. In addition, ring scission of the cyclic salt **31** afforded boronic acid **32** in 69% yield (Table 3).

Table 3. Borylation of Quaternary Arylammonium Salts. ^a^a Reaction conditions: see footnote for Table 1.

We next evaluated several diboron esters as counterparts in the reaction with haloarenes (Table 4). The borylation reactions with diboron esters derived from pinacol, neopentyl glycol, 1,1,3-trimethylethylene glycol, and 1,1,4,4-tetramethylethylene glycol delivered the corresponding phenylboronic esters **33–36** in high yields using acetonitrile as a solvent. The reaction scope was further tested with several bromoarenes with varied substitution patterns. In all cases the corresponding borolanes **37–40** were produced in excellent yields without any noticeable phototransposition.³⁵ Interestingly, the MIDA boronate ester **41** was also prepared, indicating that bifunctional borylated arenes can be efficiently accessed using this method.

Table 4. Photoinduced Reaction of Haloarenes with Diboronic Esters. ^a

^a Bromoarenes were used unless specified otherwise. Reaction conditions: haloarene (0.5–1 mmol), diboron ester (1–2 mmol), CH₃CN (6 mL), 15 °C, 4–14 h, UV lamp (254 nm). Bpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Although further work is necessary to clarify the mechanism, it is possible that homolytic substitution³⁶ in the diboron reagents and sp²-sp³ Lewis base–diboron adducts by a photogenerated aryl radical and aryl triplet cation can be responsible for the observed reactivity.³³

In summary, this paper describes a simple, scalable, metal- and additive-free method of photoinduced borylation of haloarenes and quaternary arylammonium salts. The borylation produces aromatic boronic acids and esters in good to excellent yields under mild conditions and with formation of innocuous, easy-to-remove byproducts. The reaction is distinguished by a broad scope that includes electron-rich fluoroarenes.

ASSOCIATED CONTENT

Supporting Information

Experimental and spectral details for all new compounds and all reactions reported. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Financial support by the Welch Foundation (AX-1788), the NSF (CHE-1455061), the Max and Minnie Tomerlin Voelcker Fund, and UTSA is gratefully acknowledged. Mass spectroscopic analysis was supported by a grant from the NIMHD (G12MD007591).

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