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Boron−Heteroatom Addition Reactions via Borylative Heterocyclization: Oxyboration, Aminoboration, and Thioboration

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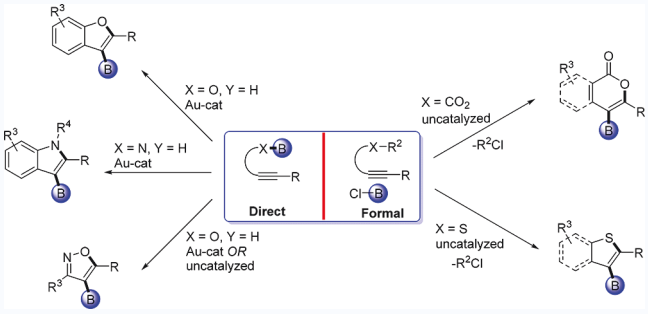
CONSPECTUS: Organoboron compounds and heterocycles are powerful building blocks and precursors for organic synthesis, including for drug discovery and agrochemical and material synthesis. The common strategy for the synthesis of borylated heterocycles involves two separate synthetic steps: first, synthesis of the heterocyclic core, and second, borylation of the core through established methods such as transition-metal-catalyzed C−H or C−X activation/borylation or lithiation/borylation.



In this Account, we describe our laboratory's development of borylative heterocyclization reactions that access the heterocyclic core and install boron in one synthetic step. These methods provide complementary bond disconnections, regiochemistry, and functional-group compatibility to current methods. We describe our methods with two categories: a **direct borylation** method that refers to addition reactions starting from a preformed B−element σ bond, which is essential in the mechanistic route to product formation, and a **formal borylation** method that refers to addition reactions that do not require formation of a B−element bond but instead proceed through carbon−carbon π-bond activation by an electrophilic boron source followed by dealkylation or deacylation. Through electrophilic activation of the alkyne rather than activation of the B−element bond, formal borylation provides a complementary strategy toward neutral organoboron reagents. We first studied direct oxyboration toward the formation of borylated benzofurans, where a preformed boron−oxygen σ bond is added across an alkyne activated by a carbophilic gold catalyst. We describe detailed mechanistic and kinetic studies of this class of reactions. Application of the knowledge gained from these studies aided in the future development of additional direct borylation reactions involving boron−nitrogen and boron−oxygen σ bonds to form borylared indoles and isoxazoles, respectively.

Formal addition of boron/oxygen equivalents to effect oxyboration to form borylated lactones from *o*-alkynyl esters is then described. This class of reactions takes advantage of bifunctional ClBcat as a carbophilic carbon−carbon π-bond activator and eventual dealkylating agent. We describe our motivation in developing this new class of catalyst-free borylation reactions and subsequently applying the formal borylation strategy to the thioboration of *o*-alkynylthioanisole substrates to form borylated benzothiophenes. We then proceed to describe our investigations into the details of the mechanism of the formal thioboration reaction. These collaborative mechanistic studies included experimental and computational findings that elucidated the rate-determining step and intermediates of the reaction. These studies further compared different boron sources as electrophiles, including those used in other known reactions, providing fundamental knowledge about the capabilities of commercially available boron reagents toward borylative heterocyclization. Our findings provide guiding principles for reaction design and information leading toward the design of a diverse set of boron−heteroatom addition reactions and their formal equivalents that proceed through borylative heterocyclization.

1. INTRODUCTION

Organoboron reagents are building blocks of choice for organic synthesis and drug discovery.[1] Heterocycles containing oxygen, nitrogen, and sulfur are found in many diverse classes of natural products,[2] and ethers and amines were present in nearly 25% and 85%, respectively, of the top-grossing pharmaceuticals in the United States in 2012. However, a number of desirable heterocyclic building blocks are unavailable in borylated form, and existing routes to others are incompatible with key functional groups or lack access to complementary regioisomers.[3−7] Thus, there is a need to develop efficient approaches toward borylated versions of such heteroatom-containing building blocks. Motivated by this need, our laboratory initiated a research program to develop borylative heterocyclization methods with and without catalysts through direct and formal addition reactions of B−O, B−N, and B−S bonds or their net equivalents to carbon−carbon π bonds.

In this Account, we summarize our recent developments on the fundamentally new reactivity of B−O, B−N, and B−S σ bonds and/or their formal equivalents as addition partners to C−C π bonds. These borylation methods enable the preparation of synthetically useful building blocks[2] via new bond disconnections with complementary regiochemistry and with

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tolerance of functional groups that are incompatible with existing methods (e.g., aryl halides, competing heterocycles, and/or electrophilic groups).[3−7]

We use the term **direct** when referring to addition reactions starting from a preformed B−element σ bond that is part of the productive reaction mechanism and **formal** when referring to addition reactions without formation of the B−element bond at any point in the productive reaction (Figure 1).

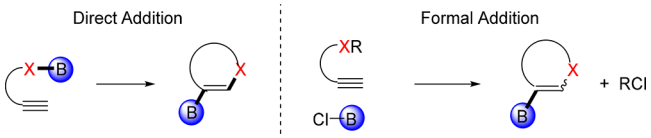

Figure 1. (left) Direct addition: from a preformed B−heteroatom σ bond. (right) Formal addition: from separate reagents.

The typical strategy in the field is to activate B−X bonds through oxidative addition or σ-bond metathesis to prime them for addition to C−C π bonds (Figure 2). In contrast, the B−X

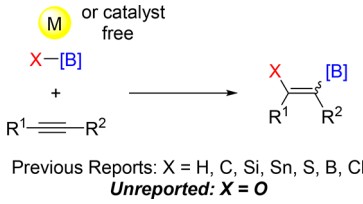

Figure 2. Previous work on developing addition of B−X bonds to alkynes through activation of the B−X bond by a metal catalyst (direct addition).

addition reactions described here activate the C−C π bonds. Additionally, the common synthetic approach to borylated building blocks in the field is to perform a two-step sequence to construct an O-, N-, or S-heterocyclic core and then to borylate the resulting heterocycle in the next step. In our approach, heterocyclization and borylation occur in the same synthetic step, enabling complementary synthetic strategies. There are multiple reports on the direct addition of B−element bonds across C−C multiple bonds for element = H,[8,9] C,[10] Si,[9,11] Sn,[9,12] S,[13] B,[9,14] Cl,[15] Br,[16] and I[16] that proceed through oxidative addition into the B−element σ bond using transition metal catalysts such as Ni(0), Pd(0), or Pt(0). However, because of the extremely high strength of the B−O bond,[17] there was no report on the corresponding activation of B−O bonds and direct addition to C−C multiple bonds until our discovery of the first direct oxyboration reaction in 2014.[18,19]

Existing formal borylative heterocyclization reports used $B(C_6F_5)_3$ in the cyclization of alkynyl amides,[20] esters,[21,22] and anilines[23] to make zwitterionic products (Figure 3). These products, though obtained in one synthetic step, lack the neutral heterocycle and the diverse potential to be functionalized at the $B(C_6F_5)_3$ group because cross-coupling conditions and other derivatization reactions for this group are not yet widely established.[24] Here we discuss the development of commercially available ClBcat as an alternative reagent for formal boron−heteroatom addition reactions through borylative heterocyclization. Reactions with ClBcat proceed through spontaneous cyclization/dealkylation sequences. The resulting neutral borylated products are primed to take advantage of the rich cross-coupling and derivatization chemistry available to organoboron compounds. We also describe the fundamental

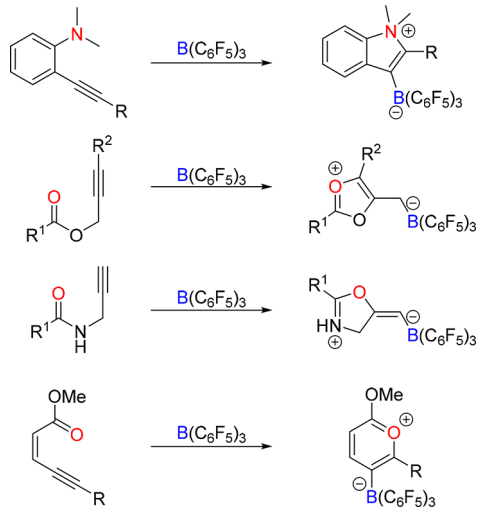

Figure 3. Previous work on borylative heterocyclization using $B(C_6F_5)_3$ (formal addition).

mechanistic studies of both direct and formal addition reactions and provide further insight into the development of future reactions in these areas.

2. DIRECT BORON−HETEROATOM ADDITION: BORYLATIVE CYCLIZATION FROM B−O AND B−N σ BONDS

Initial thought process: Prior to our group's development of boron−heteroatom addition reactions, we had been developing dual catalytic systems with gold and palladium.[25] These studies addressed a shortfall in gold catalysis, namely, that organogold intermediates[26,27] had limited subsequent reactivity: turnover in these systems was almost always achieved by quenching with proton,[28] carbocation,[29] silyl,[30] or sulfonyl.[31] We considered whether these intermediates could instead be trapped by palladium under dual catalytic gold/palladium conditions, leading to increased carbon−carbon bond-forming opportunities. While this concept was successful, it remained limited by the oxidative addition that produced the organopalladium partner[32,33] (a limitation overcome later by Nevado with aryl iodides[34]). We therefore wondered whether we might be able to trap these intermediates with stoichiometric boron rather than catalytic palladium, as boron would provide cheap and stable products that could be stored indefinitely. Through a future synthetic step, the resulting organoboron products could be cross-coupled to diverse oxidative addition partners using known chemistry. This initial thought process guided our first discovery of gold-catalyzed direct boron−element addition reactions (Figure 4).

2.1. Gold-Catalyzed Direct Oxyboration

We initially focused on the addition of the B−O σ bond in **2**, derived from phenol **1**. Initial studies identified IPrAuTFA as the optimal catalyst. We hypothesized that the carbophilic Lewis acid IPrAu cation might activate the C−C π bond toward attack by the B−O σ bond (intermediate **5** or **6**). Cyclization would afford organogold **7** and boric ester **8**, which then would undergo a previously unreported organogold-to-boron transmetalation to generate the desired borylated benzofuran **9** (Scheme 1).

The oxyboration reaction successfully transformed alkynyl phenols **1** into borylated benzofurans **9** through a one-pot procedure (Table 1). The reaction was tolerant of a variety of

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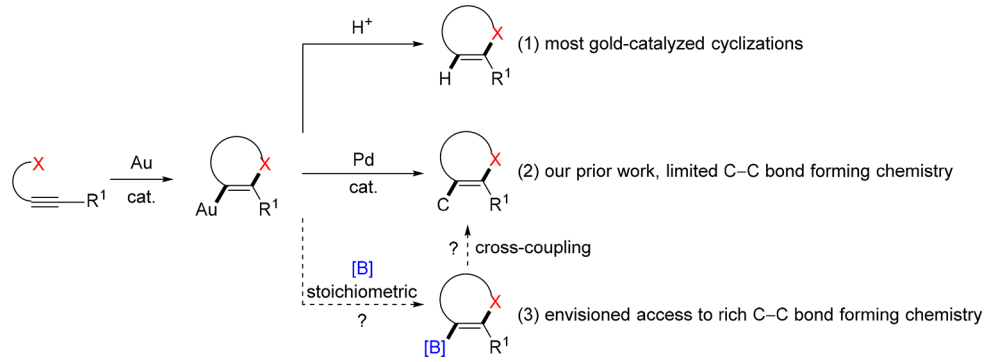


Figure 4. Initial thought process for the development of borylative heterocyclizations.

Scheme 1. Plausible Mechanism for the Direct Oxyboration of Alkynyl Phenols

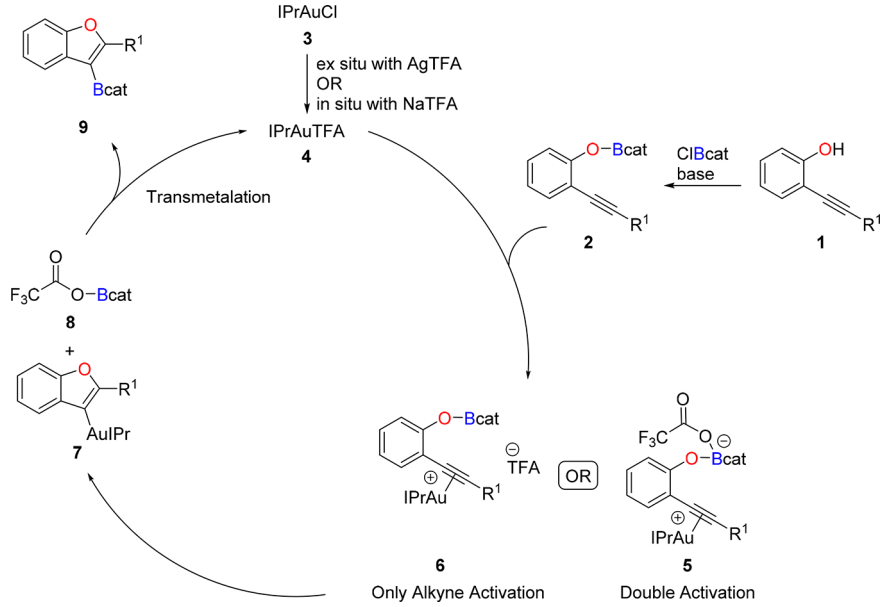
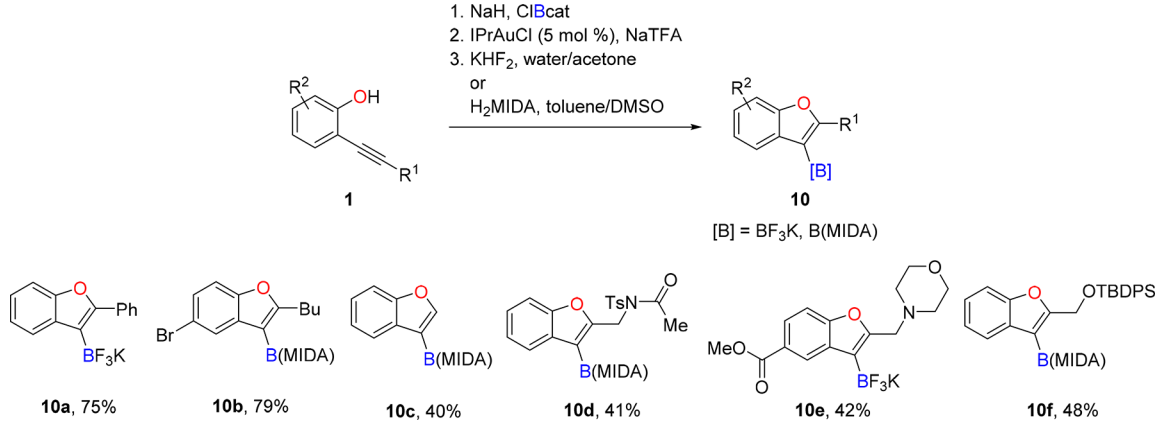
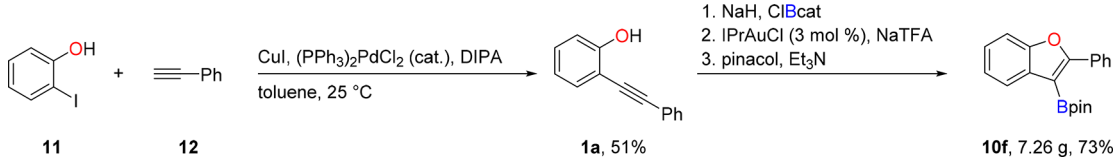


Table 1. Representative Products of the Gold-Catalyzed Direct Oxyboration of Alkynyl Phenols



Scheme 2. Optimized Procedure



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functional groups, some of which are incompatible with current competing borylation methods.[3,5,7] The catechol boronic esters are labile toward hydrolysis and not stable toward silica column chromatography. They were converted to the organotrifluoroborate, *N*-methyliminodiacetic acid (MIDA) boronate, or pinacolboronate esters as bench-stable derivatives, which were readily available for downstream functionalization.

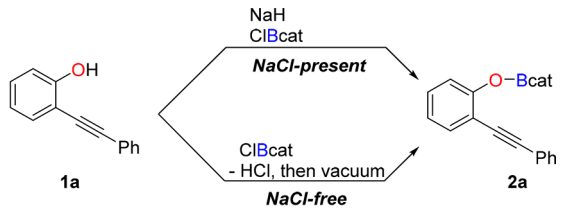
After the publication of our first direct oxyboration reaction, we refined the method to shorten the substrate synthesis from three steps to one step. Further optimization of the isolation conditions achieved a robust 8 g synthesis of **10f** (7.26 g, 73%), as detailed in an *Organic Syntheses* publication (Scheme 2).[35]

2.2. Mechanistic Studies of Gold-Catalyzed Direct Oxyboration

In order to expand the method to additional substrate classes and catalysts, it was helpful to gain a deeper understanding of the reaction mechanism.[36] We decided to first investigate the possibility of TFA coordination to boron in an activation step (shown in structure **5**) by comparing the reactivity with that of a counterion that coordinates more weakly than TFA^- to both gold and boron (e.g., BF_4^-).[37] The results indicated that the TFA counterion was not essential to product formation and suggested that the reaction could be catalyzed by only the $IPrAu^+$ species (Scheme 1, intermediate **6**).

We observed that the reaction rate and conversion depended on the method used to synthesize boric ester **2** (Scheme 3).

Scheme 3. Two Routes to the Synthesis of Boric Ester 2



This observation led to the discovery that residual chloride from the NaCl byproduct in step 1 was quenching the gold catalyst, plausibly through shifting the equilibrium in eq 1 to the right, resulting in a decrease in the concentration of active IPrAuTFA catalyst; this effect occurred despite the low solubility of NaCl in toluene.

$$\underset{\text{active}}{\text{IPrAuTFA}} + \underset{\text{byproduct from 1}}{\text{NaCl}} \rightleftarrows \underset{\text{inactive}}{\text{IPrAuCl}} + \text{NaTFA} \quad (1)$$

According to our proposed mechanism, the last step of the oxyboration reaction involved an organogold-to-boron transmetalation. The microscopic reverse reaction had been studied prior to our report,[38] but organogold-to-boron transmetalation had not been reported, plausibly because of sensitive electronic factors that dictated the position of this equilibrium and accessibility of transition states from either direction. We decided to investigate the electronic factors that could affect the thermodynamics and kinetics of the proposed transmetalation (Table 2). Arylgold complex **13** was selected as a model for intermediate **7**. Electron-rich boron compounds were shown to be poor acceptors for the anisyl group from organogold complex **13**, from which no detectable quantities of product **16** were observed. As the electrophilicity of the boron reagent increased, a detectible equilibrium was established, and this equilibrium shifted toward increasing ratios of the corresponding ion pairs **15** and the final neutral transmetalation product **16**. Thus, this transmetalation step is plausibly accessible within the oxyboration catalytic cycle.

2.3. Direct Aminoboration

We next examined an aminoboration strategy.[39] The B–N σ bond is weaker than the B–O σ bond (105 kcal/mol for B–N versus 130 kcal/mol for B–O) and thus could be easier to manipulate.[17] Our target structures were borylated indoles, which are privileged scaffolds for biologically active compounds[40,41] and offered an opportunity to study the compatibility of the working mechanistic hypothesis of gold-catalyzed π-bond activation with B–N bonds. The optimized aminoboration reaction tolerated a variety of functional groups that are incompatible with one or more of the traditional strategies for borylated heterocycle synthesis (Table 3).[3,5,7] As one example, because of the challenges in functional group compatibility with major synthetic routes, borylated bromoindoles were synthesized previously with mercury acetate.[42] However, our aminoboration method provided a mercury-free route to borylated bromoindole **19f**, .

The versatility imparted through the aryl halide tolerance was showcased through the production of 1.02 g of **19f**, which then underwent two sequential chemoselective Suzuki cross-coupling reactions to generate biindole **22** (Scheme 4).[42]

This was an early report of an aminoboration reaction that adds B–N σ bonds across C–C π bonds. As such, it expands

Table 2. Study of Electronic Effects on Organogold-to-Boron Transmetalation Reactions

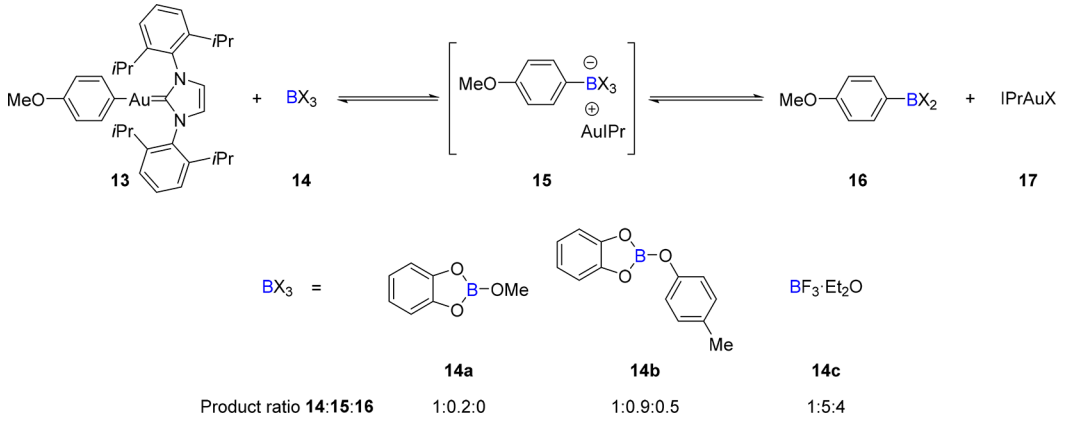


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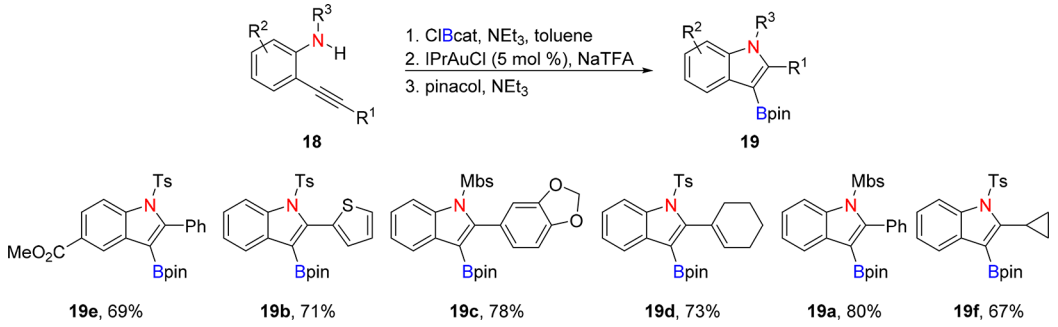
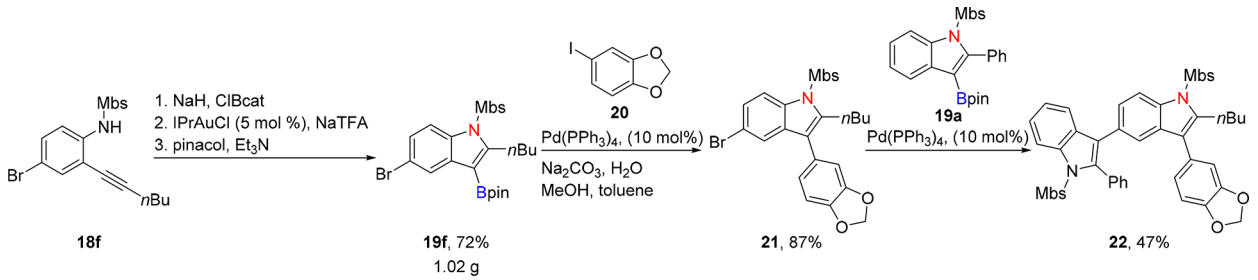
Table 3. Representative Borylated Indole Products of Gold-Catalyzed Direct Aminoboration



Scheme 4. Gram-Scale Aminoboration and Downstream Functionalization



boron−heteroatom addition reactions[43] and provides a new tool for the preparation of borylated indole building blocks.

2.4. Direct Oxyboration with and without a Catalyst

At this point in our studies, we were surprised to identify a substrate class for which oxyboration proceeded without a catalyst, albeit at higher temperature and longer time than with a catalyst. We were initially interested in borylated isoxazoles because of the biological relevance of isoxazoles.[44] We rationalized that we could use a similar carbophilic Lewis acid cyclization/borylation method as in our first report of direct oxyboration[18] to activate the C−C π bonds in alkynyl oximes (depicted in **23** in Figure 5).[45]

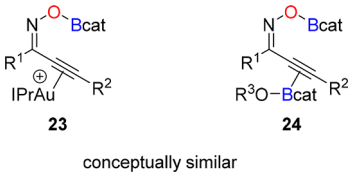
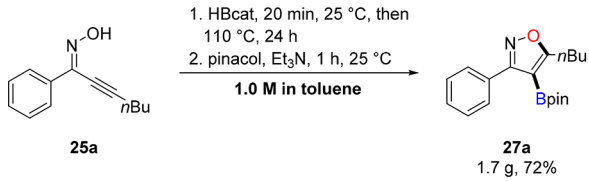


Figure 5. Proposed structures leading to activation in the catalyzed and uncatalyzed oxyboration reactions, showing their conceptual similarity.

This transformation was the first example of an uncatalyzed direct oxyboration reaction, although the reason for this difference remains unclear. It may be that the nucleophilic lone pair of starting oxime **25** coordinates to and activates the boron atom in a neighboring boric ester molecule. Alternatively, this substrate class has Michael acceptor/dipolar character that could lower the barrier for cyclization. Table 4 shows a comparison of reaction times and ^{1}H NMR spectroscopy yields for the catalyzed and uncatalyzed reactions. Both the uncatalyzed and catalyzed oxyboration reactions tolerated a variety of functional groups that would be incompatible with one or more of the major alternative borylation methods (Table 4).

A bimolecular rate-determining step for the uncatalyzed oxyboration reaction was supported by a strong concentration dependence of the rate of the reaction: while **25a** underwent full conversion to the desired catechol boronic ester **26a** in 111 h at 0.2 M, this reaction required only 24 h at 1.0 M to afford 1.7 g of the isolated pinacol boronic ester **27a** (eq 2).



(2)

This concentration dependence was consistent with bimolecular activation of the alkyne by another molecule of starting material or product and provided a hint about plausible mechanisms for the uncatalyzed reaction (Figure 5, compound **24**).

The synthetic utility of the oxyboration method was showcased in the synthesis of valdecoxib, a nonsteroidal anti-inflammatory drug (NSAID), and its ester analogue (Scheme 5).

These data introduced the first glimpse into the possibility of uncatalyzed oxyboration reactions,. A few hypotheses had been proposed to explain this new uncatalyzed reactivity as mentioned earlier, the most consequential of which, with respect to our thinking and subsequent reaction design, was activation of the C−C π bond by boron rather than gold as shown in structure **24**. The testing of this hypothesis merged with the development of formal boron−element addition reactions, which are described next.

3. FORMAL BORON/HETEROATOM ADDITION: BORYLATIVE HETEROCYCLIZATION FROM EQUIVALENTS OF SEPARATE B AND X REACTANTS

After realizing the direct borylation/cyclization methods that resulted in boron−element addition across C−C π systems,[18,19,35,36,39,45] we attempted to extend our strategy toward other substrate classes using a similar borylation route. To our surprise, it proved challenging to extend this method to thiophenols and benzoic acids. Our efforts to form B−S and B−O

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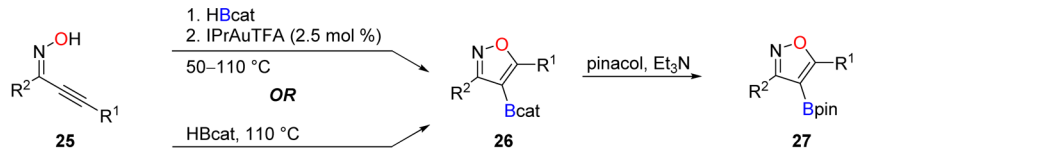
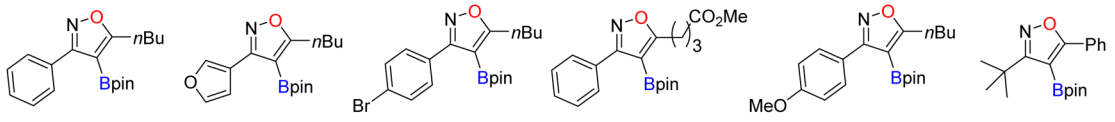
Table 4. Representative Products from Direct Oxyboration of Alkynyl Oximes and Comparison of the Gold-Catalyzed and Uncatalyzed Approaches

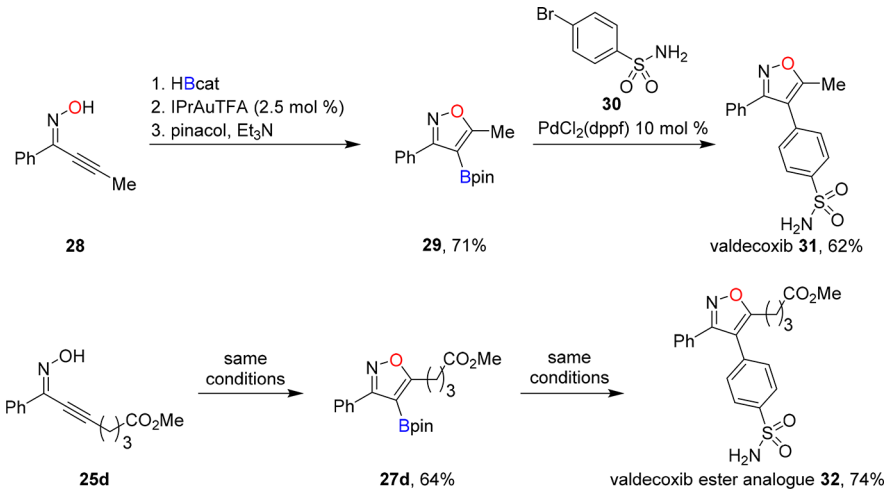




	27a	27b	27c	27d	27e	27f
Au-catalyzed	6 h, (90%), 75%	24 h, (85%), 71%	6 h, (93%), 65%	8 h, (94%), 64%	24 h, (92%), 74%	4 h, (95%), 94%
Uncatalyzed	111 h, (89%)	18 days, (68%)	20 h, (91%)	52 h, (83%)	65 h, (90%)	7 days, (24%)

Time, (NMR yield), isolated yield

Scheme 5. Syntheses of Valdecoxib and Its Ester Analogue



σ bonds from these precursors resulted in intractable mixtures. In addition, we encountered competing premature cyclization of the substrates prior to the installation of boron, which made these functional groups less suitable for direct boron–heteroatom addition methods. Therefore, inspired by established electrophilic heteroatom cyclization/dealkylation reactions with I_2, ICl, Br_2, and PhSeCl,[46−50] we decided to explore a formal borylation approach that would be complementary to our direct method (Figure 6).

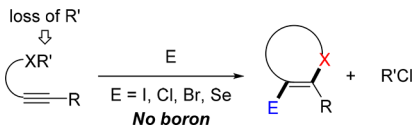


Figure 6. Previous work on electrophilic cyclization reactions.

We hypothesized that the commercially available Lewis acidic ClBcat could combine the advantages of a dealkylation reagent with a reactive handle for future cross-coupling reactions. In this context, ClBcat would activate the C−C π system to afford the cyclized borylated product, with the chloride acting as a subsequent dealkylating agent. This reaction sequence would be in contrast to the previously reported cyclizations with $B(C_6F_5)_3$, described in Figure 3, in that the Bcat products would offer a route to established functionalization reactions. Despite the well-known reactivity of catecholborane derivatives in downstream functionalization to form new C−C bonds (e.g., Suzuki cross-coupling reactions),[51] ClBcat had not been reported as a promoter of formal borylative heterocyclization reactions.

Our investigations led to the discovery of the formal oxyboration and formal thioboration methods described below.[52,53] In these reactions, the alkylated starting materials, benzoates (instead of carboxylic acids) and thioanisoles (instead of thiophenols), were transformed into the corresponding borylated heterocyclic products as catecholboronic ester derivatives, building blocks primed to take advantage of downstream functionalization reactions.

3.1. Catalyst-Free Formal Oxyboration Reactions of Alkynes

The reagent ClBcat promoted an electrophilic cyclization reaction that yielded borylated product **36** (Scheme 6).[52] Our mechanistic experiments illustrated that the catalyst-free oxyboration reaction with ClBcat likely proceeds in three main steps: (1) boron-induced activation of the π system through a type of interaction shown in **34** promotes nucleophilic attack; (2) anti addition of oxygen across the alkyne affords cyclized zwitterionic intermediate **35**; (3) S_N2 attack on the methyl (or other alkyl) group by chloride (either dissociated, "free" from the boronic ester, or directly from a borate complex) yields the borylative cyclization product **36** and chloromethane.

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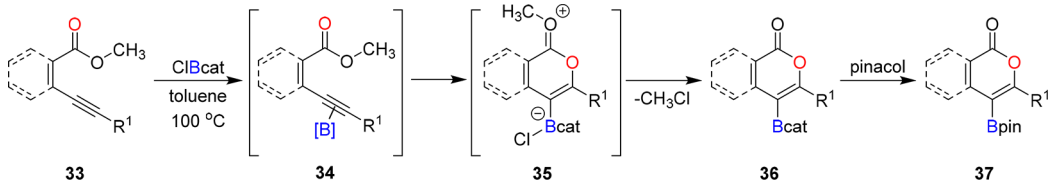
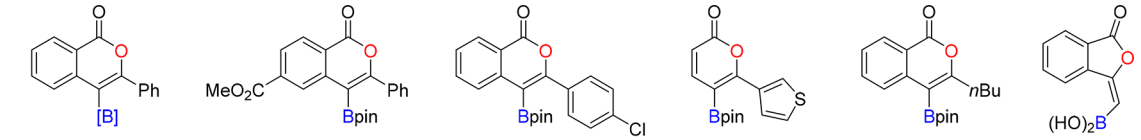
Scheme 6. Overall Formal Oxyboration Reaction and Proposed Mechanistic Steps



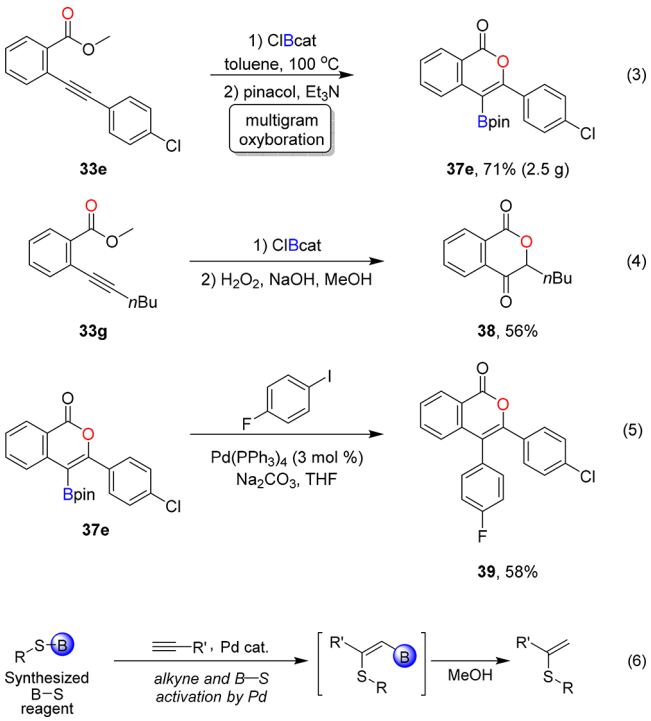
Scheme 7. Representative Products from Catalyst-Free Formal Oxyboration



Transformation of **36** to pinacolboronate **37**, boronic acid **37b**, or organotrifluoroborate salt **37c** produced bench-stable borylated heterocycles that were primed for future reactivity (Scheme 7). Isocoumarins and 2-pyrones had limited reported borylated analogues prior to this method.[54]

Formal oxyboration provided predictable and mechanistically controlled regiochemistry and tolerance of functional groups (e.g., esters (**37d**), halides (**37e**), and thiophenes (**37f**)) complementary to previously known borylation methods (Scheme 7). The product **37h** derived from a terminal alkyne was the only five-membered-ring isocoumarin. We attribute this selectivity to a disfavored buildup of cationic character on the terminal carbon of the alkyne in the reaction pathway toward the unobserved six-membered-ring isomer. This hypothesis is consistent with the proposed formal borylation mechanism, described in detail later.

The method was scalable (eq 3). The resulting borylated isocoumarins participated in oxidation chemistry (**38**; eq 4) and Suzuki cross-coupling, which demonstrated the viability of these building blocks in the construction of new C−C bonds (**39**, eq 5).



The development of the formal oxyboration method resulted in the discovery of a new role for ClBcat as a bifunctional reagent in electrophilic cyclization reactions. This development illustrated a conceptual expansion of borylation chemistry and in doing so broadened the toolbox available for reaction design.

3.2. Catalyst-Free Formal Thioboration Reactions of Alkynes

Similar to benzoic acids, thiophenols had proved to be challenging substrates for direct borylation. Hence, extending the formal borylation methodology to thioanisoles toward thioboration of alkynes seemed appropriate to pursue next. Though there was a prior report of thioboration through activation of B−S σ bonds and C−C π bonds with palladium (eq 6),[13] our report was the first catalyst-free thioboration route that furnished a B−C σ bond in the product.[55]

In this reaction, readily synthesized *o*-alkynylthioanisoles **40** were treated with ClBcat, which resulted in the addition of sulfur and boron across the alkyne to generate borylated benzothiophene cores **41** in one synthetic step (Scheme 8).[53]

The thioboration products **41** were transesterified with pinacol to obtain bench- and column-stable pinacolboronate derivatives **42** (Scheme 8). The reaction tolerated functional groups complementary to other borylation strategies (e.g., halides (**42b**), amines (**42c**), cyano groups (**42d**), and heterocycles (**42e**); Scheme 8).[56−59] In view of the fact that benzothiophenes are scaffolds in biologically active molecules,[60] efficient formation of their borylated analogues with regiocontrol and broad functional group tolerance creates a potentially useful synthetic advance.

We discovered that intermediate **41a** can be successfully functionalized in situ through a variety of established boron chemistry to produce derivatives **43**, **44**, **45**, and **46** without the need for isolation of the organoboron intermediate (Scheme 9).

An extension of the thioboration reaction to obtain dihydrothiophenes **50** likely proceeds via the analogous methyl- and acylsulfonium intermediates **48** and **52** (eqs 7 and 8).

Shortly after publication of our work, Ingleson reported that BCl_3 promotes an analogous thioboration reaction at 20 °C,[61] compared with 100 °C using ClBcat, presumably as a result of the higher electrophilicity of BCl_3 (eq 9). However, this transformation

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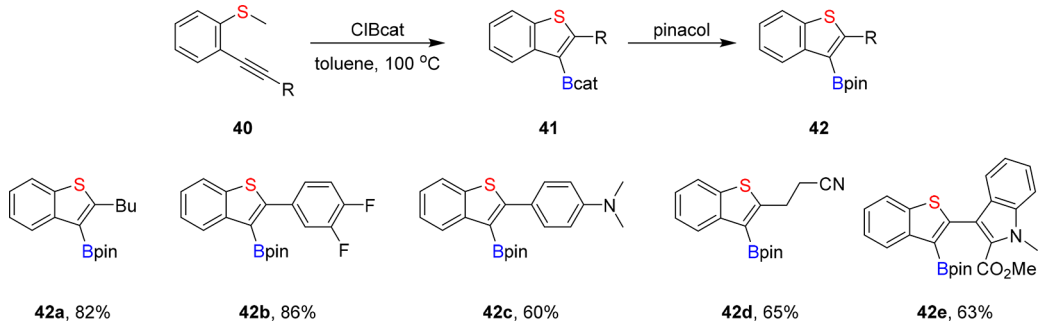
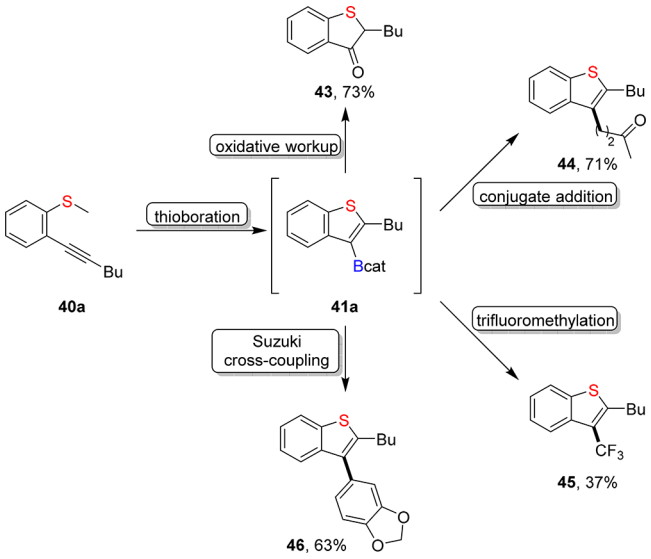
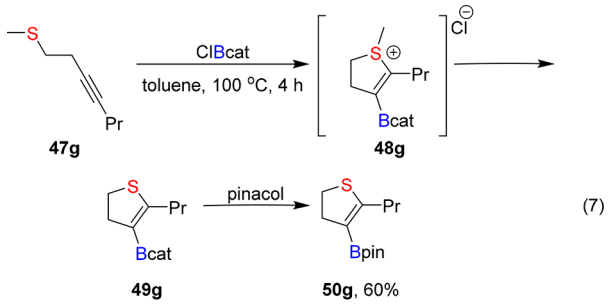
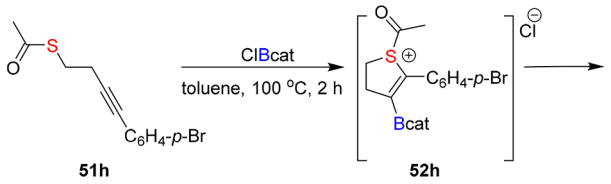
Scheme 8. Catalyst-Free Formal Thioboration Reaction and Representative Products

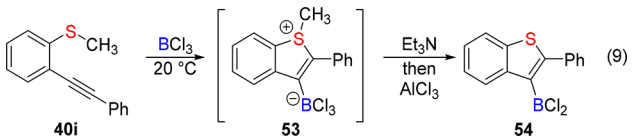


Scheme 9. In Situ Functionalization









requires additional reagents to promote demethylation and chloride extraction, leading to the final neutral borylated heterocycle **54**.

Calculations from a collaborative study between our group, Berionni, and Singleton indicate that the difference in electrophilicity between BCl_3 and ClBcat is responsible for the ability of chloride to dissociate from boron and facilitate demethylation in ClBcat but not in BCl_3.[62] Balancing of electrophilicity and nucleophilicity such that the boron source is sufficiently Lewis acidic to activate the alkyne but not Lewis acidic enough to prevent dissociation of chloride for demethylation is the key to the success of this transformation without the requirement for additional reagents. These calculations and a series of mechanistic studies helped us to better understand this reactivity, as described next.

3.3. Mechanistic Studies of Formal Borylation/Cyclization Reactions

Two mechanistic pathways were initially considered for the thioboration reaction with ClBcat (Scheme 10). In the top pathway, the highly electrophilic ClBcat activates the alkyne in **40** to generate vinyl cation **55**. Nucleophilic attack by sulfur then forms zwitterionic cyclized intermediate **57**, which is common to both pathways. Subsequent demethylation by chloride in **58** yields the thioboration product **41**. In the bottom pathway, a less electrophilic route is considered. Carbophilic activation of **40** by ClBcat is concerted with a nucleophilic attack by sulfur and formation of intermediate **57** through transition state **56** in an Ad_E2/Ad_E3 mechanism. Demethylation of **58** then furnishes the desired product **41**. Alternative mechanistic pathways that would proceed via a B−S σ-bond intermediate or haloboration/cyclization were ruled out earlier.[53]

Because the two possible mechanisms differed in their degree of positive charge buildup on the alkyne, we decided to conduct a Hammett study to test the substitution effect (Figure 7). A series of molecules with electronically different para substituents were subjected to competition experiments, and the relative reaction rates were determined. A plot of σ^+ versus log(relative reaction rate) resulted in a ρ^+ value of −1.7. This negative slope is indicative of the buildup of positive charge character at the alkyne carbon in the rate-limiting transition state, which rules out dealkylation as the rate-limiting step. The relatively low magnitude of ρ is consistent with absence of a full carbocation, implicating the Ad_E3 mechanism (bottom pathway in Scheme 10).

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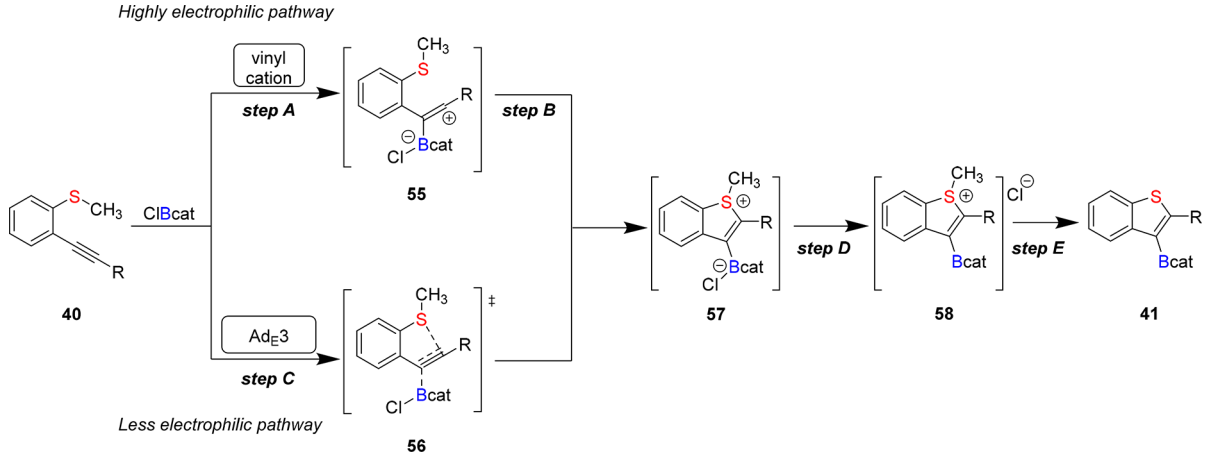
Scheme 10. Two Possible Mechanistic Pathways for the Thioboration Reaction of Alkynylthioanisoles



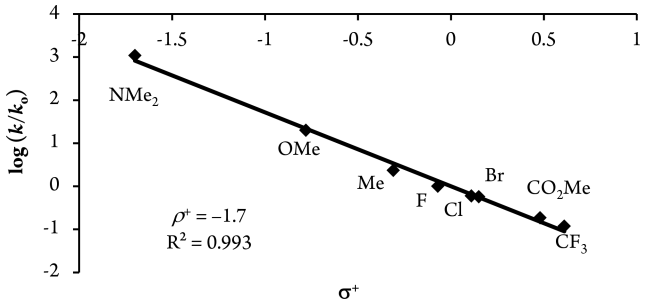


Figure 7. Hammett study showing the correlation between $\log(k/k_0)$ and σ^+ at 100 °C.

Formation of the thioboration product **41** in these reactions showed a second-order kinetic dependence globally: first order with respect to each of the components of the reaction. Eyring analysis yielded activation parameters of $\Delta G^{\ddagger}$ = 27.1 ± 0.1 kcal mol^{-1} at 90 °C, $\Delta H^{\ddagger}$ = 13.8 ± 1.0 kcal mol^{-1}, and $\Delta S^{\ddagger}$ = −37 ± 3 cal mol^{-1} K^{-1}, obtained from reactions performed at 70−90 °C. The value of $\Delta S^{\ddagger}$ is within the range observed for bimolecular association reactions,[63] which suggests that Cl$^-$ is not released prior to the rate-determining step.

The ^{13}C kinetic isotope effects (KIEs) at natural abundance were determined for the thioboration reaction (Figure 8). The butyl-substituted carbon displayed the larger KIE of the two alkyne carbons, consistent with an asynchronous Ad$_E$2/3 mechanism (Scheme 10, bottom pathway).

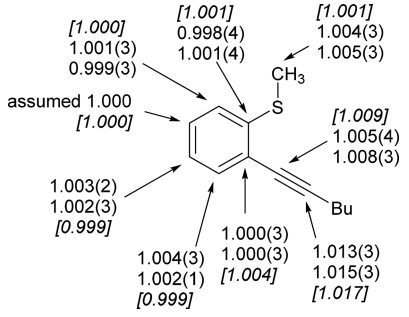
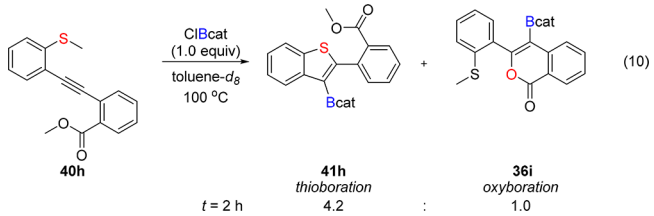


Figure 8. Experimental and B3LYP-D3/6-31+G**/PCM(toluene)-predicted (italicized and in brackets) ^{13}C KIEs (k^{12}_C/k^{13}_C) at 85 °C for the thioboration reaction. The 95% confidence limits on the last digit are shown in parentheses with the experimental values.

An intramolecular competition experiment with **40h** provided more information about the nature of the internal alkyne activation by ClBcat (eq 10). In this molecule, two nucleophiles



(10)

compete for the same alkyne, for oxy- and thioboration, to generate heteroborylated products **36i** and **41h**, respectively. The product ratios denoted a minor preference for the formation of the thioboration product, corresponding to $\Delta\Delta G^{\ddagger}$ = 1.1 kcal/mol at 373 K. The small value of $\Delta\Delta G^{\ddagger}$ is consistent with boron−carbon bond formation being more advanced at the transition state than the formation of the heteroatom−carbon bond. Along with previous observations, this provides strong support for an asynchronous Ad$_E$3 mechanistic route for the thioboration reaction with ClBcat.

The bifunctional and balanced role of ClBcat (i.e., carbophilic enough to activate the alkyne but not chlorophilic enough to prevent release of chloride for dealkylation) was shown to be key to furnish neutral organoboron building blocks that can be functionalized. We envision that this information will facilitate reaction development by indicating the proper balance for new reagents.

4. CONCLUSION AND OUTLOOK

From the described studies, guiding principles regarding which approach to use for which substrates have emerged. We identified an operative structure−function relationship between the pK_a of the corresponding heteroatom−H bond and its ability to serve as a practical substrate for direct borylative heterocyclization. The primary challenges observed with the direct addition reactions of the aforementioned substrates derived from carboxylic acids and thiols were premature cyclizations facilitated by the acidic proton (**59** and **60**; Scheme 11) and the insufficient transformation of the substrates to the B−heteroatom bond prior to cyclization (**61** and **62**; Scheme 11). These substrate classes corresponded to the lower end of the tested pK_a range. As a result, functional groups that have a low pK_a of the corresponding heteroatom−H bond act as poor substrates for

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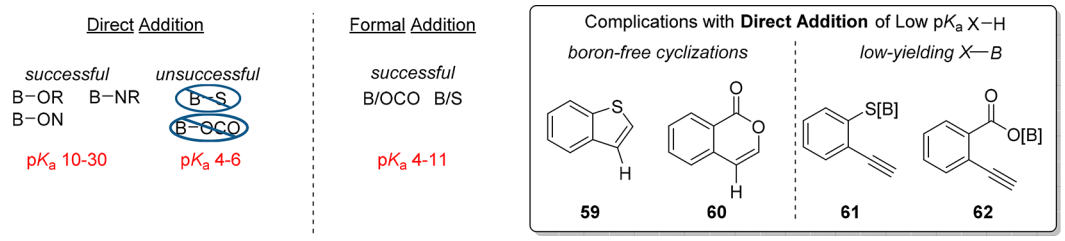
Scheme 11. Exploration of the pK_a Structure−Reactivity Design Principle



direct addition reactions, whereas substrates with p$K_a \gtrsim 10$ (on the basis of our tested pool) show increased potential for direct borylation (Scheme 11). This behavior establishes a preliminary guiding cutoff point, considering that the pK_a of alkynylphenols (~10) corresponded to the first substrate that exhibited successful direct borylation.

Our group has developed several direct and formal borylation strategies leading toward borylated heterocyclic building blocks. The heterocycle classes include borylated benzofurans, indoles, isoxazoles, isocoumarins, benzothiophenes, and thiophenes. Borylated heterocycles amenable to rich established downstream chemistry are reactive synthetic intermediates for one-pot procedures or generate isolable compounds for future reactivity. These findings offer valuable knowledge for the expansion of the field of borylation chemistry through mechanistically distinct pathways, alternative bond disconnections, and readily available reagents.

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Notes

The authors declare no competing financial interest.

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Kim N. Tu was born in 1988 in Binh Dinh, Vietnam. She received her B.S. in Chemistry in 2010 from the University of California, Los Angeles, and her M.S. in Chemistry in 2013 from the California State University, Long Beach, under the guidance of Professor Kensaku Nakayama. She is currently a Ph.D. student working with Professor Suzanne A. Blum to investigate borylative heterocyclization reactions.

Suzanne A. Blum received a B.S. in Chemistry at the University of Michigan, working with Prof. Edwin Vedejs, and a Ph.D. from the University of California, Berkeley, under the supervision of Professors Robert G. Bergman and Jonathan A. Ellman. After an NIH Postdoctoral Fellowship with Professor Christopher T. Walsh at the Harvard Medical School, she joined the Chemistry Department at the University of California, Irvine, in 2006. Her research interests include mechanistic and synthetic studies of chemical reactions.

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