Communication

Catalyst-Free Synthesis of Borylated Lactones from Esters via Electrophilic Oxyboration

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Catalyst-Free Synthesis of Borylated Lactones from Esters via Electrophilic Oxyboration

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Supporting Information Placeholder

ABSTRACT: The catalyst-free oxyboration reaction of alkynes is developed. The resulting borylated isocoumarins and 2-pyrones are isolated as boronic acids, pinacolboronate esters, or potassium organotrifluoroborate salts, thus providing a variety of bench stable organoboron building blocks for downstream functionalization. This method has functional group compatibility, is scalable, and proceeds with readily available materials: *B*-chlorocatecholborane and methyl esters. Mechanistic studies indicate that the *B*-chlorocatecholborane acts as a carbophilic Lewis acid toward the alkyne, providing a mechanistically distinct pathway for oxyboration that avoids B–O σ bond formation and that enables this catalyst-free route.

Addition reactions of boron reagents to carbon–carbon π systems have provided powerful routes to organoboron compounds for over 65 years.[1–6] The first oxyboration reaction of carbon–carbon π systems, however, was only recently reported in 2014,[7,8] possibly due to the high strength of B–O σ bonds (~136 kcal/mol).[9] This reaction proceeded through a B–O σ bond intermediate and required a gold catalyst. We herein report a boron reagent that promotes oxyboration of alkynes in the absence of a catalyst. This reaction does not proceed via a B–O σ bond intermediate, instead accessing an electrophilic oxycyclization pathway. The fact that boron is able to access an oxycyclization pathway—previously known only for other elements[10–16]—provides the first example of an important class of mechanistically distinct oxyboration reactions, which yield borylated heterocycles without the use of strongly basic reagents[17] or transition metal catalysts (Figure 1).[18,19] The absence of previously reported oxyboration/cyclization reactions with electrophilic boron may be due to competitive formation of boron–oxygen bonds, formation of which are here shown surprisingly to inhibit oxyboration rather than promote it. We herein apply this method to the synthesis of borylated isocoumarins and 2-pyrones, classes of compounds with important biological activity[20,21] but with few prior reports of their borylated analogs.[22–24] We envision that demonstration of this mechanistically distinct pathway for oxyboration will open up new pathways for the practical synthesis of borylated heterocyclic building blocks for drug discovery and materials synthesis.

Primary competing strategies to synthesize borylated heterocycles include lithiation/electrophilic trapping[17] and transition metal-catalyzed borylation.[18,19,25] The few prior reports of borylated lactones employed Pd-catalyzed cross coupling[26] and lithiation/borylation.[27] The oxyboration strategy demonstrated here provides complementary functional group tolerance to these leading alternative borylation strategies.

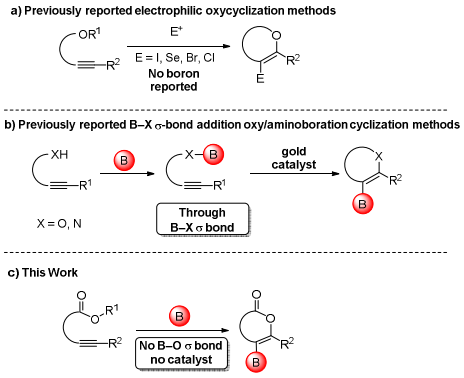
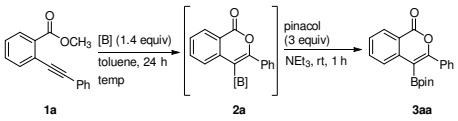


Figure 1. (a) Previously reported electrophilic cyclization/dealkylation methods to generate *O*-heterocycles from ethers or esters. (b) Previously reported heterocycle-forming B–X σ-bond addition. (c) This work demonstrating mechanistically distinct oxyboration.

Given that boron halides are known to dealkylate esters to generate B–O σ bonds,[28,29] we anticipated that boron trihalides should promote oxyboration of **1a** due to previously reported carboboration and haloboration reactivity with alkynes.[30] To our surprise, both trihalogenated boron sources BBr_3 and BCl_3 (Table 1, entries 1 and 2, respectively) failed to yield any desired borylated isocoumarin **3aa**. *B*-Chlorocatecholborane (ClBcat), on the other hand, which to our knowledge has not been previously used for alkyne activation, provided the borylated isocoumarin in yields of 25% and 75% at 45 °C and 100 °C, respectively (entries 3 and 4). The use of *B*-bromocatecholborane, which is known to demethylate methyl esters more quickly than ClBcat (and thus would be expected to yield **2** more quickly or at the same rate),[31] provided a lower isolated yield of the desired oxyboration product (entry 5). These results provided an early indication that the operative oxyboration pathway proceeded without initial dealkylation/B–O σ-bond formation and thus may be mechanistically distinct from prior reports that proceeded through the B–O σ bond.

The commercially available ClBcat (1.4 equiv) was identified as the electrophile that provided the best yield, and 100 °C was identified as the optimal temperature at 1.0 M concentration with the mass balance at lower temperatures being starting material (see SI for optimization data).

Table 1. Boron Reagent Variation



1a 2a 3aa

Entry	*Boron Electrophile [B]*	*Temp*	*Yield (%)[a] 3aa*
1	BBr_3[b]	45 °C	0
2	BCl_3[b]	45 °C	0
3	*B*-chlorocatecholborane	45 °C	25
4	*B*-chlorocatecholborane	100 °C	75
5	*B*-bromocatecholborane	100 °C	48

[a]Isolated yield. [b]1.0 M solution in DCM.

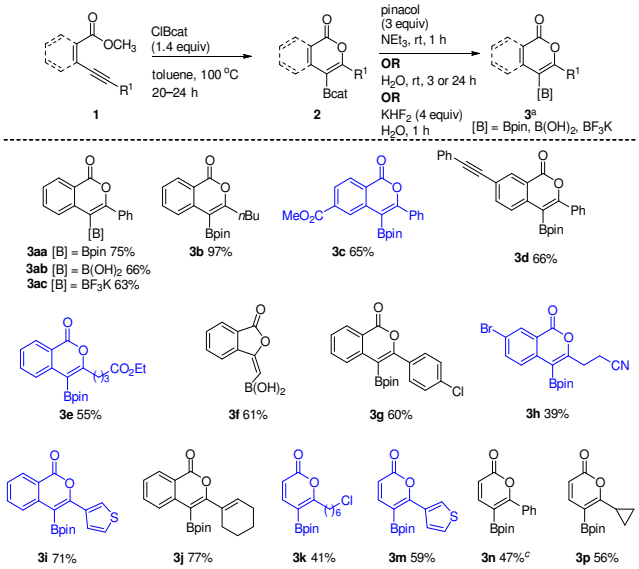
The product isolation scope and substrate scope were next investigated (Table 2). For synthetic variety, the products can be isolated three different ways: as the pinacolboronic ester (**3aa**), the boronic acid (**3ab**), or the potassium organotrifluoroborate salt (**3ac**). Each method provides complementary advantages. Pinacolboronic esters are stable toward silica gel chromatography, provided the best isolated yield for the test compound, and can be easily cross-coupled under basic conditions; it was therefore chosen as the preferred isolation method.[32] Boronic acids, although not as bench stable as the other options, are a preferred transition metal-catalyzed cross coupling partner and provide the best atom economy.[33] Potassium organotrifluoroborates, although slightly lower yielding, provide a column-free workup procedure after oxyboration, making them a practical target for large-scale synthesis.[34,35] The use of *B*-chloropinacolborane rather than ClBcat, which would provide a direct route to analogous isolable products, was avoided due to this reagent's lack of commercial availability and poor thermal stability (decomposition above -70 °C),[36] which would preclude oxyboration reactions above this temperature.

We attempted an alternative oxyboration through the corresponding carboxylic acid rather than methyl ester. An intractable product mixture was produced. The route from the methyl ester is fortunately much cleaner. The methyl esters are also bench stable and therefore a more practical synthetic precursor than the *o*-alkynylbenzoic acids, which decompose via tautomerization/cyclization.

Functional groups that can be tolerated with this oxyboration strategy include esters, cyanides, aryl bromides and chlorides, and thiophenes, which are incompatible with competing lithiation/borylation routes and/or palladium catalyzed oxidative addition routes. The tolerance towards esters (**3c**) was particularly noteworthy given that these boron reagents are known to dealkylate esters; this tolerance was examined further in mechanistic studies (vide infra). Similarly, the tolerance of alkynes distal to esters (**3d**) implies that independent reactivity of the alkyne (e.g., haloboration[5,6]) is not part of the operative pathway. An aromatic backbone was not a requirement for the oxyboration reaction. Alkenyl esters also underwent the oxyboration reaction to produce 2-pyrones **3k**–**3p**, albeit in lower yields. Because of the reactivity of *B*-chlorocatecholborane, ethers, an *O*-TBDPS protecting group, furans, and a ketone with α protons were not tolerated by the oxyboration reaction.

The oxyboration reaction could theoretically produce either the regioisomer from *5-exo-dig* or *6-endo-dig* cyclization.[37] X-ray crystallographic analysis of **3aa** confirmed that it was the product of *6-endo-dig* cyclization (Figure 2). No other regioisomer was observed in the crude ^{1}H NMR spectrum. Compound **3f** is the only product formed from *5-exo-dig* cyclization (see SI for characterization data). Consistent with the mechanistic proposal, formation of the unobserved *6-endo-dig* product would have required disfavored build up of primary cationic character on the terminal carbon of the unsubstituted alkyne (vide infra).

Table 2. Synthesis of Borylated Isocoumarins and 2-Pyrones via the Oxyboration Reaction[a,b]



[a]Isolated yield. [b]Blue molecules contain functional groups not compatible with other leading borylation strategies. [c]From ethyl ester.

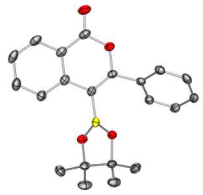


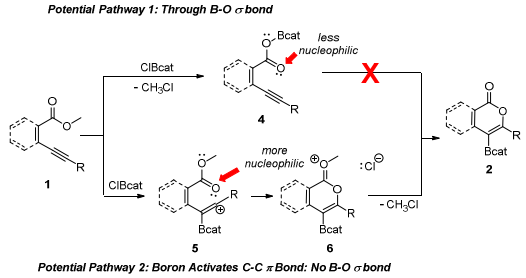
Figure 2. X-ray crystallographic structure of **3aa** confirming 6-membered ring formation, with the thermal ellipsoids shown at 50% probability (B, yellow; C, gray; O, red).

Mechanistic studies. Two mechanistic pathways were considered for this oxyboration reaction (Scheme 1). In the top pathway, dealkylation occurs first to produce intermediate **4**, followed by the oxyboration/cyclization with the alkyne. In the bottom pathway, however, boron-induced electrophilic cyclization, possibly through a formal vinylic cation, **5**, or alternatively directly from **1** to **6**, as has been proposed for alkyne activation by BCl_3,[38,39] precedes dealkylation (bottom). Cyclized oxocarbenium ion **6** is then primed for rapid dealkylation due to the increased positive charge on the oxygen. The oxygen in **4** would be less nucleophilic toward cyclization than the oxygen in **5** due to donation of the electron density of the carboxy group into the empty *p* orbital on boron. This decrease in nucleophilicity may rationalize why direct dealkylation of **1** via the top pathway inhibits the oxyboration reaction rather than promotes it.

If demethylation occurred before cyclization, in the operable pathway to the oxyboration product, then the similar esters (*a* and *b*) in **1c** should demethylate at similar rates (Scheme 2). This demethylation would produce intermediates **7** and **8** in approximately equal quantities, resulting in formation of **3c** and **9**. Product **9** is not observed, however, in the crude reaction mixture by

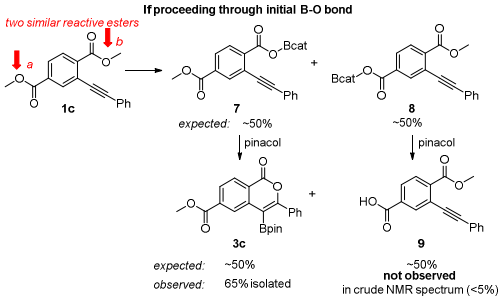
^{1}H NMR spectroscopy. Product **3c** was isolated in 65% yield, with the majority of the mass balance being unreacted **1c**. Therefore, ester *b* demethylates significantly faster than ester *a*, consistent with cyclization preceding demethylation. The position

Scheme 1. Two proposed pathways: demethylation-cyclization through B–O bond (top) and cyclization-demethylation without B–O bond formation (bottom).

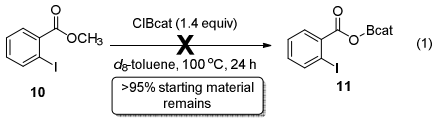


of ester *a* does not permit cyclization, thus it does not have access to that pathway for demethylation. This data is inconsistent with operation of the top pathway (dealkylation-cyclization) and is consistent with the bottom pathway (cyclization-dealkylation) in the overall oxyboration reaction.

Scheme 2. Intramolecular Competition Experiment

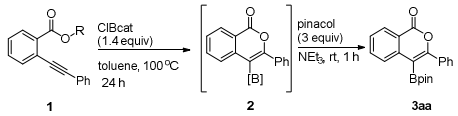


To further probe the operative mechanism, demethylation of test compound **10** was examined. Compound **10** has no alkyne; therefore, if demethylation occurs, it must proceed directly, rather than through a precyclization pathway. Under identical conditions that produced compound **3aa** from **1a** in 75% isolated yield, compound **10** led to no detectible decrease in starting methyl ester as determined by ^{1}H NMR spectroscopy relative to 1,3,5-triisopropylbenzene internal standard (<5%, eq 1). No borenium species were detected via ^{11}B NMR spectroscopy, in contrast to the arene borylation conditions reported by Ingleson.[40] Thus, the rate of reactivity of methyl esters with ClBcat in the absence of tethered alkynes is insufficiently rapid to account for the observed oxyboration reactivity. This data further supports that cyclization precedes demethylation in the operative oxyboration reaction mechanism (Scheme 1, bottom).



Various *O*-alkyl esters were examined with the oxyboration method (Table 3). The oxyboration reaction tolerated methyl, ethyl, and isopropyl groups with iterative reductions in ^{1}H NMR yields. The *t*-butyl ester, in contrast, failed to furnish any of the desired borylated isocoumarin, despite successful dealkylation, as characterized by isobutylene formation and the quantification of the benzoic acid derivative of **1a** in 68% ^{1}H NMR spectroscopy yield. This detection is consistent with the reported ability of ClBcat to dealkylate *t*-butyl esters at ambient temperature while ethyl esters remain unreacted.[31] This result provides further evidence that cyclization precedes dealkylation in the pathway that generates the oxyboration product, because when dealkylation occurs rapidly at ambient temperature, presumably generating B–O σ bonds, oxyboration does not occur even at elevated temperatures.

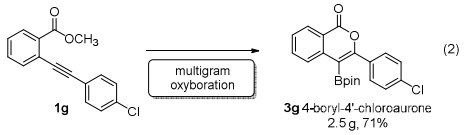
Table 3. Mechanistic Insight from *O*-Alkyl Group Variance of the Oxyboration Reaction



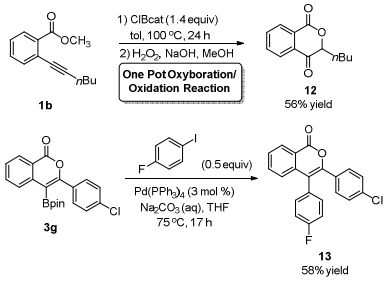
Entry	*R*	*^{1}H NMR Yield (%)^a 3aa*
1	Me	81
2	Et	68
3	*i*Pr	60
4	*t*Bu	0

^{a}Yield determined relative to mesitylene internal standard.

Synthetic applications. The oxyboration reaction provides scalable access to borylated building blocks of bioactive cores (eq 2). Subjecting 2.5 g of methyl benzoate ester **1g** to the standard oxyboration reaction conditions yielded 2.5 g (71%) of the desired borylated isocoumarin **3g**. Compound **3g** is the 4-borylated analogue of the marine natural product chloroaurone, isolated from *Spatoglossum variabile*.[41]

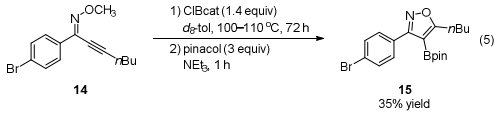


Moreover, the boron functional group provides a handle for downstream functionalization of the newly formed lactone core. One example of this utility is demonstrated in the synthesis of isochroman-1,4-diones, biologically relevant compounds.[42,43] The previously reported synthesis of **12** employed chromium trioxide and sulfuric acid.[44] Subjecting butyl alkynyl ester **1b** to the standard oxyboration conditions, followed by oxidative workup, furnished **12** in 56% yield over two steps in one pot (eq 3). The utility of these borylated isocoumarins in the construction of new C–C bonds was highlighted in a Suzuki crosss-coupling reaction of borylated lactone **3g** with *p*-fluoroiodobenzene to generate isocoumarin **13** (eq 4).



Extension of the mechanistic concept to other systems. Having established the feasibility of using an external boron electrophile to generate borylated isocoumarin products, we explored the applicability of the oxyboration strategy to synthesize borylated isoxazoles, an important pharmaceutical heterocyclic motif (eq 5).[45,46] Treatment of *O*-methyl oxime **14** with ClBcat at 100–110 °C for 72 h furnished the desired borylated isoxazole **15** in 35% yield. This illustrates the potential for the mechanistic concept to

be applied to other systems to generate value-added borylated heterocycles from simple alkylated heteroatoms.



In summary, this reaction is the first report of a transition-metal free oxyboration reaction that adds boron and oxygen to carbon–carbon π systems. It is also the first formal carboxyboration—addition of the CO_2 group and boron—across alkynes. This new reactivity is enabled by dioxaborole activation of an alkyne to promote oxycyclization.[47] The reactivity lessons learned converge on employing electrophilic boron reagents with the right balance of carbophilicity vs. oxyphilicity, and with substrates exhibiting slow competitive dealkylation prior to cyclization. These balances enable the desired reactivity by avoiding competitive formation of the strong B–O σ bond, which prevents oxyboration reactivity under these catalyst free conditions. These balances are conveniently achieved with commercially available ClBcat and readily available methyl ester substrates. This scalable method can tolerate a variety of functional groups that are incompatible with the alternative strongly basic or oxidative-addition pathways that comprise other leading borylation strategies. Additional mechanistic studies and substrate class expansions are currently ongoing in our research group. We envision that this mechanistically distinct oxyborylation strategy will serve as a springboard toward broader application of catalyst-free boron–element addition reactions to generate valuable borylated heterocyclic products.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and characterization data, including CIF data for **3aa**. 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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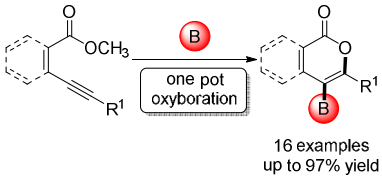

16 examples
up to 97% yield

- *catalyst free*
- *new reactivity*
- *no B–O σ bond intermediate*
- *multigram scale*