JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

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

Darius J. Faizi, Adena Issaian, Ashlee J. Davis, and Suzanne A. Blum*

Department of Chemistry, University of California, Irvine, California 92617-2025, United States

Supporting Information

ABSTRACT: A catalyst-free oxyboration reaction of alkynes is developed. The resulting borylated isocoumarins and 2-pyrones are isolated as boronic acids, pinacol-boronate esters, or potassium organotrifluoroborate salts, 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 enables this catalyst-free route.

Addition reactions of boron reagents to C−C π systems have provided powerful routes to organoboron compounds for over 65 years.[1] The first oxyboration reaction of C−C π systems was only recently reported in 2014,[2] possibly due to the high strength of B−O σ bonds (~136 kcal/mol).[3] This reaction proceeded through a B−O σ bond intermediate and required a gold catalyst. We 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[4]—provides the first example of an important class of mechanistically distinct oxyboration reactions, which yield borylated heterocycles without the use of strongly basic reagents[6] or transition-metal catalysts (Figure 1).[7] The absence of previously reported oxyboration/cyclization reactions with electrophilic boron may be due to competitive formation of B−O bonds, formation of which are here shown surprisingly to inhibit oxyboration rather than promote it. We apply this method to the synthesis of borylated isocoumarins and 2-pyrones, classes of compounds with important biological activity[8] but with few prior reports of their borylated analogues.[9] 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[6] and transition-metal-catalyzed borylation.[7,10] Prior reports of borylated lactones employed Pd-catalyzed cross-coupling[11] and lithiation/borylation.[12] The oxyboration strategy demonstrated here provides complementary functional group tolerance to these leading alternative borylation strategies.

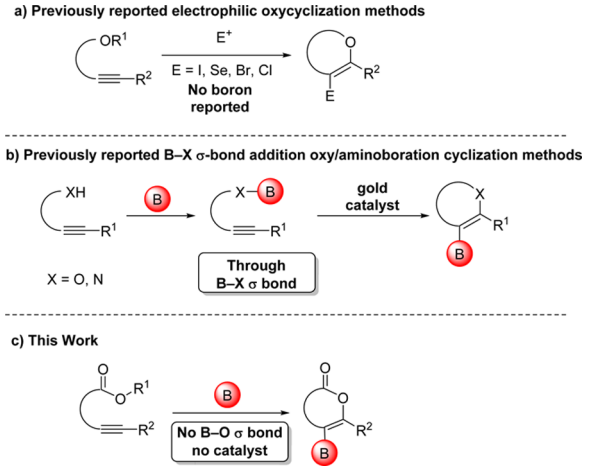
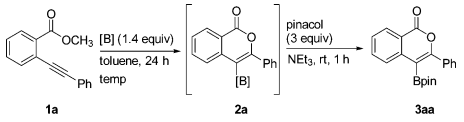


Figure 1. (a) Previously reported electrophilic cyclization/dealkylation methods to generate O-heterocycles from ethers or esters. (b) Previously reported heterocycle-forming B−X σ bond addition. (c) This work demonstrating mechanistically distinct oxyboration.

Given that boron halides are known to dealkylate esters to generate B−O σ bonds,[13] we anticipated that boron trihalides should promote oxyboration of **1a** due to previously reported carboboration and haloboration reactivity with alkynes.[14] 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), which to our knowledge has not been previously used for alkyne activation, provided the borylated isocoumarin in yields of 25 and 75% at 45

Table 1. Boron Reagent Variation



1a 2a 3aa

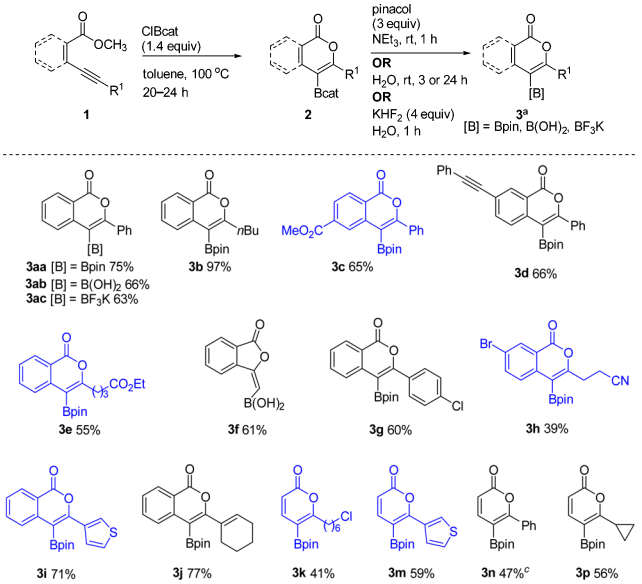
entry	boron electrophile [B]	temp (°C)	yield (%)[a] of **3aa**
1	BBr_3[b]	45	0
2	BCl_3[b]	45	0
3	*B*-chlorocatecholborane	45	25
4	*B*-chlorocatecholborane	100	75
5	*B*-bromocatecholborane	100	48

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

Received: December 11, 2015
Published: February 5, 2016

DOI: 10.1021/jacs.5b12989
J. Am. Chem. Soc. 2016, 138, 2126−2129

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.

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),[15] 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 may be mechanistically distinct from prior reports that proceeded through the B−O σ bond.

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).

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.[16] 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.[17] Potassium organotrifluoroborates, although slightly lower yielding, provide a column-free workup procedure after oxyboration, making them a practical target for large-scale synthesis.[18] The use of *B*-chloropinacolborane rather than ClBcat, which would provide a direct route to analogous isolable products, was avoided due to its lack of commercial availability and poor thermal stability (decomposition above −70 °C),[19] precluding 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 a more practical synthetic precursor than the *o*-alkynylbenzoic acids, which decompose via tautomerization/cyclization.

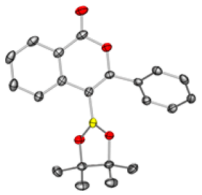


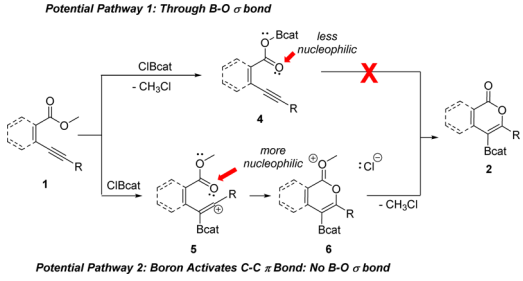
Figure 2. X-ray crystallographic structure of **3aa**, confirming six-membered ring formation, with the thermal ellipsoids shown at 50% probability (B, yellow; C, gray; O, red).

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 Pd-catalyzed oxidative addition routes. The tolerance toward **3c** was particularly noteworthy because these boron reagents dealkylate esters; this tolerance was examined further in mechanistic studies. Similarly, tolerance of alkynes distal to **3d** implies that independent reactivity of the alkyne (e.g., haloboration[1e,f]) 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** in lower yields. Because of ClBcat's reactivity, 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.[20] X-ray crystallographic analysis of **3aa** confirmed it was the product of 6-*endo*-*dig* cyclization (Figure 2). No other regioisomer was observed in the crude ^{1}H NMR spectrum. **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 required disfavored buildup of primary cationic character on the terminal carbon of the unsubstituted alkyne.

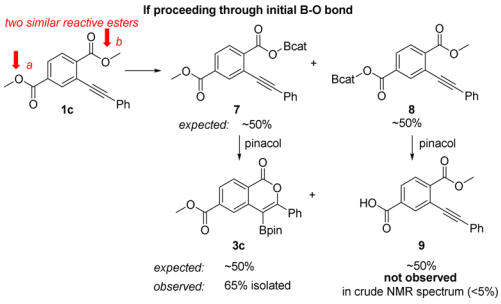
Two mechanistic pathways were considered for this oxyboration reaction (Scheme 1). In the top pathway, dealkylation occurs first to produce intermediate **4**, followed by the oxyboration/cyclization with the alkyne. In the bottom pathway, boron-induced electrophilic cyclization, possibly through a formal vinylic cation, **5**, or alternatively directly from **1** to **6**, as has been proposed for alkyne activation by BCl_3,[21] precedes dealkylation. Cyclized oxocarbenium ion **6** was then primed for rapid dealkylation due to the increased positive charge on the oxygen. Oxygen in **4** would be less nucleophilic toward cyclization than oxygen in **5** due to donation of the electron density of the

Scheme 1. Two Potential Oxyboration Pathways



DOI: 10.1021/jacs.5b12989
J. Am. Chem. Soc. 2016, 138, 2126−2129

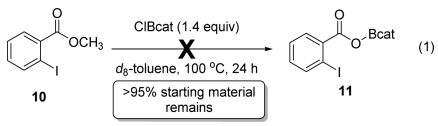
Scheme 2. Intramolecular Competition Experiment



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 occurs before cyclization, in the operable pathway to the oxyboration product, then 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**. **9** was not observed in the crude reaction mixture by ^{1}H NMR spectroscopy. **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 of ester *a* does not permit cyclization, thus it does not have access to that pathway for demethylation. This is inconsistent with operation of the top pathway (dealkylation/cyclization) and is consistent with the bottom pathway (cyclization/dealkylation) in the overall oxyboration reaction.

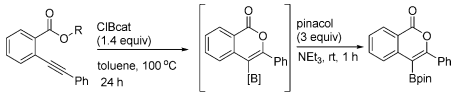
Demethylation of test compound **10** was examined. **10** has no alkyne; therefore, if demethylation occurs, it must proceed directly, rather than through a precyclization pathway. Under identical conditions that produced **3aa** from **1a** in 75% isolated yield, **10** led to no detectable decrease in starting methyl ester, as determined by ^{1}H NMR spectroscopy relative to a 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.[22] 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. These data support 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). Oxyboration reaction tolerated methyl, ethyl, and isopropyl groups with iterative reductions in ^{1}H NMR yields. The *t*-butyl ester did not furnish any of the desired borylated isocoumarin, despite successful dealkylation, as characterized by isobutylene formation and quantification of the benzoic acid derivative of **1a** in 68% ^{1}H NMR yield. This detection is consistent with the reported ability of ClBcat to dealkylate *t*-butyl esters at ambient temperature while ethyl esters remain unreacted[15] and provides further evidence that cyclization precedes dealkylation in the pathway that generates the oxyboration product because

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

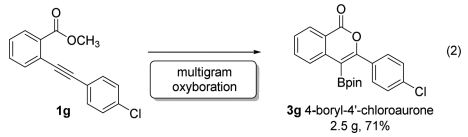


entry	R	^{1}H NMR yield (%)[a] of **3aa**
1	Me	81
2	Et	68
3	*i*Pr	60
4	*t*Bu	0

[a]Yield determined relative to mesitylene internal standard.

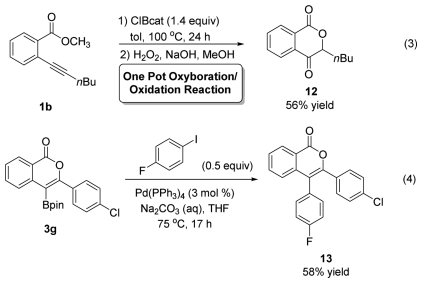
when dealkylation occurs rapidly at ambient temperature, presumably generating B−O σ bonds, oxyboration does not occur even at elevated temperatures.

Oxyboration reaction provides scalable access to borylated building blocks of bioactive cores (eq 2). Subjecting 2.5 g of



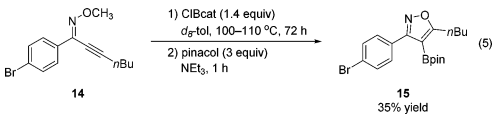
methyl benzoate ester **1g** to the standard oxyboration reaction conditions yielded 2.5 g (71%) of the desired borylated isocoumarin **3g**. Compound **3g** is the 4-borylated analogue of the marine natural product chloroaurone, isolated from *Spatoglossum variabile*.[23]

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.[24] Previously reported synthesis of **12** employed chromium trioxide and sulfuric acid.[25] 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).

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 (eq 5).[26] Treatment of *O*-methyl



DOI: 10.1021/jacs.5b12989
J. Am. Chem. Soc. 2016, 138, 2126−2129

oxime **14** with ClBcat at 100−110 °C for 72 h furnished 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 C−C 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.[27] 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12989.

Experimental details and characterization data (PDF)
X-ray data for **3aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*blums@uci.edu

Notes

The authors declare the following competing financial interest(s): U.S. patent no. 9,238,661.

■ ACKNOWLEDGMENTS

This work was supported by a grant from the NIH (1R01-GM098512-01), the University of California, Irvine, and an Allergan Foundation Graduate Fellowship to D.J.F. We thank Ms. Nicole A. Nava and Dr. Mohammad Al-Amin for synthesis of starting materials, Dr. Joseph W. Ziller and Mr. Jason R. Jones for X-ray diffraction analysis, and Dr. Phillip R. Dennison for NMR spectroscopy assistance.

■ REFERENCES

(1) (a) Brown, H. C. *Tetrahedron* **1961**, *12*, 117. (b) Miyaura, N. Hydroboration, Diboration, and Stannylboration. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, 2001; pp 1−46. (c) Barbeyron, R.; Benedetti, E.; Cossy, J.; Vasseur, J.; Arseniyadis, S.; Smietana, M. *Tetrahedron* **2014**, *70*, 8431. (d) Sakae, R.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 6460. (e) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. (f) Cade, I. A.; Ingleson, M. J. *Chem. - Eur. J.* **2014**, *20*, 12874.

(2) (a) Hirner, J. J.; Faizi, D. J.; Blum, S. A. *J. Am. Chem. Soc.* **2014**, *136*, 4740. (b) Hirner, J. J.; Blum, S. A. *Tetrahedron* **2015**, *71*, 4445.

(3) Sanderson, R. T. *Polar Covalence*; Academic Press: San Diego, CA, 1983.

(4) (a) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1128. (b) Pal, S.; Chatare, V.; Pal, M. *Curr. Org. Chem.* **2011**, *15*, 782. (c) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (d) Oliver, M. A.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 558. (e) Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 7401. (f) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067.

(5) (g) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.

(6) Nagaki, A.; Moriwaki, Y.; Yoshida, J. *Chem. Commun.* **2012**, *48*, 11211.

(7) (a) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287. (b) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.

(8) (a) Janecki, T., Ed. *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*; Wiley-VCH: Weinheim, 2014; pp 147−192. (b) Pochet, L.; Frederick, R.; Masereel, B. *Curr. Pharm. Des.* **2004**, *10*, 3781.

(9) (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Pelter, A. *Chem. Soc. Rev.* **1982**, *11*, 191. (c) Dimitrijević, E.; Taylor, M. *ACS Catal.* **2013**, *3*, 945.

(10) Chong, E.; Blum, S. A. *J. Am. Chem. Soc.* **2015**, *137*, 10144.

(11) Gravett, E. C.; Hilton, P. J.; Jones, K.; Romero, F. *Tetrahedron Lett.* **2001**, *42*, 9081.

(12) Fletcher, C. J.; Wheelhouse, K. M. P.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2503.

(13) (a) Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427. (b) Manchand, P. S. *J. Chem. Soc. D* **1971**, 667.

(14) Warner, A. J.; Lawson, J. R.; Fasano, V.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 11245.

(15) Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

(16) Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457.

(17) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170.

(18) (a) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (b) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288.

(19) Bettinger, H. F.; Filthaus, M.; Bornemann, H.; Oppel, I. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4744.

(20) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979.

(21) (a) Lawson, J. R.; Clark, E. R.; Cade, I. A.; Solomon, S. A.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7518. (b) For an example of alkyne activation by boron, see: Hansmann, M. M.; Melen, R. L; Rudolph, M.; Rominger, F.; Wadepohl, H.; Stephan, D. W.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **2015**, *137*, 15469.

(22) Del Grosso, A.; Singleton, P. J.; Muryn, C. A.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2102.

(23) Venkateswarlu, S.; Panchagnula, G.; Gottumukkala, A.; Subbaraju, G. *Tetrahedron* **2007**, *63*, 6909.

(24) (a) Jansen, R.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **2002**, *2002*, 917. (b) Neil, A.; Gordon, A.; Urquhart, M. Patent Appl. WO2012/80243 A2, 2012.

(25) Hobson, S. J.; Parkin, A.; Marquez, R. *Org. Lett.* **2008**, *10*, 2813.

(26) (a) Liu, J.; Yu, L.-F.; Eaton, J. B.; Caldarone, B.; Cavino, K.; Ruiz, C.; Terry, M.; Fedolak, A.; Wang, D.; Ghavami, A.; Lowe, D. A.; Brunner, D.; Lukas, R. J.; Kozikowski, A. P. *J. Med. Chem.* **2011**, *54*, 7280. (b) Tu, K.; Hirner, J. J.; Blum, S. A. *Org. Lett.* **2016**, *18*, 480.

(27) Electrophilic activation of C−C π systems in other contexts has been reported employing the more electrophilic boron reagents (e.g., BCl_3, BBr_3, BR_3, and borenium species BO_2L^+), but not with neutral dioxyboron systems (BO_2X). See refs 1f and 22 and the following: (a) Hansmann, M. M.; Melen, R. L.; Rominger, F.; Hashmi, A. S. K.; Stephan, D. W. *Chem. Commun.* **2014**, *50*, 7243. (b) Wilkins, L. C.; Wieneke, P.; Newman, P. D.; Kariuki, B. M.; Rominger, F.; Hashmi, A. S. K.; Hansmann, M. M.; Melen, R. L. *Organometallics* **2015**, *34*, 5298. (c) Yang, C. H.; Zhang, Y. S.; Fan, W. W.; Liu, G. Q.; Li, Y. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 12636.

DOI: 10.1021/jacs.5b12989
J. Am. Chem. Soc. 2016, 138, 2126−2129