

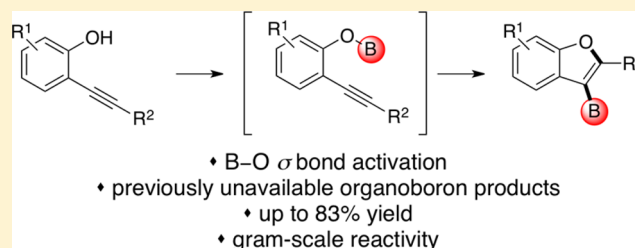
# Alkoxyboration: Ring-Closing Addition of B–O $\sigma$ Bonds across Alkynes

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**S** Supporting Information

**ABSTRACT:** For nearly 70 years, the addition of boron–X  $\sigma$  bonds to carbon–carbon multiple bonds has been employed in the preparation of organoboron reagents. However, the significantly higher strength of boron–oxygen bonds has thus far precluded their activation for addition, preventing a direct route to access a potentially valuable class of oxygen-containing organoboron reagents for divergent synthesis. We herein report the realization of an alkoxyboration reaction, the addition of boron–oxygen  $\sigma$  bonds to alkynes. Functionalized *O*-heterocyclic boronic acid derivatives are produced using this transformation, which is mild and exhibits broad functional group compatibility. Our results demonstrate activation of this boron–O  $\sigma$  bond using a gold catalysis strategy that is fundamentally different from that used previously for other boron addition reactions.



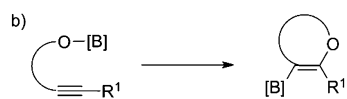
## INTRODUCTION

Boronic acids and their derivatives are versatile reagents in modern organic synthesis, and the hydroboration reaction is a well-established method for generating these building blocks through the addition of B–H bonds across C–C multiple bonds.<sup>1</sup> First described by Hurd<sup>2</sup> in 1948 and later developed in detail by Brown,<sup>3</sup> this reaction has inspired many catalyzed variants.<sup>4,5</sup> Recently, several compelling examples of related B–X bond addition reactivity have been reported for X = C,<sup>6,7</sup> Si,<sup>5,8,9</sup> Sn,<sup>5,10</sup> S,<sup>11</sup> B,<sup>5,12</sup> Cl,<sup>13</sup> Br,<sup>14</sup> and I<sup>14</sup> (Figure 1a). Many of these transformations proceed through the oxidative addition of a catalytic transition metal such Ni(0), Pd(0), or Pt(0) into the B–X  $\sigma$  bond.



**Seminal Previous Reports**

X = H: Hurd and Brown  
 X = C: Suginome  
 X = Si: Ito and Suginome  
 X = Sn: Tanaka  
 X = S: Miyaura and Suzuki  
 X = B: Miyaura and Suzuki  
 X = Cl, Br, I: Lappert, Suzuki  
 X = O: **unreported**



**This Work**

**Figure 1.** (a) Previous work developing addition of B–X bonds across alkynes. (b) This work demonstrating the first addition of B–O bonds across alkynes.

Despite this progress, the corresponding activation of B–O bonds and addition to C–C multiple bonds—alkoxyboration—has remained elusive for 65 years.<sup>15,16</sup> This striking dearth of B–O bond activation reactivity may be due to the extremely high strength of the B–O bond, ~136 kcal/mol, compared to less than 105 kcal/mol for all others entries in the series.<sup>17</sup> This high stability may render the B–O bond unreactive toward oxidative addition, thus preventing the successful application of Ni, Pd, or Pt catalysis<sup>6–11</sup> in an alkoxyboration reaction. Organoboron reagents are the building blocks of choice for medicinal chemistry and drug discovery.<sup>18</sup> Given that ethers are found in many diverse classes of natural products<sup>19</sup> and in nearly 25% of the top-grossing pharmaceuticals in the United States for 2012,<sup>20</sup> the development of such a transformation allows for the preparation of oxygen-containing building blocks useful in drug discovery and materials science.<sup>20,21</sup>

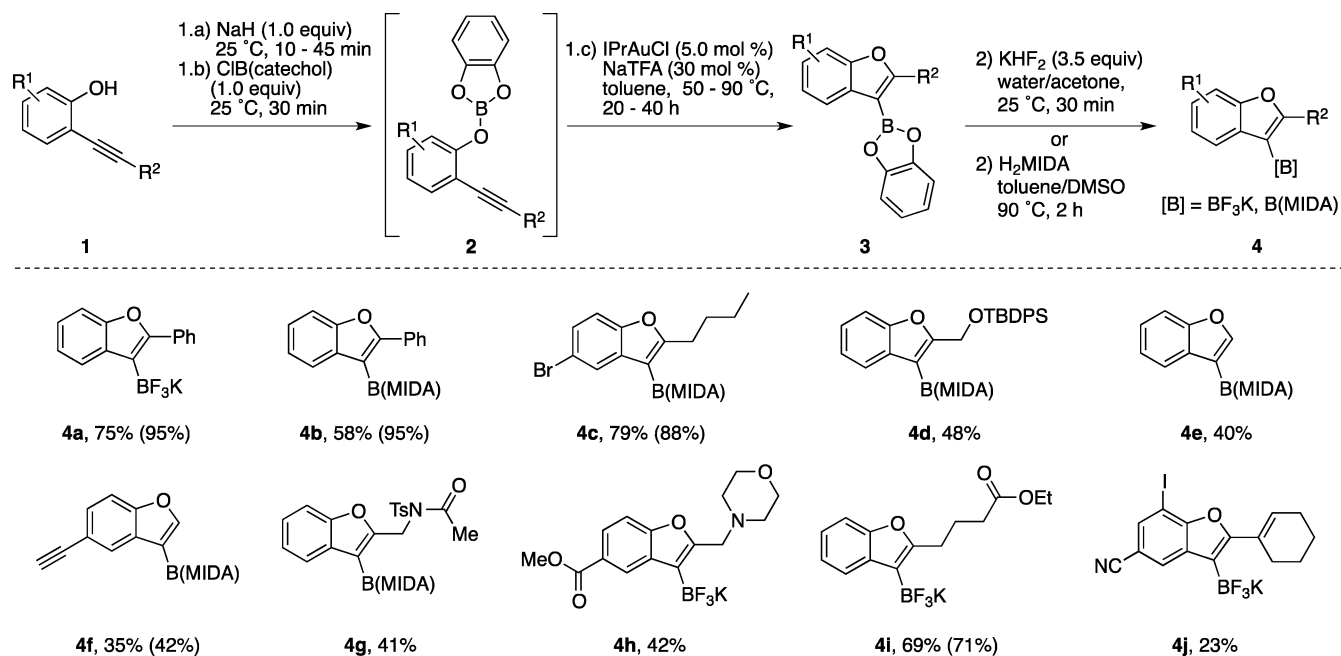
## RESULTS AND DISCUSSION

Herein we report the realization of an alkoxyboration reaction of alkynes (Figure 1b), through which new *O*-heterocyclic organoboronate coupling partners are available for downstream functionalization. The high functional group tolerance of this reaction enables downstream divergent synthesis of functionalized benzofurans—the ability to access multiple benzofurans from one bench stable precursor. In contrast, current methods for synthesizing benzofurans often rely on harsh conditions that limit compatibility with functional groups desirable for divergent synthesis.<sup>22</sup>

We envisioned that the desired alkoxyboration reactivity could be promoted through an activation pathway employing a

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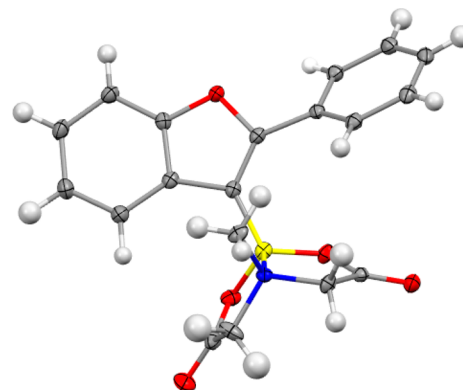
**Figure 2.** Functionalized benzofuran boronic acid derivatives available through the alkoxyboronation reaction. Values represent isolated yields of organotrifluoroborate or MIDA boronate products **4**. Values in parentheses represent <sup>1</sup>H NMR yields of the corresponding catechol boronic ester **3** versus an external mesitylene standard using the ERETIC method.

bifunctional Lewis acidic/Lewis basic catalyst, which could simultaneously activate both the alkyne and the B–O  $\sigma$  bond partners. We anticipated that this unique strategy could allow for the *anti* addition of B–O bonds across alkynes by circumventing the previous problematic strategy of oxidative cleavage of the B–O bond.

Our optimized one-pot procedure begins with 2-alkynyl phenols (**1**), which are converted into the requisite boric ester intermediate **2** using the readily available reagent *B*-chlorocatecholborane (Figure 2). Treatment of this intermediate with the commercially available Lewis acidic gold(I) precatalyst IPrAuCl and NaTFA affords alkoxyboronation product **3** in good to excellent conversion as determined by the ERETIC method.<sup>23</sup> Interestingly, our examination of alternative  $\pi$ -Lewis acidic transition metal catalysts revealed no other active catalysts aside from Au(I).<sup>24</sup> For synthetic ease, the catechol boronic ester alkoxyboronation product **3** was converted into either the organotrifluoroborate<sup>25</sup> or *N*-methyliminodiacetic acid (MIDA) boronate<sup>26</sup> derivative, **4**, both of which are air stable indefinitely.

Organotrifluoroborate **4a** is readily isolated in high yield using a chromatography-free purification, making this derivatization method particularly amenable to applying the alkoxyboronation reaction on preparative scale. The corresponding MIDA derivative (**4b**) provides an option for purification by silica gel chromatography, but this comes at the cost of slightly diminished yield. Single-crystal X-ray diffraction analysis of **4b** allowed for the unambiguous identification of the alkoxyboronation product (Figure 3).

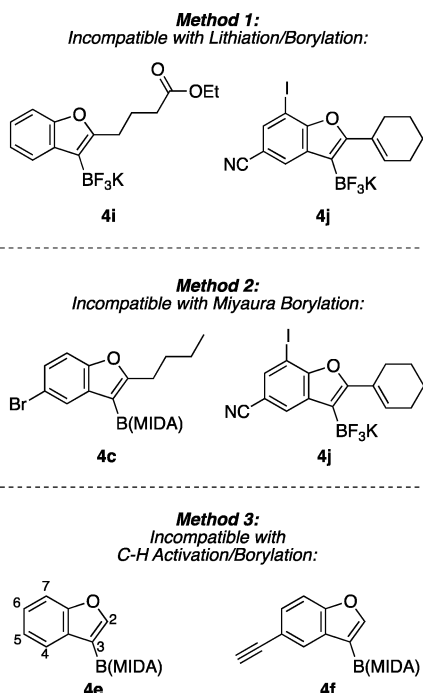
The alkoxyboronation reaction is tolerant of a variety of functional groups suitable for downstream reactivity. Aryl bromide **4c**, silyl-protected alcohol **4d**, terminal alkyne **4f**, amide **4g**, esters **4h** and **4i**, and the functionally dense iodonitrile **4j** are compatible with the reaction conditions. Many of these alkoxyboronation reactions proceed smoothly at 50 °C, although the reactions generating **4d**, **4g**, **4h**, and **4j**



**Figure 3.** X-ray structure of **4b** with the thermal ellipsoids set at the 50% probability level (B, yellow; C, gray; H, white; O, red; N, blue).

required heating to 90 °C in order to affect full conversion. We attribute the relatively slow formation of **4d** to the high steric encumbrance from the silyl ether at the 2-position of the benzofuran. The cyclization of substrates containing Lewis basic nitrogen atoms (forming **4g**, **4h**, and **4j**) was likely retarded by reversible N–B coordination that was observed by <sup>11</sup>B nuclear magnetic resonance (NMR) spectroscopy. For all substrates, the mass balance was largely attributable to protonolysis of the product C–B bond.

Notably, many of these products contain functional groups incompatible with commonly employed methods of benzofuran synthesis, including via other borylation techniques (Figure 4). In one frequently used borylation technique, an aryl lithium intermediate is trapped by a boron electrophile (Method 1); thus, electrophiles such as carbonyl or nitrile groups and enolizable protons are not generally tolerated due to the highly nucleophilic and basic nature of the requisite organolithium intermediate.<sup>27</sup> Aryl halides may also suffer from undesired lithium/halogen exchange. The Miyaura borylation is a more

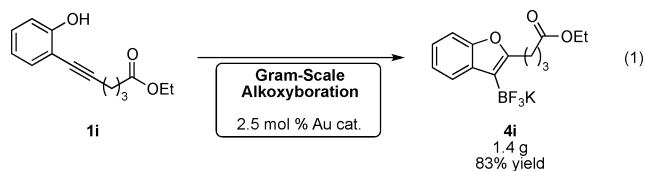


**Figure 4.** Benzofuran boronic acid derivatives inaccessible using conventional borylation methods but newly accessible using the alkoxyboration reaction.

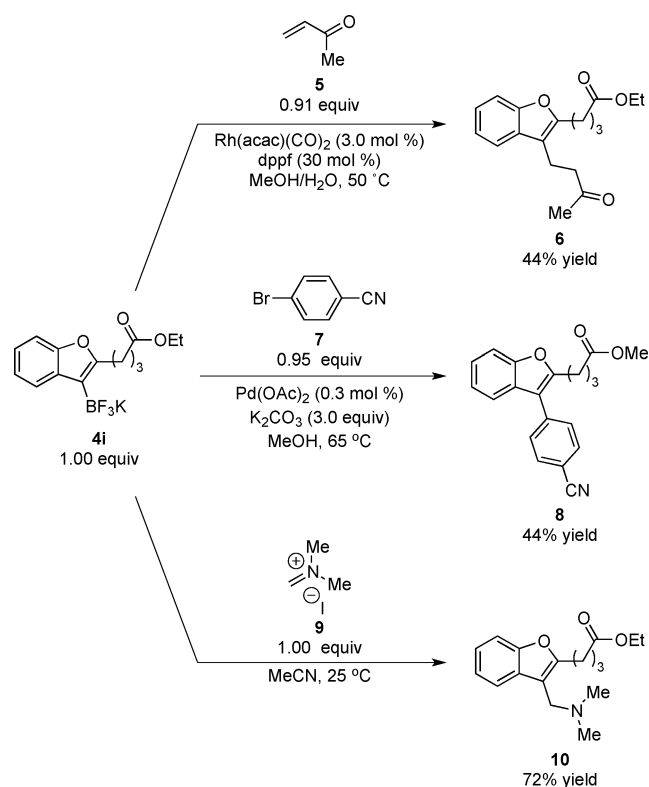
mild alternative that is compatible with electrophilic functional groups (Method 2), but aryl halides are borylated through this Pd(0)-catalyzed reaction<sup>28</sup> and are therefore not spectator functional groups under these conditions. Finally, the Ir-catalyzed C–H activation/borylation reaction<sup>29</sup> is an effective means of accessing aryl boronic acid derivatives (Method 3), but this reaction is regioselective for either 2- or 7-borylation; 3-borylated benzofurans such as those available through the alkoxyboration reaction cannot be synthesized regioselectively through C–H activation/borylation.<sup>30</sup>

We set out to demonstrate the utility in divergent synthesis of the alkoxyboration products enabled through this synthesis in subsequent divergent functionalization steps (Scheme 1). Rh-catalyzed conjugate addition of **4i** into methyl vinyl ketone using the method developed by Batey<sup>31</sup> provides  $\beta$ -benzofuran-aryl ketone **6** in moderate yield. Subjection of the same benzofuran trifluoroborate to Suzuki–Miyaura coupling conditions described by Molander and Biolatto<sup>32</sup> afforded 3-arylated benzofuran **8** with concomitant methanolysis of the ethyl ester. Finally, addition of **4i** to an iminium ion was used to prepare aminated benzofuran **10**. Thus, a single bench-stable alkoxyboration product can be functionalized in a variety of ways, which is important in diversity-oriented syntheses to develop compound catalogs for drug discovery.<sup>18</sup>

We next explored the scalability of the alkoxyboration reaction. Ester-containing phenol **1i** was successfully converted to more than 1 g of organotrifluoroborate **4i** on a 5 mmol scale with 2.5% gold catalyst (eq 1). Full conversion of starting

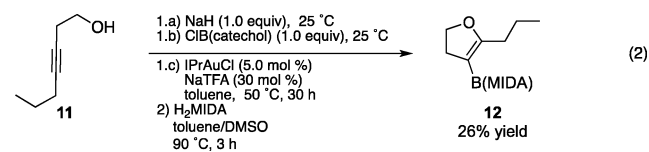


### Scheme 1. Versatility of an Alkoxyboration Product in Diversity-Oriented Synthesis



material was affected even with this lower Au catalyst loading. This convenient scalability demonstrates that quantities of *O*-heterocyclic boronic acid derivatives sufficient for multistep synthesis may be prepared using the alkoxyboration method.

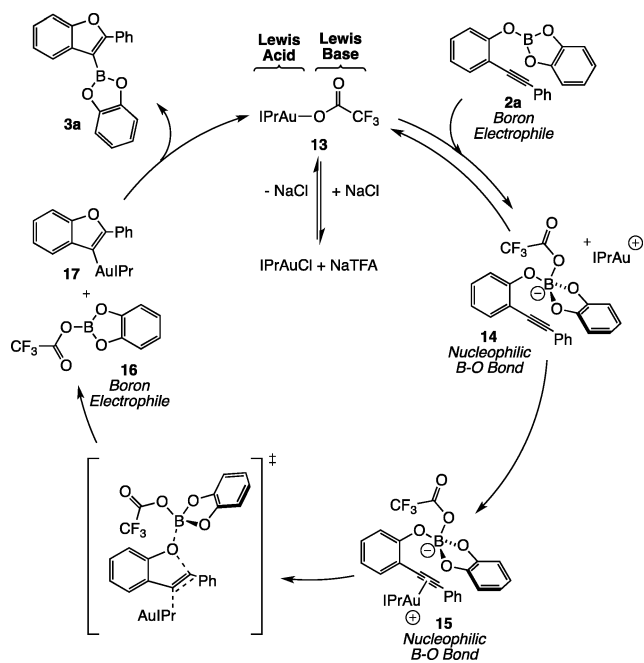
Having demonstrated the utility of this transformation in generating members of the benzofuran class of *O*-heteroaryl boronic acid derivatives, we explored its application to the synthesis of a nonaromatic oxygen-containing heterocycle (eq 2). Simple and commercially available homopropargyl alcohol



**11** was subjected to standard alkoxyboration reaction conditions to prepare dihydrofuran product **12**. A large number of unidentifiable trace coproducts were detected in this reaction, possibly consistent with intermolecular reactivity. This substrate demonstrates the potential for generality in the alkoxyboration reaction: The reaction features low labor “setup cost” by employing simple, commercially available starting materials to generate highly value-added *O*-heterocyclic organoboronate compounds in one synthetic step, and the cyclization proceeds without requiring the gain of product aromaticity or the need for a fused ring system that enforces a conformational bias toward cyclization.

A number of Lewis-acidic metal catalysts have been developed for the addition of oxygen-electrophile bonds across alkynes, albeit not with boron and thus not generating these building blocks for downstream functionalization.<sup>33</sup> We propose the catalytic cycle shown in Scheme 2 featuring bifunctional

**Scheme 2. Mechanistic Hypothesis Featuring the Bifunctional Lewis Acidic/Lewis Basic Catalyst IPrAuTFA**



Lewis acidic/Lewis basic substrate activation. The bifunctional catalyst IPrAuTFA can be generated *in situ* from IPrAuCl and NaTFA. Reaction of the Lewis basic trifluoroacetate moiety with electrophilic boric ester **2a** gives nucleophilic borate **14**. The resulting Lewis acidic Au(I) cation may then bind to the alkyne (**15**), increasing its electrophilicity. Nucleophilic attack on the alkyne–Au  $\pi$  complex by the phenol B–O bond would provide two neutral intermediates: boron electrophile **16** and organogold nucleophile **17**, which could recombine to regenerate **13** with concomitant formation of the observed alkoxyboration product **3a**. Thus, the IPrAu<sup>+</sup> moiety of the catalyst activates the alkyne for nucleophilic attack, and the TFA counterion allows for reversible tuning from a boron electrophile to a nucleophilic borate adduct. This reaction manifold is fundamentally unique from the metal-catalyzed addition of B–C, B–Si, B–Sn, and B–S  $\sigma$  bonds, which often proceed through oxidative addition of a low-valent metal catalyst into the B–X bond. We believe that the new activation strategy employed in the alkoxyboration reaction could be extended to other types of B–X bonds in order to provide additional reactivity complementary to preexisting methods. Notably, this approach also suggests a new generalizable mechanism for Au catalyst turnover by trapping with electrophilic boron to generate other previously inaccessible organoboron building blocks.

## CONCLUSIONS

This alkoxyboration reaction proceeds through an unprecedented activation of the strong B–O  $\sigma$  bond. This fundamentally new activation is showcased in a mild, scalable technique for the preparation of *O*-heterocyclic boronic acid derivatives and downstream-functionalized benzofurans. The reaction provides a simple new bond disconnection for constructing these motifs with different regioselectivity and broader functional group compatibility than existing methods. This compatibility yields highly functionalized bench-stable building blocks for divergent synthesis that are not directly

accessible using alternative methods. The carbophilic Lewis acid activation mechanism for B–X addition reactions suggests its broader application to other B–X addition reactions and the ability to synthesize previously inaccessible organoboron building blocks via this new strategy for turning over gold and other carbophilic metal catalysts.

## EXPERIMENTAL SECTION

**General Methods.** All chemicals were used as received from commercial sources unless otherwise noted. Sodium trifluoroacetate was dried at 130 °C at 10 mTorr for 18 h before use. Toluene and dichloromethane were purified by passage through an alumina column under argon pressure on a push-still solvent system. Anhydrous dimethylsulfoxide was obtained by stirring over activity I alumina 18 h under N<sub>2</sub> atmosphere, decanting the liquid, and distilling the liquid at 10 Torr over CaH<sub>2</sub>. Acetone was dried by distillation over anhydrous CaSO<sub>4</sub> under N<sub>2</sub> atmosphere. Toluene-*d*<sub>8</sub> was dried over CaH<sub>2</sub>, degassed using three freeze–pump–thaw cycles, and vacuum transferred prior to use. All manipulations were conducted in a glovebox under nitrogen atmosphere or using standard Schlenk techniques unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using Merck F<sub>250</sub> plates. Plates were visualized under UV irradiation (254 nm) and/or using a basic aqueous solution of potassium permanganate. Flash chromatography was conducted using a Teledyne Isco Combiflash Rf 200 Automated Flash Chromatography System, and Teledyne Isco Redisep 35–70  $\mu$ m silica gel. All proton and carbon nuclear magnetic resonance (<sup>1</sup>H and <sup>13</sup>C NMR) spectra were recorded on a Bruker DRX-400 spectrometer, Bruker DRX-500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE-600 spectrometer. All boron nuclear magnetic resonance (<sup>11</sup>B NMR) spectra were recorded on a Bruker AVANCE-600 spectrometer. All fluorine nuclear magnetic resonance (<sup>19</sup>F NMR) spectra were recorded on a Bruker DRX-400. All chemical shifts ( $\delta$ ) are reported in parts per million (ppm) downfield of tetramethylsilane, and referenced to the residual protiated solvent peak ( $\delta$  = 7.26 ppm for CDCl<sub>3</sub>,  $\delta$  = 2.50 ppm for DMSO-*d*<sub>6</sub>, or  $\delta$  = 1.94 ppm for CD<sub>3</sub>CN in <sup>1</sup>H NMR spectroscopy experiments;  $\delta$  = 77.16 ppm for CDCl<sub>3</sub>,  $\delta$  = 39.52 ppm for DMSO-*d*<sub>6</sub>, or  $\delta$  = 1.34 ppm for CD<sub>3</sub>CN in <sup>13</sup>C NMR spectroscopy experiments). <sup>11</sup>B and <sup>19</sup>F NMR spectroscopy experiments are referenced to the absolute frequency of 0 ppm in the <sup>1</sup>H dimension according to the Xi scale. Low- and high-resolution mass spectrometry data were obtained at the University of California, Irvine.

**General Considerations for Alkoxyboration Reactions.** All alkoxyboration reactions were conducted in a N<sub>2</sub>-filled glovebox due to the high moisture sensitivity of the boric ester intermediate **2**. All glassware and reagents must be rigorously dry for optimal yield. The reaction progress was monitored by removing a small aliquot of the reaction mixture from the glovebox and diluting it in 1:1 EtOAc:water. This results in rapid hydrolysis of boric ester intermediate **2** back to the phenol starting material **1**. Thus, co-spotting the reaction mixture versus phenol **1** provides a convenient method for determining whether or not intermediate **2** has been fully consumed. The addition of PPh<sub>3</sub> to quench the Au catalyst<sup>34</sup> between the alkoxyboration step and the formation of the organotrifluoroborate or MIDA boronate was essential. Full synthetic protocols for the alkoxyboration reaction are available in the Supporting Information.

**Benzofuran Trifluoroborate 4a.** A solution of phenol **1a** (97.0 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL of toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (69 wt % purity, 17.4 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL of toluene over 2 min. A suspension of NaTFA (20 mg, 0.15 mmol, 30 mol %) in 0.5 mL of toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation. To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2  $\times$  0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2a**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **1a**. After 24 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2a**. The reaction mixture was cooled to 25 °C, and a solution of PPh<sub>3</sub> (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 22 h at 25 °C in order to quench IPrAuTFA before proceeding. The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with toluene (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (4.5 mL) and added to a stirring solution of KHF<sub>2</sub> (140 mg, 1.8 mmol, 3.5 equiv) in water (1.5 mL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. To this residue was added 2 mL of Et<sub>2</sub>O and the solution was subsequently concentrated at ca. 10 mTorr for 30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et<sub>2</sub>O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional washing/extraction cycle to yield **4a** as a white powder (113 mg, 75% yield) after removing volatiles at 25 °C and ca. 10 mTorr for 18 h. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 600 MHz): δ 8.10 (d, *J* = 7.4 Hz, 2H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.13 (td, *J* = 6.5 Hz, 1.2 Hz, 1H), 7.08 (td, *J* = 7.4, 0.9 Hz, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz): δ 154.7 (q, *J*<sub>C-F</sub> = 4.6 Hz), 153.8, 135.4, 133.3, 127.9, 126.8, 126.7 (q, *J*<sub>C-F</sub> = 2.3 Hz), 124.1 (q, *J*<sub>C-F</sub> = 2.8 Hz), 122.7, 109.6. [Note: As with many organotrifluoroborates, the *ipso* carbon was not detected, presumably due to broadening through coupling to the <sup>11</sup>B nucleus. The quaternary carbon at the benzofuran 2 position was also not detected.] <sup>11</sup>B NMR (DMSO-*d*<sub>6</sub>, 193 MHz): δ 3.2 (br s). <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 376 MHz): δ -131.9 (br s). HRMS (ESI<sup>-</sup>): Calculated for C<sub>14</sub>H<sub>3</sub>BF<sub>3</sub>O ([M - K]<sup>-</sup>), 261.0701; found, 261.0706.

**MIDA Boronate 4b.** A solution of phenol **1a** (97.0 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL of toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL of toluene over 2 min. A suspension of NaTFA (20 mg, 0.15 mmol, 30 mol %) in 0.5 mL of toluene was added next, and the resulting suspension was stirred for 15 min to affect full deprotonation. To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2a**. Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **1a**. After 24 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2a**. The reaction mixture was cooled to 25 °C, and a solution of PPh<sub>3</sub> (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding. Anhydrous DMSO (2.0 mL) and H<sub>2</sub>MIDA (81 mg, 0.55 mmol, 1.1 equiv) were added to the quenched alkoxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2 h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from

100% Et<sub>2</sub>O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **4b** as a white powder (101 mg, 58% yield). Crystals suitable for X-ray diffraction analysis were prepared by slow diffusion of Et<sub>2</sub>O into a saturated solution of **4b** in Et<sub>2</sub>O/acetone at 25 °C over 3 days. TLC (10% MeCN/Et<sub>2</sub>O): *R*<sub>f</sub> = 0.39. <sup>1</sup>H NMR (CD<sub>3</sub>CN, 600 MHz): δ 7.72 (dd, *J* = 7.8 Hz, 0.8 Hz, 1H), 7.67–7.65 (m, 2H), 7.55 (d, *J* = 9.7 Hz, 1H), 7.47–7.44 (m, 3H), 7.35–7.31 (m, 1H), 7.29–7.26 (m, 1H), 3.97 (d, *J* = 17.1 Hz, 2H), 3.65 (d, *J* = 17.1 Hz, 2H), 2.56 (s, 3H). <sup>13</sup>C NMR (CD<sub>3</sub>CN, 125 MHz): δ 169.0, 156.0, 133.6, 133.0, 130.6, 130.2, 129.3, 125.2, 123.9, 123.5, 111.8, 63.0, 48.2. [Note: no signals were observed for the quaternary C–B *ipso* carbon or the quaternary carbon at the benzofuran 2 position.] <sup>11</sup>B NMR (CD<sub>3</sub>CN, 193 MHz): δ 11.3 (br s). HRMS (ESI<sup>+</sup>): Calculated for C<sub>17</sub>H<sub>19</sub>BBrNO<sub>5</sub> ([M + Na]<sup>+</sup>), 372.1023; found, 372.1016.

## ■ ASSOCIATED CONTENT

### ☛ Supporting Information

Full experimental procedures and characterization data, including CIF data for **4b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare the following competing financial interest(s): Provisional patent applications (no. 61/836,391 and no. 61/906,040) have been filed by the University of California.

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## ■ REFERENCES

- (1) Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine, and Materials*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2011.
- (2) Hurd, D. T. *J. Am. Chem. Soc.* **1948**, *70*, 2053–2055.
- (3) Brown, H. C. *Tetrahedron* **1961**, *12*, 117–138.
- (4) (a) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878–879. (b) Carrol, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609–631.
- (5) Miyaura, N. Hydroboration, Diboration, and Stannylation. In *Catalytic Heterofunctionalization*; Togni, A., Grützmaier, H., Eds.; Wiley-VCH: Weinheim, 2001; pp 1–46.
- (6) (a) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358–6359. (b) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2009**, *128*, 14438–14439.
- (7) Suginome, M. *Chem. Rec.* **2010**, *10*, 348–358.
- (8) Suginome, M.; Nakamura, H.; Ito, Y. *Chem. Commun.* **1996**, 2777–2778.
- (9) Suginome, M.; Nakamura, H.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2516–2518.
- (10) Onozawa, S.; Hatanaka, Y.; Sakakura, T.; Shimada, S.; Tanaka, M. *Organometallics* **1996**, *15*, 5450–5452.
- (11) Ishiyama, T.; Nishijima, K.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 7219–7225.

- (12) (a) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018–11019. (b) Marder, T. B.; Norman, N. C. *Top. Catal.* **1998**, *5*, 63–73.
- (13) Lappert, M. F.; Prokai, B. *J. Organomet. Chem.* **1964**, *1*, 384–400.
- (14) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731–734.
- (15) Cragg, R. H.; Lappert, M. F.; Tilley, B. P. *J. Chem. Soc.* **1964**, 2108–2115.
- (16) Matsumi, N.; Chujo, Y. *Macromolecules* **1998**, *31*, 3802–3806.
- (17) Sanderson, R. T. *Polar Covalence*; Academic Press: New York, 1983.
- (18) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095–14104.
- (19) Domínguez de María, P.; van Gemert, R. W.; Straathof, A. J. J.; Hanefeld, U. *Nat. Prod. Rep.* **2010**, *27*, 370–392.
- (20) Drugs.com, U.S. Pharmaceutical Sales – 2012 (<http://www.drugs.com/stats/top100/2012/sales>).
- (21) Anderson, S.; Taylor, P. N.; Verschoor, G. L. B. *Chem.—Eur. J.* **2004**, *10*, 518–527.
- (22) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley: Chichester: United Kingdom, 2010.
- (23) Akoka, S.; Barantin, L.; Trierweiler, M. *Anal. Chem.* **1999**, *71*, 2554–2557.
- (24) Full experimental details are available in the Supporting Information.
- (25) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286.
- (26) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085.
- (27) Nagaki, A.; Moriwaki, Y.; Yoshida, J. *Chem. Commun.* **2012**, *48*, 11211–11213.
- (28) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.
- (29) (a) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305–308. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 390–391.
- (30) Mkhaldid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931.
- (31) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683–1686.
- (32) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.
- (33) For select related examples of Lewis acid-catalyzed reactions, see: (a) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023. (b) Fürstner, A.; Davis, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025. (c) Nakamura, I.; Sato, T.; Yamamoto, I. *J. Am. Chem. Soc.* **2006**, *128*, 4473–4475. (d) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473–4475. (e) Körner, C.; Starkov, P.; Sheppard, T. D. *J. Am. Chem. Soc.* **2010**, *132*, 5968–5969. (f) Malona, J. A.; Cariou, K.; Spencer, W. T., III; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 1891–1908. (g) Blanco Jaimes, M. C.; Weingand, V.; Rominger, F.; Hashmi, A. S. K. *Chem.—Eur. J.* **2013**, *19*, 12504–12511. (h) Marder, T. B.; Chan, D. M.-T.; Fultz, W. C.; Calabrese, J. C.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1885–1887.
- (34) Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022–18023.