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Metal- and Additive-Free, Photoinduced Borylation of Haloarenes

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Abstract

Boronic acids and esters have crucial roles in the areas of synthetic organic chemistry, molecular sensors, materials science, drug discovery, and catalysis. Many of the current applications of boronic acids and esters require materials with very low levels of transition metal contamination. Most of the current methods for the synthesis of boronic acids require, however, transition metal catalysts and ligands that have to be removed via additional purification procedures. This protocol describes a simple, metal- and additive-free method of conversion of haloarenes directly to boronic acids and esters. This photoinduced borylation protocol does not require expensive and toxic metal catalysts and ligands and produces innocuous and easy-to-remove by-products. Furthermore, the reaction can be carried out on multigram scales in common grade solvents without the need for reaction mixtures to be deoxygenated. The setup and purification steps are typically accomplished within 1–3 h. The reactions can be run overnight, and the protocol can be completed within 13–16 h. Two representative procedures that are described in this protocol provide details for preparation of a boronic acid (3-cyanophenylboronic acid) and a boronic ester (1,1-benzenediboronic acid bis(pinacol)ester). We also discuss additional details of the method that will be helpful in the application of the protocol to other haloarene substrates.

Introduction

Boronic acids and esters are key materials in the areas of organic synthesis^{1–3}, catalysis^{4–6}, materials science^{7,8}, drug discovery^{9–11}, molecular self-assembly^{12,13}, carbohydrate analysis^{14–16}, and molecular sensing^{17–20}. Photoinduced dissociation of Ar–X bonds has enabled a number of synthetically useful carbon–carbon and carbon–heteroatom bond-forming transformations, e.g. photoinduced nucleophilic substitution^{21–24}, alkylation²⁵, arylation²⁶, and photocyclization^{27,28} reactions. We recently reported that haloarenes, including electron-rich fluoroarenes, as well as quaternary arylammonium salts readily react with diboron compounds to produce aromatic boronic acids and esters (Fig. 1a–c) under photochemical activation conditions²⁹. A similar photoinduced borylation method was also

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Note: Supporting Information with the NMR spectra of products **1** and **3** is available in the online version of the paper.

Author Contributions A.M.M., B.D.S. and W.C. carried out the experiments. O. V. L. and A.M.M. designed the experiments and analyzed the data. O.V.L. directed the research. O.V.L. and A.M.M. wrote the manuscript.

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developed by Li^{30,31}. We also showed that a 1,2- and 1,3-regioselective dual C–H/C–X borylation of haloarenes can be achieved on preparative scale³² (Fig. 1d).

The photochemical method of conversion of haloarenes directly to boronic acids and esters has a broad functional group tolerance and a scope that includes iodo-, bromo- and chloroarenes, as well as electron-rich fluoroarenes and arylammonium salts. The relevant reactions do not require heating, which is an advantage in the preparation of temperature-sensitive compounds. The present approach to borylation does not require expensive and toxic metal catalysts and ligands and produces innocuous and easy-to-remove by-products. Furthermore, the reaction can be carried out in common grade solvents without the need to deoxygenate the reaction mixtures.

The purification procedure is very simple, and, in the case of boronic acids, typically does not require chromatography. Since no metal catalysts are used, the products do not contain metal contaminants, making this method particularly suitable for the preparation of intermediates in pharmaceutical, nanotechnology, advanced materials, and analytical sensors industries that use organoboron compounds and have stringent requirements for trace metal impurities^{33,34}.

By contrast, transition metal–catalyzed borylation methods^{35–41} suffer from several limitations, including low functional group compatibility and the requirement for toxic and expensive precious metal catalysts and expensive ligands, high reaction temperatures, inert atmosphere, and difficult purification procedures that typically involve chromatography and metal scavengers.

We describe herein a detailed protocol that includes a step by step description of the reaction setup and purification procedures, as well as troubleshooting techniques. The protocol opens new avenues for the synthesis of organoboron compounds on preparative scales and reduces dependence on the transition metal–catalyzed borylation methods.

In the Procedure, we provide instructions for two exemplary syntheses of organoboron compounds using this new method. In the first part of the Procedure (steps 1–17), preparation of boronic acids is exemplified by the grams-scale synthesis of 3-cyanophenylboronic acid (**1**) from 3-bromobenzonitrile (**2**) (Fig. 2a). In the second part (steps 18–26), preparation of boronic esters is exemplified by the synthesis of 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3**) from bromoarene **4** (Fig. 2b). Naturally, the two synthetic procedures just alluded to are inherently independent of each other, and readers may decide to implement only one of them, depending on whether they plan to synthesize a boronic acid (adapting the instructions in steps 1–17) or a boronic ester (adapting the instructions in steps 18–26). Similarly, should readers decide to implement both synthetic procedures to obtain a boronic acid and a boronic ester, the relative order in which the two synthetic procedures are implemented is irrelevant.

Experimental Design

The reactions are typically carried out in quartz test-tubes. Although substantial amounts of water (>20 vol%) generally slow down the borylation reaction, the presence of trace

amounts of moisture does not affect it. Hence, commercial-grade solvents can be used without further purification. The reaction is not air-sensitive and no deoxygenation of the reaction mixture is necessary. We routinely use the photochemical reactor Rayonet RPR-100 equipped with 16 UV-C (254 nm) low-pressure lamps. However, other reactor designs can also be used (e.g. a photochemical immersion well reactor), keeping in mind that UV lamps with wavelengths other than 254 nm (e.g. 300 or 350 nm) are not effective. The yields are generally higher if the reaction mixture is placed in the narrowest possible test-tube that can accommodate the desired reaction mixture volume, to maximize exposure to light from the vertically arranged tubular UV lamps (Fig. 2c). It is also advisable to place the test-tube 1-2 cm from one of the UV lamps. The fan should be on throughout the synthesis to maintain a temperature of 26 °C in the photochemical chamber. The borylation generally proceeds smoothly at 10-30 °C. At higher temperatures, however, formation of the dehalogenated arene by-product (for example, benzonitrile from 3-bromobenzonitrile) may compete with borylation. The solvent of choice for the borylation with tetrahydroxydiboron is methanol. The borylations with diboron esters (e.g., B₂pin₂) can be carried out in methanol, acetonitrile, isopropanol, and trifluoroethanol.

For practical reasons, we typically maintain substrate concentration at 0.3–1.2 mol·L⁻¹, although in the case of poorly soluble substrates, more dilute reaction mixtures can also be used. Please be aware, however, that at substantially lower concentrations than those of the typical reaction (e.g., below 0.05 mol·L⁻¹), formation of the dehalogenated arene by-product may compete with borylation. The reactions typically do not require stirring, provided that the substrate is dissolved in the reaction mixture. The progress of the reaction, as well as formation of the dehalogenation by-product and boroxines can be monitored by means of ¹H NMR spectroscopy of an aliquot of the reaction mixture dissolved in *d*₄-methanol. We have successfully carried out borylations on 0.6-20 mmol scales with haloarenes as limiting reagents. Boronic esters that cannot be isolated by crystallization can be purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate as an eluent (typically 0-50% EtOAc in hexane).

Materials

Reagents

! CAUTION All chemicals used in this protocol should be handled with care. Standard protective equipment should be worn (lab coat, gloves, safety goggles), and all manipulations should be performed in a ventilated laboratory fume hood.

- Bis(pinacolato)diboron (B₂Pin₂) (Synthonix, cat. no. B1760G100)
- 3-Bromobenzonitrile (Matrix Scientific, cat. no. 075372)
- Deionized water
- Deuterated chloroform (Cambridge Isotope Laboratories)
- Deuterated dimethyl sulfoxide (Cambridge Isotope Laboratories)
- Deuterated methanol (Cambridge Isotope Laboratories)

- Ethyl acetate (Fisher Scientific, cat. no. E145-20, ACS grade)
- Hexane (Fisher Scientific, cat. no. H292-20, ACS grade)
- 12M Hydrochloric acid (Sigma-Aldrich, cat. no. H1758)
- Methanol (Fisher Scientific, cat. no. A412-20, ACS grade)
- Sodium hydrogen carbonate (Chem-Impex, cat. no. 00084)
- Sodium sulfate (Chem-Impex, cat. no. 00274)
- Tetrahydroxydiboron (Boron Molecular, cat. no. BM212)

Equipment

! CAUTION UV protective safety goggles, lab coat and gloves should be worn while working with sources of ultraviolet light.

- Access to NMR and IR spectrometry instruments
- 2-(4-Bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4**) (TCI America, cat. no. B4771)
- Cotton pad
- Disposable syringes and injection needles
- Erlenmeyer flasks
- Fritted glass Buchner funnel (medium porosity)
- Glass pipettes
- Magnetic Stirplate
- Melting point apparatus
- NMR tubes (5 mm width)
- pH Indicator paper (pH 0-14)
- Plastic funnel
- Polyethylene stopper (Chemglass, cat. no. CG-3021-03)
- Quartz test-tube (10 cm length $\times$ 1.2 cm internal diameter, Quartz Scientific, cat. no. 315010)
- Quartz test-tube (30 cm length $\times$ 1.5 cm internal diameter, Quartz Scientific, cat. no. 317010)
- ▲ **CRITICAL** Quartz test-tubes should be used, since borosilicate glass absorbs UV light.
- Rayonet RPR-100 photoreactor equipped with 16 Ushio 8W T5 UV-C lamps (254 nm).

▲ **CRITICAL** Photoreactor should be equipped with UV lamps emitting 254 nm light. Use of lamps with other maximum emittance wavelengths may result in lower yields.

- Rotary evaporator
- Round bottom flasks
- Rubber bulb
- Separatory funnel
- Spatulas
- Stirbar (12 mm length × 4 mm diameter, Fisher Scientific, cat. no. 14-513-93)
- Ultrasonic bath
- Weighing balance
- Weighing paper

Reagent Setup

Cold 12 M hydrochloric acid

Cool this reagent to 0-5 °C right before use in step 12 of the Procedure.

Cold hexane

Cool this reagent to 0-5 °C right before use in step 21 of the Procedure.

Procedure

Synthesis of 3-cyanophenylboronic acid (1)-reaction setup. •TIMING 15 min

1| Weigh out 1.82 g (10.0 mmol) of 3-bromobenzonitrile (**2**) and 1.34 g (15 mmol) of tetrahydroxydiboron. Place the reagents into a quartz test-tube (30 cm length × 1.5 cm internal diameter) equipped with a stirbar. Add 10 ml of methanol.

2| Stir the mixture alternately at 40 °C and room temperature (23 °C) until the solids completely dissolve and a clear solution is formed. Cap the test-tube with a polyethylene stopper, which is vented with a needle.

Synthesis of 3-cyanophenylboronic acid (1)-borylation reaction. •TIMING 12 h

3| Place the quartz test-tube containing the reaction mixture into the photoreactor and ensure that the distance between the quartz test-tube and one of the lamps is 1-2 cm. Turn on the lamps and the fan in the photoreactor. Irradiate the reaction mixture without stirring for 12 h. Please note that leaving the reaction overnight (12-17 h) typically does not affect the results.

▲ **CRITICAL** The fan should remain on for the duration of the reaction to maintain the temperature within the optimal range. Carrying out the experiment with the fan off may result in formation of the dehalogenation by-product, due to the increased temperature in the reactor chamber.

? Troubleshooting

Synthesis of 3-cyanophenylboronic acid (1)-purification. •TIMING 1 h

4| Pour the reaction mixture into a 50-ml round bottom flask. Add 1 g of sodium hydrogen carbonate and concentrate the mixture to dryness on a rotary evaporator (water bath temperature 30–35 °C).

5| Add to the flask 20 mL of hexane, swirl to mix the components and concentrate the mixture to dryness using a rotary evaporator (water bath temperature 30–35 °C).

6| Repeat step 5 three more times.

■**CRITICAL STEP** Evaporation of hexane ensures that residual methanol is removed from the crude product. Failure to remove residual methanol may prevent complete extraction of impurities and by-products (e.g. unreacted haloarene and the dehalogenation product) from the crude material in the following step.

7| Add to the residue obtained after step 6 20 mL of hexane, sonicate the resulting mixture for 30 sec then decant the hexane layer. The hexane layer may at this point be discarded.

8| Dry the residue under reduced pressure on a rotary evaporator (water bath temperature 30–35 °C).

9| Add to the residue 10 ml of methanol and concentrate under reduced pressure on a rotary evaporator (water bath temperature 30–35 °C)

■**CRITICAL STEP** Methanol needs to be added at this point to prevent the formation of boroxines.

10| Add to the residue obtained in the previous step 50 mL of ethyl acetate, swirl, and decant the ethyl acetate layer into a 250 mL separatory funnel.

11| Add 10 mL of deionized water into the round bottom flask with the remaining solid material.

12| Add 5 mL of cold 12 M hydrochloric acid dropwise to the mixture that remained in the round bottom flask to acidify the solution to pH 1, then transfer the mixture into a separatory funnel.

13| Shake the mixture in the separatory funnel vigorously. Decant the top (organic) layer into a 250-mL Erlenmeyer flask.

14| Extract the aqueous phase left in the separatory funnel with 30 mL of ethyl acetate.

15| Repeat the extraction described in the previous step.

16| Combine the ethyl acetate solutions obtained in steps 13, 14, and 15 in a 250-mL Erlenmeyer flask, and add to it 10 g of sodium sulfate and 1 g of sodium hydrogen carbonate. Stir the resulting mixture for 5 min. Filter off the solids using a plastic funnel with a cotton pad, and wash the solids three times with 10 mL of ethyl acetate each time.

17| Concentrate the filtrate obtained in the previous step on a rotary evaporator (water bath temperature 30–35 °C). Add to the resulting residue 5 mL of ethyl acetate and 40 mL of hexane. Concentrate the mixture obtained to dryness on a rotary evaporator (water bath temperature 30–35 °C). The product can now be weighed to establish the yield, and the purity of the product can be determined by means of ^1H , ^{13}C , and ^{11}B NMR spectroscopy using either CD_3OD or $(\text{CD}_3)_2\text{SO}$ as solvents.

■ **PAUSE POINT** Boronic acids like **1** may be stored at room temperature for several months or even years. However, such compounds may undergo dehydration to form boroxines in the mentioned conditions over time. Although such formation of boroxines does not usually affect the performance of the material in most of typical cross-coupling reactions, we recommend storing boronic acids at lower temperatures (e.g. 0 °C) to slow down the formation of boroxines.

? Troubleshooting

Synthesis of 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3**)— reaction setup

•TIMING 15 min

18| Weigh out 0.7 g (2.5 mmol) of 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4**) and 1.3 g (5.0 mmol) of B_2Pin_2 . Place the reagents into a quartz test-tube (10 cm length $\times$ 1.2 cm internal diameter) equipped with a stirbar and add to it 6 ml of methanol.

19| Stir the mixture at room temperature until the solids completely dissolve and a clear solution is formed. Cap the test-tube with a polyethylene stopper that is vented with a needle.

Synthesis of 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3**)-borylation reaction. •TIMING 12 h

20| Place the quartz tube containing the reaction mixture into the photoreactor and ensure that the distance between the quartz tube and the lamp is 1-2 cm. Turn on the lamps and the fan in the photoreactor. Irradiate the reaction mixture without stirring for 12 h. Please note that leaving the reaction overnight (12–17 h) typically does not affect the results. The borylation product will partially precipitate from the reaction mixture.

▲ **CRITICAL** The fan should remain on for the duration of the reaction to maintain the temperature within the optimal range. Carrying out the experiment with the fan off may result in formation of the dehalogenation by-product, due to the increased temperature in the reactor chamber.

? Troubleshooting

Synthesis of 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3**)-purification

•TIMING 2-3 h

21| Filter the solid that precipitated from the reaction mixture using a fritted glass Buchner funnel. Wash the solid left in the funnel with 10 mL of cold hexane.

22| Combine the filtrate and the hexane washings and concentrate the combined solution to dryness on a rotary evaporator (water bath temperature 30-35 °C).

23| Add 10 mL of hexane to the residue obtained in the previous step and place the flask in a refrigerator at 4 °C for 1 h, until a solid precipitate has formed.

24| Filter the precipitate and wash it with 5 mL of hexane.

25| Repeat steps 22-24 once more.

26| Combine the isolated solid product fractions obtained in steps 21-25 and dry the material in the air. The product can now be weighed to establish the yield and, the purity of the product can be determined by means of ^1H , ^{13}C , and ^{11}B NMR spectroscopy using CDCl_3 as a solvent.

■ **PAUSE POINT** Pinacol esters of boronic acids can be stored for extended periods of time (e.g. >6 months) without noticeable decomposition at room temperature in capped storage containers.

? **TROUBLESHOOTING** Troubleshooting advice can be found in Table 1.

•TIMING

Preparation of boronic acid **1**

Steps 1 and 2: 15 min

Step 3: 12 h

Steps 4–17: 1 h

Preparation of boronic ester **3**

Steps 18 and 19: 15 min

Step 20: 12 h

Steps 21–26: 2–3 h

Anticipated Results

Following the procedure described above in steps 1-17, 3-cyanophenylboronic acid (**1**) is obtained as a colorless solid in 88% yield (1.3 g).

Following the procedure described above in steps 18-26, 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3**) is obtained as a colorless crystalline solid in 75% yield (0.6 g). The products are characterized by ^1H , ^{13}C , ^{11}B NMR, and IR spectroscopy. For typical applications characterization by ^1H , ^{13}C , ^{11}B NMR is sufficient to establish the identity and purity of the isolated products.

Analytical data

3-Cyanophenylboronic acid (1): m.p. > 260 °C. – ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$): 8.43 (2 H, br s), 8.14 (1 H, s), 8.09 (1 H, dd, $J = 7.5, 1.5$ Hz), 7.89 (1 H, dd, $J = 7.5, 1.2$ Hz), 7.59 (1 H, t, $J = 7.5$ Hz) ppm. – ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{SO}$): 138.7, 137.6, 133.6, 128.7, 119.3,

110.6 ppm. – ^1H NMR (300 MHz, CD_3OD): 7.97 (2 H, br m), 7.74 (1 H, dd, $J = 7.5$, 1.5 Hz), 7.53 (1 H, t, $J = 7.5$ Hz) ppm. – ^{13}C NMR (75 MHz, CD_3OD): 139.1, 138.3, 134.2, 129.5, 120, 112.8 ppm. – ^{11}B NMR (160 MHz, CDCl_3): 27.5 ppm. – IR: 3358, 2232, 1599, 1575, 1429, 1339, 1339, 1201, 1039, 907, 850, 799 cm^{-1} . – Calcd. for $\text{C}_7\text{H}_6\text{BNO}_2$: C, 57.22; H, 4.12; N, 9.53. Found C, 57.36; H, 4.12; N, 9.39.

1,4-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (3): m.p. 241–243 °C. – ^1H NMR (300 MHz, CDCl_3): 7.80 (4 H, s), 1.34 (24 H, s) ppm. – ^{13}C NMR (75 MHz, CDCl_3): 133.8, 83.8, 24.8 ppm. – ^{11}B NMR (160 MHz, CDCl_3): 30.8 ppm. – IR: 2975, 1522, 1458, 1392, 1371, 1346, 1324, 1257, 1214, 1167, 1140, 1097, 1019, 961, 856, 844 cm^{-1} . – Calcd. for $\text{C}_{18}\text{H}_{28}\text{B}_2\text{O}_4$: C, 65.51; H, 8.55. Found C, 65.63; H, 8.50.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Photoinduced borylation of haloarenes. **(a)** General borylation scheme. **(b)** Reaction mechanism. **(c)** Typical products of the photoinduced borylation. **(d)** Regiodivergent dual 1,2- and 1,3-C-H/C-X borylation of haloarenes. ISC = intersystem crossing, HFIP = hexafluoroisopropanol, IPA = isopropyl alcohol.

Figure 2.

Photoinduced borylation reactions described in this protocol. **(a)** preparation of 3-cyanophenylboronic acid **(1)** from 3-bromobenzonitrile **(2)**. **(b)** preparation of boronic ester **3** from bromoarene **4**. **(c)** typical reaction set-up in a Rayonet RPR-100 chamber.

Table 1
Troubleshooting table

Step	Problem	Possible reason	Solution
3, 20	Incomplete reaction	The lamp wavelength is not 254 nm or the lamp intensity is insufficient	Use lamps emitting 254 nm light or use higher intensity UV sources
		The substrates utilized by the experimenter are less reactive than bromoarenes 2 and 4	Allow the reaction to proceed for a longer time until it is complete
3, 20	A substantial amount of dehalogenation by-product is formed	The temperature in the reactor is too high or the reaction mixture is too dilute	Turn on the fan or provide a cool air supply to cool the reaction mixture down to the optimal temperature (10-30 °C)
			Reduce the solvent volume
17	Boroxine is formed as by-product	The product was dried at >40 °C, causing its dehydration	Add 10 mL of methanol and evaporate the resulting solution at <40 °C
17	Impure product is obtained	The reaction did not go to completion	Allow the reaction to proceed to completion over a longer a period of time
			Make sure that the lamp emits 254-nm light
17	Boronic acid is obtained in low yield	Too much water is added in step 11, boronic acid is soluble in water, or an insoluble boroxine is formed	Use the specified amount of water in step 11. To prevent formation of boroxines, dissolve the solid obtained after the hexane wash in step 7 in methanol and evaporate the solution. Repeat the process