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## Catalyst-Free Formal Thioboration to Synthesize Borylated Benzothiophenes and Dihydrothiophenes

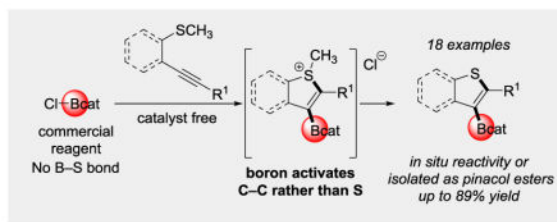
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### Abstract

The first ring-forming thioboration reaction of C–C  $\pi$  bonds is reported. This catalyst-free method proceeds in the presence of a commercially available external electrophilic boron source (B-chlorocatecholborane) in good to high yields. The method is scalable and tolerates a variety of functional groups that are intolerant of other major borylation methods. The resulting borylated benzothiophenes participate in a variety of in situ derivatization reactions, showcasing that these borylated intermediates do not need to be isolated prior to downstream functionalization. This methodology has been extended to the synthesis of borylated dihydrothiophenes. Mechanistic experiments suggest that the operative mechanistic pathway is through boron-induced activation of the alkyne followed by electrophilic cyclization, as opposed to S–B  $\sigma$  bond formation, providing a mechanistically distinct pathway to the thioboration of C–C  $\pi$  bonds.

### Borylative Cyclizations



The first ring-forming thioboration reaction of C–C  $\pi$  bonds is reported. The resulting borylated benzothiophenes participate in a variety of in situ derivatization reactions, showcasing that these borylated intermediates do not need to be isolated prior to downstream functionalization. Mechanistic experiments suggest that the operative mechanistic pathway is through boron-induced activation of the alkyne followed by electrophilic cyclization.

### Keywords

Boron; C–C Activation; Sulfur Heterocycles; Sulfur; Cyclization

Thioboration, the addition of sulfur and boron across C–C  $\pi$  bonds, holds promise as an efficient route to synthesize functionalized thioethers.<sup>[1]</sup> This area of research has focused on

reagents containing B–S  $\sigma$  bonds that are capable of adding in a direct fashion to  $\pi$  systems. In 2015, Bo, Fernández, and Westcott demonstrated the ability of B–S  $\sigma$  bonds from in-house synthesized reagents to add across Michael acceptors through boron activation of the carbonyl oxygen (Figure 1a, top), but without generation of a B–C bond for downstream functionalization.<sup>[2]</sup> In 1993, Miyaura and Suzuki developed a thioboration reaction of B–S  $\sigma$  bonds across alkynes.<sup>[3,4]</sup> This method similarly employed in-house synthesized reagents containing B–S  $\sigma$  bonds, however it used a carbophilic palladium catalyst to activate the C–C  $\pi$  bond. Protodeboration and in situ Suzuki cross-coupling reactions of these thioboration products were demonstrated, establishing the utility of such synthetic intermediates (Figure 1a, bottom).

In contrast, *formal* thioboration, wherein the equivalents of boron and sulfur add across a C–C  $\pi$  bond, is underexplored, despite the potential advantages of employing commercially available boron reagents as opposed to the thioboration reagents requiring synthesis, and the plausibility of avoiding a palladium catalyst as previously required in the direct thioboration of alkynes.<sup>[3,4]</sup> Although little is known about the thiophilicity versus carbophilicity of boron reagents in synthesis, such knowledge would facilitate the development of thioboration reactions by indicating when B–S  $\sigma$  bonds are necessary and when such bonds can be avoided, aiming instead for previously unknown carbophilic activation of the C–C  $\pi$  bond by boron with simultaneous attack by sulfur via an  $Ad_E3$  or  $Ad_E2$  reaction mechanism (Figure 1b).<sup>[5,6]</sup> Herein the first formal thioboration of C–C  $\pi$  bonds is reported, concurrently developing fundamental knowledge about guiding principles of relative carbophilicity and thiophilicity. The experiments were motivated by a broader study on gold-catalyzed and catalyst-free oxyboration and aminoboration (B–O and B–N addition) reactions in our research group.<sup>[7–10]</sup> This catalyst-free thioboration method generates borylated benzothiophene derivatives, a heterocyclic scaffold found in a variety of bioactive molecules and pharmaceuticals, such as raloxifene and sertaconazole (Figure 2).<sup>[11–13]</sup> These borylated benzothiophenes can then be further elaborated using the wide range of established boron functionalization chemistry.<sup>[14–16]</sup> This reaction employs a commercial boron reagent, *B*-chlorocatecholborane (ClBcat), removing the need for B–S  $\sigma$  bond formation in starting materials or in intermediates and making the reaction mechanistically distinct for thioboration.

Primary competing strategies for the synthesis of borylated benzothiophenes include lithiation/electrophilic trapping<sup>[17,18]</sup> and transition metal-catalyzed borylation of the benzothiophene core.<sup>[19,20]</sup> The formal thioboration strategy described herein provides complementary functional group tolerance to these other borylation methods, and also furnishes the benzothiophene core in the same synthetic step. Alternative routes to borylated benzothiophenes, in contrast, require separate steps for borylation and generation of the benzothiophene core.

We hypothesized that 2-alkynylthioanisoles (**1**) would react upon treatment with ClBcat to yield thioboration products **2** (Table 1). After initial identification of successful reactivity, reaction conditions were optimized. Examination of the equiv of ClBcat (1.0–1.4 equiv) identified 1.4 equiv as the optimal value at 1.3 M concentration in substrate **1** as determined by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-triisopropylbenzene as an internal standard.

Transesterification of **2** to the more air and moisture stable pinacolboronic ester (**3**) provided bench-stable organoboron building blocks. The use of ClBpin as an alternative electrophilic boron reagent, which would theoretically provide direct access to the desired pinacolboronic ester **3** from **1**, was not evaluated because of its instability above  $-35\text{ }^{\circ}\text{C}$  and its difficulty of synthesis.<sup>[21]</sup>

The functional group compatibility of the thioboration reaction was next examined (Table 1). Esters, aryl and alkyl halides, amines and cyano groups, an *O*-silyl protecting group, and several heterocycles tolerated the thioboration reaction conditions in good yields. Functional groups that were incompatible with the thioboration reaction included pyridinyl and alcohol (in both cases, only starting material was observed by  $^1\text{H}$  NMR spectroscopy, consistent with reaction inhibition by the heteroatom lone pairs). Consistent with the need to favor carbophilicity and avoid competing heteroatomphilicity of boron in the formal thioboration reaction, amide-containing compound **3p** required 24 h rather than the standard 4 h to reach complete conversion (70% isolated yield at 24 h vs 25% isolated yield at 4 h). The slower reactivity was attributed to competitive coordination of the amide to boron. Notably, functional groups that cannot be tolerated by existing methods of borylation of benzothiophenes (i.e., lithiation/electrophilic trapping or Pd-catalyzed Miyaura borylation)<sup>[17–20]</sup> were tolerated by these thioboration reaction conditions (e.g., substrates **3f–3h**, **3j**, **3m**, **3n**). Thus, this thioboration reaction provided access to borylated benzothiophenes that had limited accessibility through traditional methods. A crystal structure confirmed the regioselectivity of the thioboration method (Figure 3).

## Scale up

In addition to its good functional group tolerance, the thioboration reaction was scalable. Alkynylthioanisole **1d** underwent smooth thioboration at the 2.0 g scale to generate **3d** in 69% yield (Table 1).

## In situ functionalizations

We hypothesized that the catalyst-free conditions of the formal thioboration reaction would provide minimal interference to downstream functionalization conditions due to the absence of residual metal salts. Indeed, synthetic intermediate **2a** participated in a wide range of C–B  $\sigma$ -bond functionalization reactions without the need for the additional synthetic manipulations of boron ligand exchange from catechol to pinacol or the requirement to isolate any boron-containing compound (Scheme 1).

Oxidative workup of the C–B bond furnished 1-benzothiophene-3(2H)-one derivative **4**, a heterocyclic motif that has been examined as a donor-acceptor chromophore,<sup>[22]</sup> in 73% yield from **1a**. Rhodium-catalyzed conjugate addition to methyl vinyl ketone furnished product **5** in 71% yield over two steps.<sup>[23,24]</sup> Subjecting intermediate **2a** to two different Suzuki conditions<sup>[15,25]</sup> produced products **6** and **7** in 65% and 56% yield over two steps, respectively. Trifluoromethylation using a modification of a procedure developed by Sanford<sup>[26]</sup> furnished **8** in 37% yield over two steps. Albeit in low yield, this reaction provided access to 3-trifluoromethylated benzothiophenes, which have limited alternative

synthetic routes.<sup>[27,28]</sup> These in situ reactions illustrate strategies for efficiently generating the heterocyclic core and functionalizing at the 3-position in one pot.

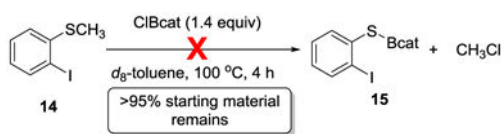
### Mechanistic studies: boron as a thiophilic or carbophilic Lewis acid

Three main mechanistic pathways were considered for the thioboration reaction (Scheme 2). The first route was through thiophilic activation of **1** via coordination of ClBcat to the sulfur rather than the C–C  $\pi$  bond, forming activated intermediate **9** (Scheme 2, top). Demethylation furnishes thioboric ester **10**; subsequent B–S bond addition across the alkyne yields product **2**, which is a known pathway for several other B–X  $\sigma$  bond addition reactions.<sup>[29–32]</sup> In order to examine the thiophilicity of ClBcat toward **1a** at ambient temperature, the initial reaction mixture was evaluated by NMR spectroscopy in *d*<sub>8</sub>-toluene. <sup>1</sup>H and <sup>11</sup>B NMR spectra obtained at *t* = 0 at ambient temperature showed no evidence of sulfur coordination to boron as judged by persistence resonances corresponding to starting material **1a** and ClBcat and the absence of other resonances. This result provided an early indication of the lack of thiophilicity of this reagent, but did not rule out sulfur–boron coordination or activation leading to possible reaction intermediates, which was next investigated.

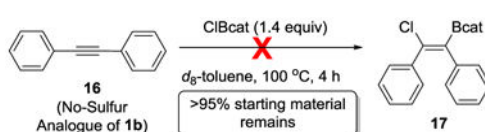
If demethylation were occurring first, through activated sulfonium intermediate **9** and B–S bond containing **10**, then a no-alkyne control would demethylate at the same rate (or faster, but not slower) than the thioboration reaction proceeds (4 h at 100 °C). Treatment of *o*-iodothioanisole **14**, however, under these conditions resulted in no reaction: >95% of the starting material remained after 4 h as determined by <sup>1</sup>H NMR spectroscopy using mesitylene as an internal standard, with no demethylated product **15** observed (eq 1). Moreover, by <sup>11</sup>B NMR spectroscopy, only the ClBcat peak at  $\delta$  = 28.6 ppm was detected, suggesting that the sulfur was not significantly coordinating to ClBcat, even after extended reaction times. This lack of chemical shift change in the <sup>11</sup>B NMR spectrum also ruled out formation of detectable amounts of sulfur-based borenium species.<sup>[33,34]</sup> This mechanistic control reaction demonstrated that demethylation of **1** is too slow relative to the timescale of the overall thioboration reaction (4 h) to be a step in the operative pathway and therefore ruled out the thiophilic activation pathway.

Next, two pathways were considered in which the ClBcat acts as a carbophilic Lewis acid by activating the C–C  $\pi$  system.<sup>[34]</sup> The first is through a haloboration/cyclization pathway proceeding through a chloroboration reaction analogous to that reported for alkynes,<sup>[30]</sup> generating intermediate **11** (Scheme 2, middle). This chloroboration product then undergoes cyclization to form sulfonium **12**. This mechanism was probed by using a substrate without sulfur (eq 2). Chloroboration of alkynes with other reagents containing B–Cl bonds is thermodynamically downhill;<sup>[30, 35]</sup> we therefore hypothesize that the chloroborated products in this system would be observable. Treatment of diphenylacetylene **16**, which is the no-sulfur analogue of substrate **1b**, under the otherwise standard thioboration conditions resulted in no reaction by <sup>1</sup>H (>95% **16** remaining using mesitylene as an internal standard) or <sup>11</sup>B NMR spectroscopy (only signal detected at  $\delta$  = 28.6 ppm, corresponding to unreacted ClBcat) in 4 h. This demonstrated that chloroboration product **17** did not form, and thus is an unlikely operative pathway in this thioboration reaction.

On the basis of these mechanistic experiments, a role for boron as a carbophilic Lewis acid in this cyclization is proposed, plausibly through an  $Ad_E2/Ad_E3$  mechanism<sup>[5,6]</sup> (Scheme 2, bottom). Subsequent attack by the sulfur via transition state **13** generates sulfonium intermediate **12**. Demethylation furnishes borylated benzothiophene **2**. Notably, this proposed pathway has no productive B–S coordination.



(1)

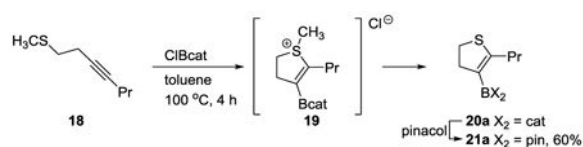


(2)

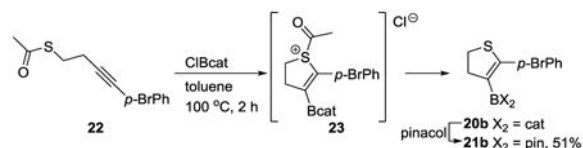
## Extension of the mechanistic concept to other substrate classes

Having established the feasibility of this thioboration reaction, we hypothesized that this method could be extended towards the synthesis of dihydrothiophenes, a class of compounds that are useful toward anti-HIV therapeutics<sup>[36]</sup> and in agricultural products.<sup>[37]</sup> Subjecting alkynyl thioether **18** to the standard thioboration reaction conditions furnished the desired cyclic thioether **20a**, which was transesterified to the bench-stable pinacolboronic ester **21a** in 60% overall yield (eq 3). This additional substrate class established that the thioboration reaction did not require the entropic assistance of a rigid backbone or the enthalpic assistance of a gain of aromaticity to proceed.

The formal thioboration reaction also proceeded from thioacetate **22**, expanding the reactivity concept from dealkylation to deacylation of sulfur. Subjecting thioacetate **22** to ClBcat at 100 °C for 2 h furnished the desired cyclic thioether **20b**, plausibly via the analogous sulfonium intermediate **23** (eq 4). Compound **20b** was transesterified to the bench-stable pinacolboronic ester **21b** in 51% overall yield.



(3)



(4)

In conclusion, the first formal thioboration of C–C  $\pi$  bonds is reported. This scalable method efficiently generates both the benzothiophene core and a C–B functional group handle in one synthetic step. These borylated products are primed for downstream in situ functionalization reactions or for isolation as bench-stable building blocks. The mechanistic concept of this thioboration reaction was extended to the synthesis of borylated dihydrothiophenes via both demethylation and deacylation pathways. Mechanistic studies documented an unusual pathway for thioboration reactions in which an S–B  $\sigma$  bond is not formed. This thioboration reaction demonstrates a strategy for harnessing the carbophilic reactivity of boron without concurrent thiophilicity. We envision that this knowledge gained about the thiophilic versus carbophilic reactivity available to boron reagents can be used as a guiding principle for the design of catalyst-free direct or formal boron–element addition reactions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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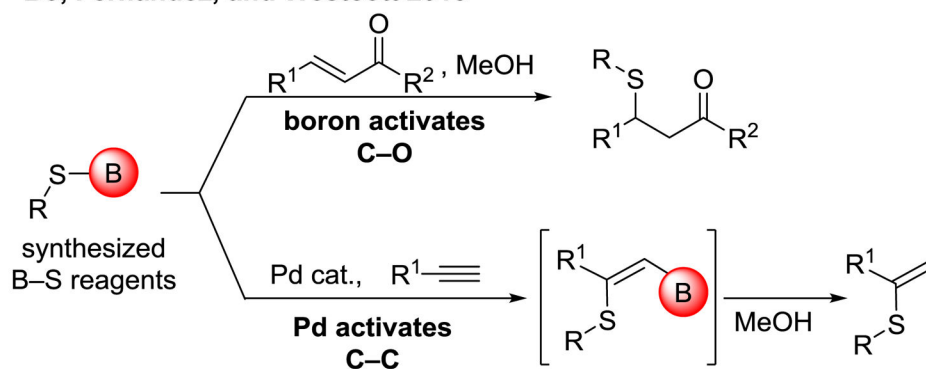
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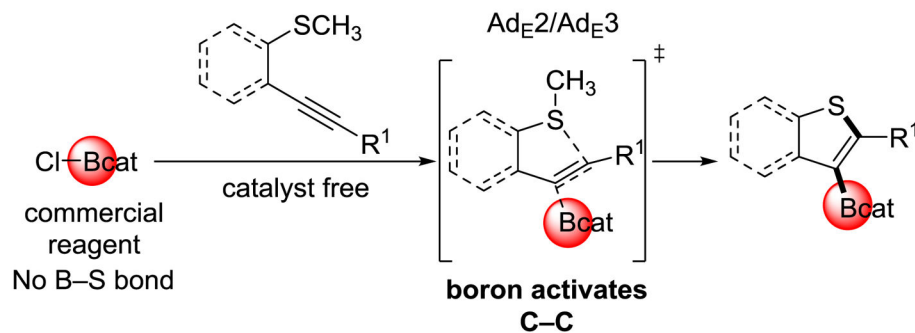
a) Previous reports of direct thioboration reactions of C–C bonds

Bo, Fernandez, and Westcott 2015



Miyaura and Suzuki 1993

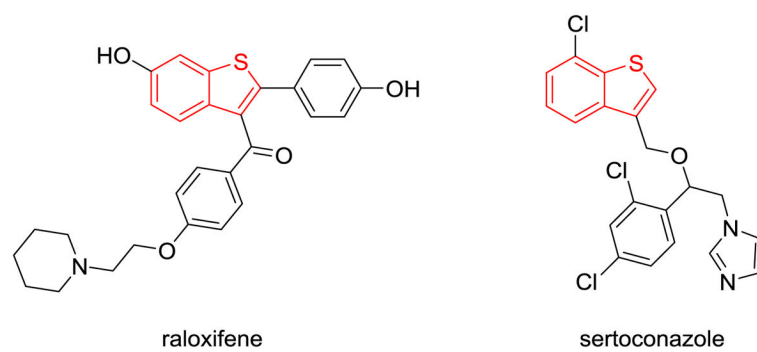
b) This Work: formal thioboration reaction of C–C bonds via carbophilic activation by ClBcat



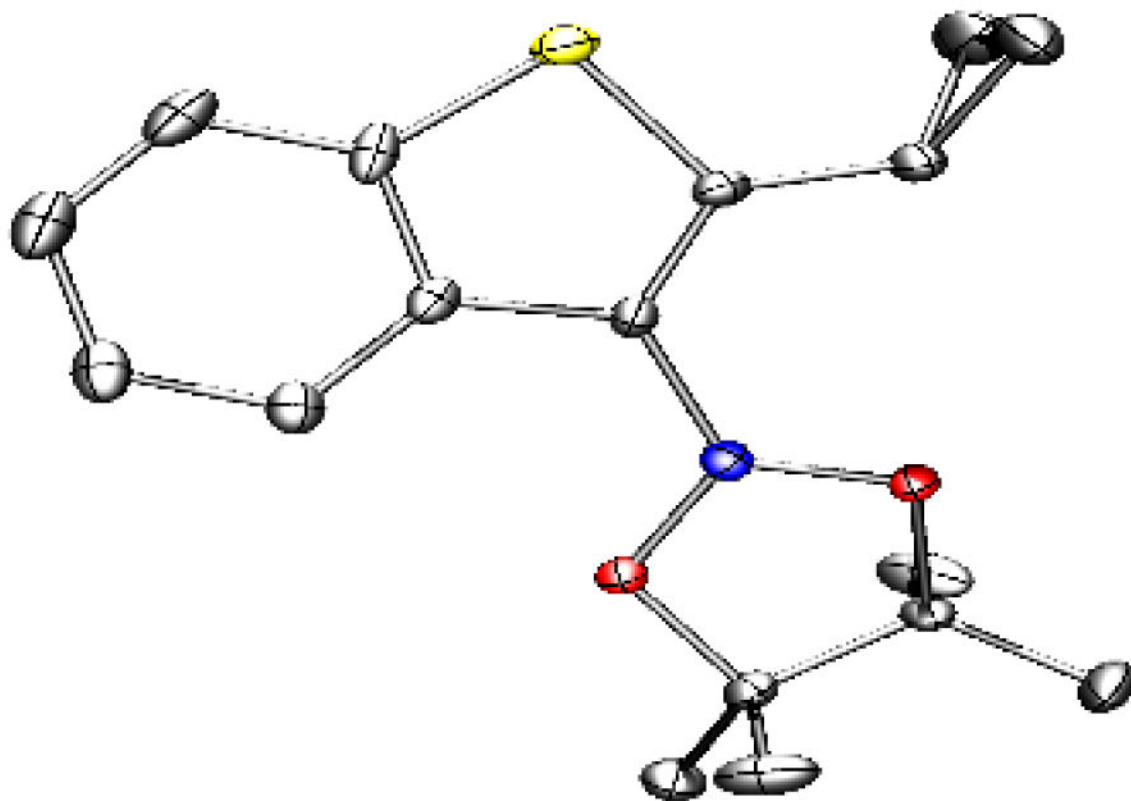
**Figure 1.**

(a) Previously reported thioboration methods. (b) This work demonstrating formal thioboration. ClBcat = *B*-chlorocatecholborane.

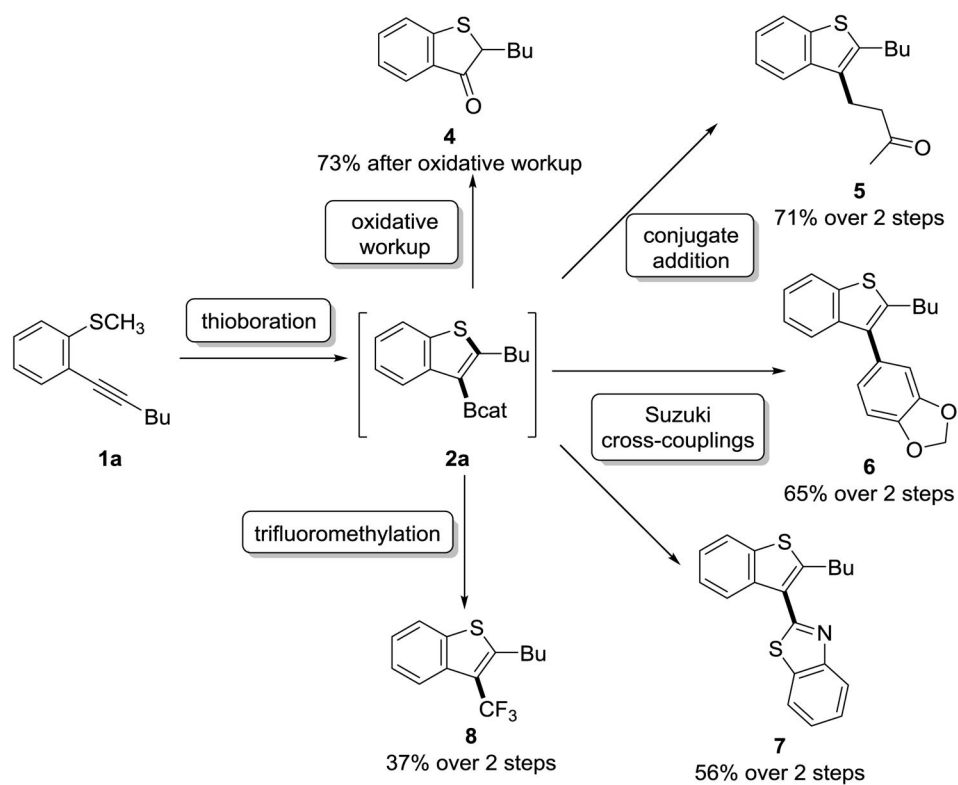




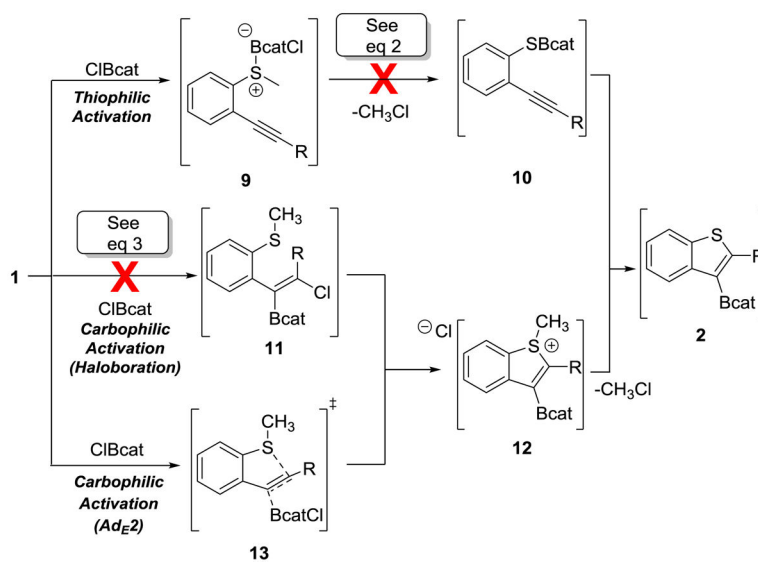
**Figure 2.** Two bioactive molecules that contain a benzothiophene core (in red). Raloxifene is used in the treatment of osteoporosis, and sertaconazole is used to treat skin infection.



**Figure 3.**  
X-ray crystallographic structure of 3d, with the thermal ellipsoids shown at 50% probability (B, blue; C, gray; S, yellow; O, red).



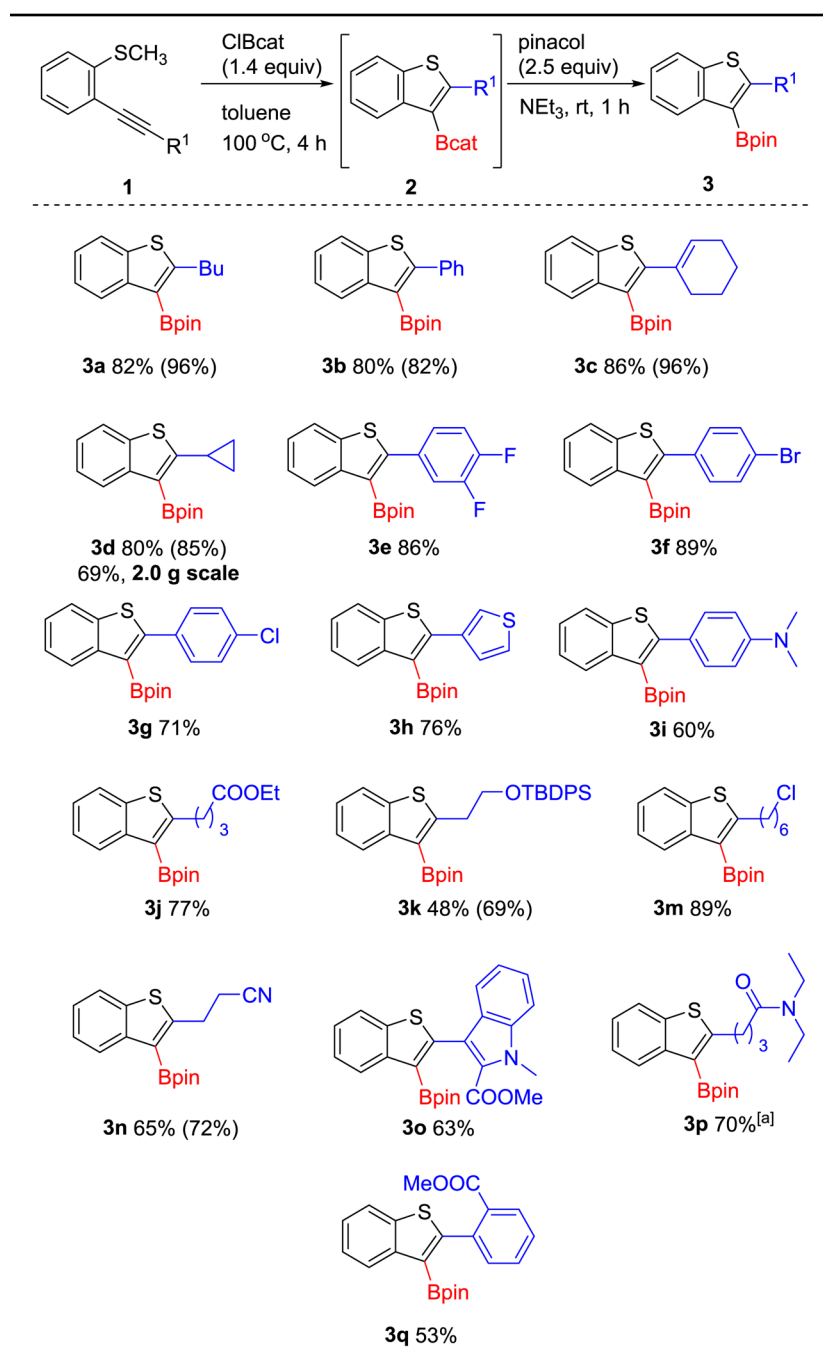
**Scheme 1.**  
In Situ Functionalization without Isolation of Organoboron Intermediates: Direct Access to Downstream Products.

**Scheme 2.**

Three Possible Mechanistic Pathways: B-S  $\sigma$  Bond Formation (top), Haloboration (middle), and Alkyne Activation by ClBcat (bottom).

Table 1

Synthesis of Borylated Benzothiophenes via the Formal Thioboration Reaction.



Yield is that of the isolated product.

<sup>1</sup>H NMR yields were determined using mesitylene as an internal standard in *o*-toluene, and are listed in parantheses. [a] required 24 h.