

An Oxyboration Route to a Single Regioisomer of Borylated Dihydrofurans and Isochromenes

Kim N. Tu, Chao Gao, and Suzanne A. Blum

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01790 • Publication Date (Web): 25 Jul 2018

Downloaded from <http://pubs.acs.org> on July 26, 2018

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.



An Oxyboration Route to a Single Regioisomer of Borylated Dihydrofurans and Isochromenes

Kim N. Tu, Chao Gao, and Suzanne A. Blum*

Department of Chemistry, University of California, Irvine, Irvine, California 92697–2025, United States

ABSTRACT: An oxyboration reaction that employs B–O σ bonds as addition partners to C–C π bonds to form borylated dihydrofurans and isochromenes has been developed. By nature of the mechanism, the reaction produces exclusively one borylated regioisomer, in contrast to and/or complementary to alternative routes that produce these borylated heterocycles via C–H activation. Access to the borylative heterocyclization route is demonstrated from alcohols directly or from a hydroboration–oxyboration sequence starting from the corresponding ketone, forming the heterocyclic core and installing the boron in one synthetic step. Catechol boronates were directly used as coupling partners in the in situ Suzuki cross coupling reactions without transesterification to pinacol boronates.

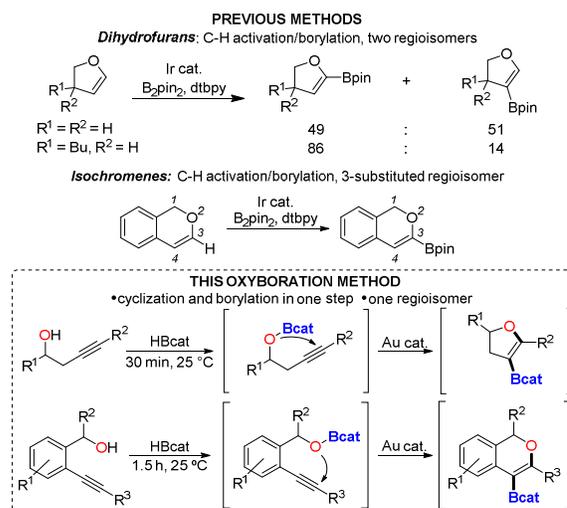
INTRODUCTION

Borylated heterocycles are versatile synthetic intermediates, such as building blocks for drug discovery and for the synthesis of materials.^{1,2} The common approach to constructing borylated heterocycles is through construction of the heterocycle followed by borylation in a separate synthetic step.³ A method for constructing the heterocyclic core and installing the boron in one synthetic step through a borylative heterocyclization reaction would be synthetically appealing due to its complementary bond disconnections, regiochemistry, and functional group tolerance.^{4–11} Herein we develop one-step cyclative oxyboration routes to two *O*-heterocycle classes, dihydrofurans and isochromenes, for which existing iridium-catalyzed C–H activation–borylation methods provide unsatisfactory or complementary regioselectivity.^{12,13}

We describe the motivation for developing an approach to each of these two *O*-heterocyclic cores separately in more detail: Substituted 2,3-dihydrofurans are found in a range of natural and synthetic products such as Aflatoxin B₁,¹⁴ with many exhibiting interesting biological activity.^{15–21} Yet currently, there is only one report on the synthesis of borylated dihydrofurans, by Miyaura.¹² That reported iridium-catalyzed C–H activation–borylation method proceeded with low regioselectivity, however (Scheme 1). Given that the regioselectivity of oxyboration is dictated by the cyclization step, in contrast, we envisioned that an alternative borylative heterocyclization strategy may overcome the challenge of poor regioselectivity in the synthesis of this compound class.^{4–6,9}

Similarly, isochromenes are common cores in biologically active compounds, including natural products and pharmaceuticals.^{22–32} Due to their ubiquity,^{22,23,25–28} developing synthetic methods from simple and readily available starting materials has been the focus of ongoing research.^{22,23,25}

Scheme 1. Comparison of Previous Method and Oxyboration Method



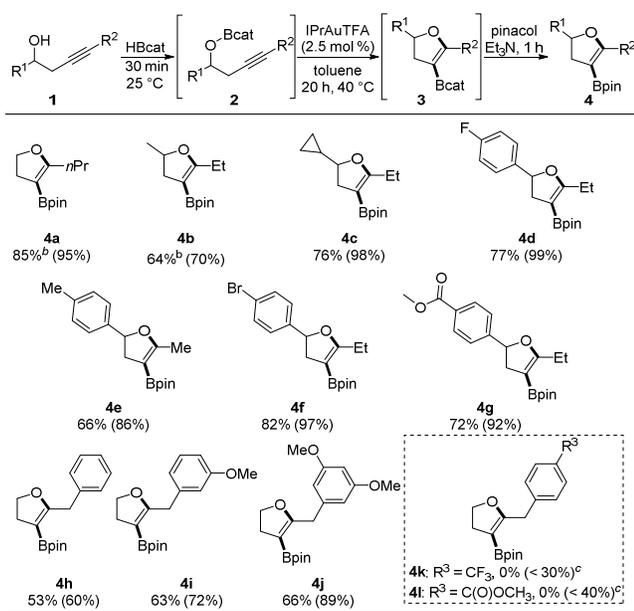
Synthetic methods to borylated isochromenes, specifically, are synthetically appealing because such compounds could be further functionalized through established cross-coupling reactions.^{33,34} There are, however, limited examples for the generation of borylated isochromenes, by Miyaura,^{12,13} again via iridium-catalyzed C–H activation/borylation. In that case, exclusive access to the 3-borylated isochromene was reported, whereas we envisioned that the borylative heterocyclization described here would access the complementary 4-borylated isochromene. The development of an oxyboration route to dihydrofurans and isochromenes will now be described in sequence, providing the chronology of the investigations and allowing for comparison and contrast between the two ring systems.

RESULTS AND DISCUSSION

As part of prior oxyboration studies, we had previously identified an initial condition that resulted in gold-catalyzed formation of a borylated dihydrofuran, albeit in low yield.⁴

This reaction was an extension of our work accessing other ring systems through oxyboration reactions, wherein we identified that quenching the gold catalyst at the end of the reaction resulted in higher product yields,⁴ including on scale.³⁵ Yet optimization studies herein in the dihydrofuran system (Scheme 2) found the opposite result. Quenching the active gold catalyst using triphenylphosphine at the end of the reaction was detrimental to the integrity of the desired product, causing decomposition of the product after 15 h; thus we herein optimized conditions that were absent of triphenylphosphine. Furthermore, the cyclization reaction (**2a** to **3a**) was particularly sensitive to temperature. Reactions at 40 °C or 50 °C produced similar ¹H NMR spectroscopy yields, but reactions at 60–100 °C resulted decreased yields of desired product by promoting product decomposition. Transesterification of the moisture-sensitive catechol boronic ester to the bench-stable pinacol boronic ester (Bpin) at ambient temperature was performed for final product isolation.^{5–9}

Scheme 2. 3-Borylated Dihydrofurans Substrate Scope^a



Under the optimized reaction conditions, the substrate scope was examined (Scheme 2). The oxyboration method tolerated functional groups including fluoride (**4d**), electron-rich (**4e**, **4i**, **4j**) and electron-poor aryl groups (**4g**), and aliphatic substitution (**4a–4c**). The reaction tolerated cyclopropyl (**4c**), a fragment of interest in pharmaceutical discovery.^{36–41} In contrast to palladium-catalyzed routes to borylated heterocycles,⁴² the optimized oxyboration route tolerated bromoarenes (**4f**), granting the opportunity for a subsequent cross-coupling reaction at that orthogonal functional group. The borylative cyclization step for these substrates provided intermediate **3** in moderate-to-quantitative ¹H NMR spectroscopy yields of a single regioisomer, which was then transesterified to bench-stable **4**. The reaction is not compatible with electron-rich R¹ as no conversion to **3** was observed when R¹ = *p*-anisyl (See Supporting Information (SI) for more information). Due to the synthetic difficulty of accessing the requisite starting material, no substitution at the 4-position was attempted.

Aryl substitution at R², however, resulted in a reaction that did not fully consume **2**, stopping at less than 50% consump-

tion. We hypothesized that the phenyl ring in direct conjugation with the alkyne might slow the desired cyclization relative to the rate of catalyst decomposition. This hypothesis was tested by changing to benzyl substituents (i.e., removing the direct conjugation); the reaction then indeed proceeded in good yields for electron-rich or neutral benzyl groups (**4h**, **4i** and **4j**). However, substitution with electron-poor benzyl groups (substrate leading to attempted formation of **4k** and **4l**, CF₃ and COOCH₃, respectively), led to the corresponding dihydrofurans **5** with a hydrogen in the place of the desired boron (Figure 1; plausibly arising from protodeborylation) as the major reaction products as determined by ¹H NMR spectroscopic analysis of the crude reaction mixtures of corresponding **3k** and **3l**. These relatively low ¹H NMR spectroscopy yields of **3k** and **3l** could not be determined accurately due to overlap between the resonances corresponding to the desired oxyboration product and undesired protiated product. The minor desired catechol boronates in these cases nevertheless did not undergo successful transesterification to isolable pinacol boronates, possibly due to the presence of reactive byproducts under these conditions.

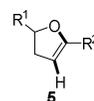
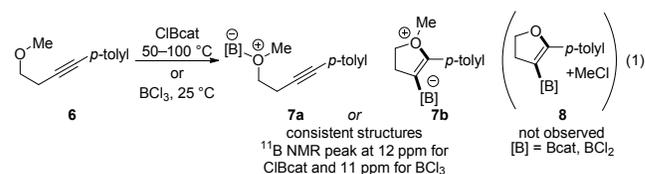


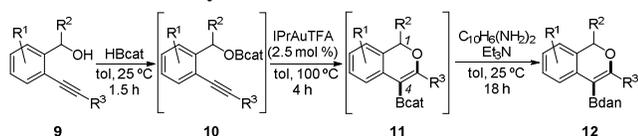
Figure 1. Undesired dihydrofurans without boron, **5**.

For the conjugated substrates (R² = aryl), which displayed conversions <50%, we considered an alternative formal borylation method. In this method, an electrophilic boron reagent (ClBcat^{4–9} identified by our laboratory, or BCl₃ identified by Ingleson^{10,11}) activates the C–C π bond and promotes a cyclization–demethylation sequence, without requiring formation of a B–O σ bond in the starting material. We decided to test this alternative route with alkynyl ether **6** as a substrate and ClBcat and BCl₃ as activating agents. Desired product **8** did not form, but rather partial conversion occurred to a species giving rise to a ¹¹B NMR spectroscopy signal at 11–12 ppm, consistent with tetracoordinated boron, which still maintained the methyl group as depicted in compounds **7a** and **7b**⁴³ (eq 1). This lack of completed formal borylative heterocyclization reactivity is consistent with our proposed model, in which substrate classes with pK_a of the corresponding heteroatom–H bonds (in this case RO–H) that are greater than 10 have higher potential for successful direct borylation (through B–O σ bonds) than for formal borylation (through intermolecular activation by external boron electrophiles followed by dealkylation).⁹



Next, the oxyboration route to borylated isochromenes was investigated. The same catalyst was found to be optimal in this case (Scheme 3; see Supporting Information (SI) for full catalyst optimization details). The primary challenge in the extension of the method to the synthesis of borylated isochromenes occurred upon attempted product isolation (Table 1). These products showed sensitivity at both the benzylic carbon and the carbon–boron bond, indicated by positions **1** and **4** in structure **11**.

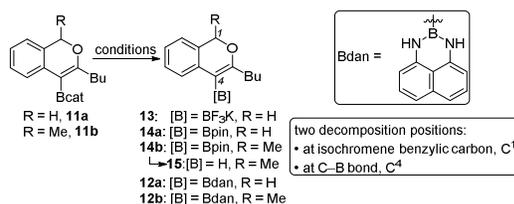
Scheme 3. 4-Borylated Isochromenes



First, **11a** was chosen as the model compound for product isolation optimization. Examination of the crude reaction mixture by ^1H NMR spectroscopy showed that cyclization was successful (>95% conversion). In contrast to the dihydrofuran systems, attempted formation of the analogous isochromene Bpin product **14a** from **11a** through transesterification proved unsuccessful as the product decomposed upon exposure to air (Table 1, entry 2).

The model substrate was switched to **11b**, which had the benzylic position hindered. With the new substrate, the resulting Bpin product **14b** could be isolated. However, the C–Bpin bond was not as robust as in the dihydrofuran systems, resulting in a formation of the protodeborylated product (**15**) upon exposure of the product to air for 5 d (Table 1, entry 3; see Supporting Information (SI) for full details). Consistent with the reports from Sugimoto⁴⁴ and Wang⁴⁵, it was found that transformation with 1,8-diaminonaphthalene (as Bdan) provided a viable isolation method, imparting the desired air stability (Table 1, entry 4 and 5, **12a** and **12b**).

Table 1. Isolation Methods

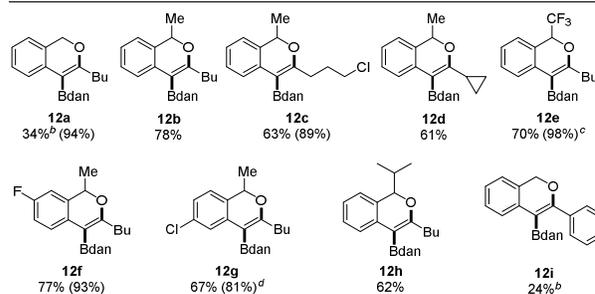


entry	substrate	boron ligand exchange (%) ^a	[B]	benzylic stability	B–C stability
1	11a	0	BF ₃ K	N/A	N/A
2	11a	>99	Bpin	18 h	N/A
3	11b	>99	Bpin	stable	5 d
4	11a	>99	Bdan	stable	stable
5	11b	>99	Bdan	stable	stable

^a Calculated through ratio of products to starting material in ^1H NMR spectra

Under standard reaction conditions of 4 h at 100 °C, with isolation as Bdan, the substrate scope was investigated (Scheme 4). Products **12c**, **12e**, **12f**, and **12g** demonstrated the reaction's tolerance of alkyl and aryl chlorides and fluorides. Products **12d** and **12e** contained a cyclopropyl and a trifluoromethyl group, respectively, which are desirable for the synthesis of pharmaceuticals and biologically active molecules.^{36–40,46}

Formation of compound **12e** required harsher conditions (120 °C, 18 h), plausibly due to the strong electron-withdrawing ability of the trifluoromethyl group adjacent to the oxygen, hindering nucleophilic cyclization. A similar result was observed with **12g**, wherein an electron-withdrawing group that was para to the nucleophile resulted a slower cyclization reaction (100 °C, 19 h). The successful synthesis of isopropyl **12h**, however, showed that a more sterically hindered nucleophile could be tolerated in this intramolecular reaction.

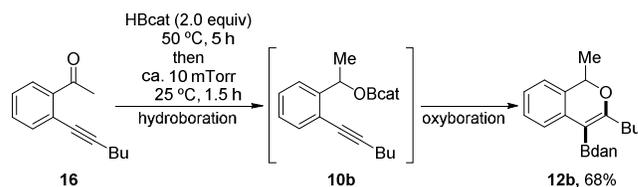
Scheme 4. 4-Borylated Isochromene Substrate Scope^a

^aYield of **12** (^1H NMR yield of **11**); ^1H NMR yield of **11** was only taken for reactions in which desired and protodeborylated product peaks in ^1H NMR spectra were well separated; ^bchallenging isolation; ^cT = 120 °C, t = 18 h; ^dT = 100 °C, t = 19 h

The ^1H NMR yield of **12a** (94%) was high, however, significant material was lost upon attempted isolation (34%), presumably due to the instability of the (non-methyl-substituted) benzylic carbon during flash column chromatography. The similarly low yield of **12i** (24%) further suggested the instability of this unsubstituted product class.

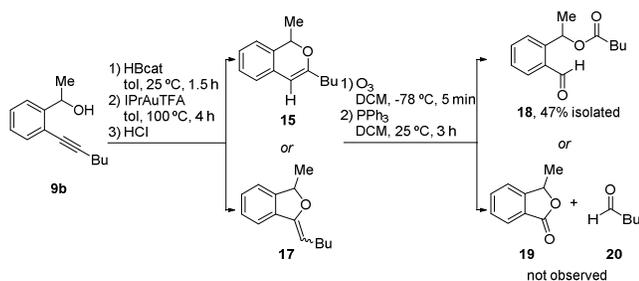
We were inspired by the work of Nöth⁴⁷ to examine if intermediate **10b** could be generated directly from **16** via reductive hydroboration (Scheme 5). This reaction proceeded at 50 °C for 5 h in the presence of 2 equiv HBcat. Removing excess HBcat under reduced pressure, followed by oxyboration, produced the desired isochromene product (**12b**) in 68% yield. Thus, ketones can serve as complementary starting materials via a hydroboration–oxyboration sequence.

Scheme 5. Synthesis of Isochromenes via Hydroboration–Oxyboration

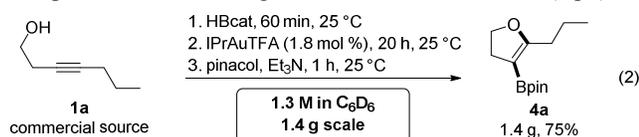


We next turned attention to closer examination of the regioisomeric characterization of product class **12**. Compound **11** (Bcat cyclization product) was regioisomerically pure on the basis of ^1H NMR spectroscopic analysis of the crude reaction mixture. Similar cyclization reactions that generate the alternative 5-membered products (e.g., **17** type) have been reported, however, and the ^1H NMR spectroscopy differentiation between the 5- and 6-membered ring products may not be straightforward.^{25,48} To establish which regioisomer was generated under the oxyboration route, a structure elucidation study was done (Scheme 6). Substrate **9b** was subjected to standard oxyboration conditions, and the product was deliberately protodeborylated via an acidic workup to make one of the two possible regioisomers, **15** or **17**, which was then purified. The ^1H NMR spectrum of this sample was consistent with that reported for **15**.²⁵ This material was then subjected to ozonolysis. ^1H NMR spectroscopic analysis of the ozonolysis products established the presence of only **18** in both the crude and purified samples, and thus that the 6-membered product (**15**) was the only cyclization product (corresponding to the 6-membered ring structures shown in Scheme 4).

Scheme 6. Structure Elucidation



Synthetic utility. A 6 mmol scale oxyboration reaction smoothly afforded 1.43 g of **4a** from **1a** in 20 h at 40 °C (75%). On this scale, a catalyst loading reduction to 1.8 mol % was possible, as was a higher substrate concentration (eq 2).

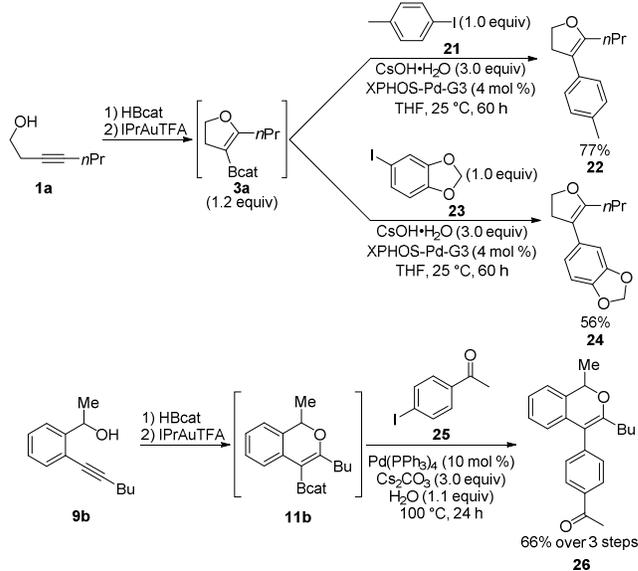


To demonstrate the utility of oxyboration to produce borylated building blocks that are suitable for downstream C–C bond-forming reactions, in situ Suzuki cross-coupling reactions were demonstrated on the Bcat intermediates of both substrate classes. These reactions established that the transesterification/boron group manipulation was not necessary in cases where immediate downstream functionalization was desired.

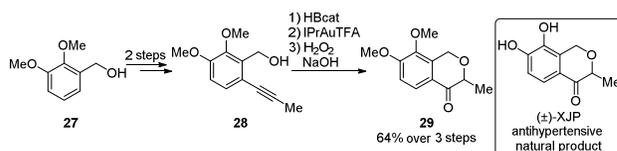
As mentioned previously, borylated dihydrofurans were found to be sensitive to high temperature during oxyboration optimization. Yet procedures for Suzuki cross-coupling reactions often require elevated temperatures of 70–100 °C.^{33,49} The conditions for mild-temperature Suzuki cross-coupling reactions and mechanistic studies by Denmark⁵⁰ motivated our examination of cesium hydroxide monohydrate as a reagent for promoting palladium-catalyzed cross-coupling reactions of Bcat intermediate **3a**. Employment of this reagent combination at ambient temperature resulted in the successful synthesis of **22** and **24** directly from catechol boronate **3a** (77% and 56% yield, respectively; Scheme 7).

In the case of borylated isochromenes, yields in cross-coupling reactions were found to be highly dependent on quantity of water employed in the reaction (Scheme 7). Addition of some water accelerated the cross-coupling reaction, but excesses lead to decomposition of **11b** through competing protodeborylation. Optimized addition of 1.1 equiv of water, with Pd(PPh₃)₄ and Cs₂CO₃, effectively catalyzed the cross-coupling reaction of **11b** with aryl iodide **25** at 100 °C to afford **26** (66% yield over three steps from alkynyl benzyl alcohol **9b**).

Scheme 7. Downstream Functionalization



Scheme 8. Formal Total Synthesis of (±)-XJP via Oxyboration



A formal total synthesis of (±)-XJP, an antihypertensive natural product isolated from peels of *Musa sapientum* L,²⁴ was also conducted. Commercially available substrate **27** was transformed to **28**, the substrate for oxyboration, in two steps (Scheme 8, see Supporting Information (SI) for details). Subsequent oxyboration followed by in situ H₂O₂ oxidation under basic conditions generated the dimethylated (±)-XJP (**29**) in 64% yield over three steps, finishing the formal total synthesis. Demethylation of **29** to afford (±)-XJP has been previously reported.²⁴

CONCLUSION

In conclusion, a method has been developed for preparing 3-borylated dihydrofurans and 4-borylated isochromenes via an oxyboration reaction that generates exclusively one regioisomer, in contrast and/or complement to alternative C–H activation routes. The method can be scaled, and generates borylated heterocycles suitable for downstream functionalization, as highlighted in the Suzuki cross-coupling of the catechol boronates and formal total synthesis of (±)-XJP. The oxyboration reaction toward borylated isochromenes can also harness the corresponding ketones instead of benzyl alcohols as substrates. The method provides a useful tool to access functionalized, regioisomerically pure borylated dihydrofurans and isochromenes as building blocks for organic synthesis.

EXPERIMENTAL SECTION

General Information. All reagents were used as received from commercial sources unless otherwise stated. 1,2-Dimethoxyethane was purchased from Sigma–Aldrich in a Sigma–Aldrich Sure/Seal™ bottle and used without further purification. Tetrahydrofuran and triethylamine were dried by passing through an alumina column under argon pressure on a push still solvent system. Chloroform was dried over K_2CO_3 ,⁵¹ degassed using three freeze-pump-thaw cycles, and vacuum transferred before use. Toluene- d_8 and C_6D_6 were dried over CaH_2 , degassed using three freeze-pump-thaw cycles, and vacuum transferred before use. Catecholborane⁵¹ was degassed using three freeze-pump-thaw cycles, and vacuum transferred before use. Ozone was generated by a ClearWater Tech, LLC M-1500 ozone generator. Cesium carbonate was dried by heating at ca. 300 °C under vacuum (ca. 30 mTorr) for ca. 12 h, and stored in a N_2 -filled glovebox. Manipulations were performed in a glovebox under nitrogen atmosphere unless otherwise noted. Analytical thin layer chromatography (TLC) was performed using Merck F₂₅₀ plates and visualized under UV irradiation at 254 nm, or using a basic aqueous solution of potassium permanganate. Flash chromatography was conducted using a Teledyne Isco Combiflash® R_f 200 Automatic Flash Chromatography System, and Teledyne Isco RediseP® 35–70 μm silica gel. All proton and carbon nuclear magnetic resonance (1H and ^{13}C) spectra were recorded on a Bruker DRX-400 spectrometer, Bruker DRX-500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE-600 spectrometer. Boron nuclear magnetic resonance (^{11}B NMR) spectra were recorded on a Bruker AVANCE-600 or on a Bruker DRX-500 spectrometer. Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker DRX-400 spectrometer or on a Bruker AVANCE-600 spectrometer. All coupling constants were measured in Hertz (Hz). Chemical shifts were reported in ppm and referenced to the residual protiated solvent peak ($\delta_H = 7.26$ ppm for $CDCl_3$, $\delta_H = 2.08$ ppm for d_8 -toluene, $\delta_H = 7.16$ ppm for C_6D_6 in 1H NMR spectroscopy experiments; $\delta_C = 77.16$ ppm for $CDCl_3$, $\delta_C = 20.43$ ppm for d_8 -toluene, $\delta_C = 128.06$ ppm for C_6D_6 in ^{13}C NMR spectroscopy experiments), except compounds with Bdan where chemical shifts were reported in ppm and referenced to TMS ($\delta_H = 0.00$ ppm). ^{11}B NMR and ^{19}F NMR spectroscopy experiments were referenced to the absolute frequency of 0 ppm in the 1H dimension according to the Xi scale. High-resolution mass spectrometry (HRMS (ESI-TOF)) data were obtained at the University of California, Irvine.

General Experimental Procedure A for the Synthesis of Alkynols 1c–g. Alkynols were prepared according to a literature procedure, repeated here for convenience and clarity.⁵² Using a standard Schlenk line, to a flame-dried round bottom flask was added zinc dust (1.63 g, 25.0 mmol, 5.00 equiv) and I_2 (1.27 g, 5.00 mmol, 1.00 equiv). The flask was capped with septum and placed under dynamic N_2 . Then aldehyde (5.00 mmol, 1.00 equiv), and propargyl bromide (6.00 mmol, 1.20 equiv) in dry THF (50 mL) was added via syringes at 25 °C. The resulting reaction mixture was sonicated at room temperature for 4 h. The reaction was quenched with sat. ammonium chloride (1 \times 20 mL). The aqueous layer was extracted with EtOAc (1 \times 30 mL). The combined organic layers were washed with brine (1 \times 30 mL), dried over anhydrous Na_2SO_4 , filtered through filter paper, and concentrated in vacuo. The resulting crude oil was purified by silica gel flash column chromatography using an elution gradient from 100% hexanes to 10% EtOAc in hexanes. Product-containing fractions were

identified by TLC, combined and concentrated in vacuo to afford **1**.

General Experimental Procedure B for the Synthesis of Alkynols 1h–j. Alkynols were prepared according to a literature procedure, repeated here for convenience and clarity.⁵³ Using a standard Schlenk line, to a flame-dried round bottom flask was added terminal alkynol (0.450 mL, 6.00 mmol, 1.20 equiv) in dry THF (35 mL) via syringe, and cooled to -78 °C under dynamic N_2 atmosphere. To this cooled solution was added *n*-butyllithium (1.60 M solution in hexane) (7.8 mL, 13 mmol, 2.5 equiv) dropwise via syringe. The resulting suspension was stirred at -78 °C for 1 h, followed by addition of a solution of dry $ZnBr_2$ (2.82 g, 12.5 mmol, 2.50 equiv) in dry THF (10 mL) via syringe. The mixture was stirred at -78 °C for 10 min, then warmed to 25 °C. The catalyst $Pd(DPEphos)Cl_2$ (35.8 mg, 0.0500 mmol, 1.00 mol%) and benzyl bromide (5.00 mmol, 1.00 equiv) were added to the clear reaction mixture via syringe at 25 °C and stirred at 40 °C for 18 h. The reaction was quenched with 1.0 M hydrochloric acid (1 \times 10 mL). The aqueous layer was extracted with ether (2 \times 20 mL). The combined organic layers were washed with sat. sodium bicarbonate (1 \times 15 mL), dried over anhydrous Na_2SO_4 , filtered through filter paper, and concentrated in vacuo. The resulting crude oil was purified by silica gel flash column chromatography using an elution gradient from 100% hexanes to 30% EtOAc in hexanes. Product-containing fractions were identified by TLC, combined and concentrated in vacuo to afford **1**.

1-cyclopropyl-3-hexyn-1-ol (1c) was prepared using procedure A and obtained as light yellow oil (199 mg, 29% yield). TLC (20% EtOAc/hexanes): $R_f = 0.27$, visualized by UV absorbance. 1H NMR (d_8 -toluene, 500 MHz): δ 2.94–2.89 (m, 1H), 2.36–2.26 (m, 2H), 1.97 (qt, $J = 7.5$, 2.5 Hz, 2H), 1.51 (d, $J = 4.0$ Hz, 1H), 0.97 (t, $J = 7.5$ Hz, 3H), 0.83–0.77 (m, 1H), 0.28–0.26 (m, 2H), 0.24–0.21 (m, 1H), 0.13–0.11 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 84.0, 76.6, 73.8, 28.3, 17.0, 14.4, 12.7, 2.4. HRMS (ESI-TOF) m/z calcd for $C_9H_{14}ONa$ ($[M+Na]^+$) 161.0942, found 161.0944.

1-(4-fluorophenyl)-3-hexyn-1-ol (1d) was prepared using procedure A and obtained as light yellow oil (303 mg, 32% yield). TLC (20% EtOAc/hexanes): $R_f = 0.22$, visualized by UV absorbance. 1H NMR (d_8 -toluene, 500 MHz): δ 7.03–7.00 (m, 2H), 6.77–6.73 (m, 2H), 4.44–4.41 (m, 1H), 2.33–2.32 (m, 2H), 1.93–1.88 (m, 2H), 1.82 (bs, 1H), 0.91 (td, $J = 7.4$, 3.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (d_8 -toluene, 150 MHz): δ 162.2 (d, $J = 93.4$ Hz), 139.2, 127.4 (d, $J = 8.1$ Hz), 114.7 (d, $J = 21.2$ Hz), 84.3, 75.6, 71.8, 30.1, 13.9, 12.3. $^{19}F\{^1H\}$ NMR (d_8 -toluene, 565 MHz): δ -115.2. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{12}FO$ ($[M-H]^-$) 191.0872, found 191.0868.

1-(4-methylphenyl)-3-pentyn-1-ol (1e) was prepared using procedure A and obtained as clear oil (175 mg, 20% yield). 1H NMR ($CDCl_3$, 600 MHz): δ 7.27 (d, $J = 7.7$ Hz, 2H), 7.16 (d, $J = 7.7$ Hz, 2H), 4.78 (m, 1H), 2.59–2.52 (m, 2H), 2.34 (s, 3H), 1.81 (s, 3H). This spectrum is in agreement with previously reported spectral data.⁵⁴

1-(4-bromophenyl)-3-hexyn-1-ol (1f) was prepared using procedure A and obtained as light yellow oil (473 mg, 37% yield). TLC (20% EtOAc/hexanes): $R_f = 0.29$, visualized by UV absorbance. 1H NMR ($CDCl_3$, 600 MHz): δ 7.47 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 4.79–4.76 (m, 1H), 2.62–2.50 (m, 2H), 2.44 (d, $J = 3.0$ Hz, 1H), 2.18 (qt, $J = 7.2$, 2.4 Hz, 2H), 1.12 (t, $J = 7.8$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ 141.9, 131.6, 127.7, 121.7, 85.5, 75.0, 72.1, 30.2,

14.2, 12.5. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{12}BrO$ ($[M-H]^-$) 251.0072, found 251.0081.

1-(methyl-4-formylphenyl)-3-hexyn-1-ol (**1g**) was prepared using procedure A and obtained as yellow oil (330 mg, 28% yield). TLC (20% EtOAc/hexanes): $R_f = 0.15$, visualized by UV absorbance. 1H NMR (d_8 -toluene, 500 MHz): δ 8.04–8.01 (m, 2H), 7.18–7.16 (m, 2H), 4.46 (s, 1H), 3.51 (t, $J = 2.5$ Hz, 3H), 2.34–2.33 (m, 2H), 1.91–1.87 (m, 3H), 0.91 (t, $J = 3.0$ Hz, 3H). $^{13}C\{^1H\}$ NMR (d_8 -toluene, 125 MHz): δ 171.1, 153.4, 134.8, 134.7, 130.8, 89.7, 80.4, 77.1, 56.2, 35.1, 19.1, 17.4. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{16}O_3Na$ ($[M+Na]^+$) 255.0997, found 255.0998.

5-phenyl-3-hexyn-1-ol (**1h**) was prepared using procedure B and obtained as yellow oil (129 mg, 16% yield). TLC (30% EtOAc/hexanes): $R_f = 0.33$, visualized by $KMnO_4$ stain solution. 1H NMR (d_8 -toluene, 500 MHz): δ 7.18 (d, $J = 7.5$ Hz, 2H), 7.11–7.10 (m, 2H), 7.02 (s, 1H), 3.36 (t, $J = 7.0$ Hz, 2H), 3.31 (s, 2H), 2.17–2.13 (m, 2H). $^{13}C\{^1H\}$ NMR (d_8 -toluene, 125 MHz): δ 137.1, 137.2, 126.7, 124.7, 79.9, 79.5, 61.5, 25.2, 23.5. HRMS (ESI-TOF) m/z calcd for $C_{11}H_{12}ONa$ ($[M+Na]^+$) 183.0786, found 183.0783.

5-(*m*-anisyl)-3-hexyn-1-ol (**1i**) was prepared using procedure B and obtained as yellow oil (179 mg, 19% yield). TLC (30% EtOAc/hexanes): $R_f = 0.18$, visualized by $KMnO_4$ stain solution. 1H NMR (C_6D_6 , 600 MHz): δ 7.08 (t, $J = 7.8$ Hz, 1H), 6.98 (s, 1H), 6.90 (d, $J = 7.8$ Hz, 1H), 6.68 (d, $J = 7.8$ Hz, 1H), 3.39–3.33 (m, 7H), 2.19–2.16 (m, 2H). $^{13}C\{^1H\}$ NMR (C_6D_6 , 150 MHz): δ 160.5, 139.2, 129.7, 120.5, 114.1, 112.3, 79.9, 79.7, 61.4, 54.7, 25.4, 23.5. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{14}O_2Na$ ($[M+Na]^+$) 213.0892, found 213.0894.

5-(3,5-dimethoxyphenyl)-3-hexyn-1-ol (**1j**) was prepared using procedure B and obtained as yellow solid (582 mg, 53% yield). TLC (30% EtOAc/hexanes): $R_f = 0.15$, visualized by $KMnO_4$ stain solution. 1H NMR (d_8 -toluene, 600 MHz): δ 6.53 (d, $J = 1.8$ Hz, 2H), 6.35 (s, 1H), 3.38–3.36 (m, 8H), 3.32 (s, 2H), 2.17–2.14 (m, 2H). $^{13}C\{^1H\}$ NMR (d_8 -toluene, 125 MHz): δ 161.6, 139.8, 106.4, 104.7, 99.0, 79.8, 79.6, 61.5, 54.7, 25.5, 23.6. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{16}O_3Na$ ($[M+Na]^+$) 243.0997, found 243.0996.

General Experimental Procedure for the Synthesis of pinacol boronates 4. In an N_2 -filled glovebox, alkynol **1** (0.40 mmol, 1.0 equiv) was dissolved in 0.1 mL toluene or benzene in a 1-dram vial equipped with stir bar. Catecholborane (42.7 μ L, 0.400 mmol, 1.00 equiv) was added via gastight syringe to this solution. The resulting solution was left uncapped to allow the release of H_2 gas and stirred at room temperature for 0.5 h, then transferred via pipet to a 1-dram vial containing the catalyst $IPrAuTFA$ (7.0 mg, 0.010 mmol, 2.5 mol%). The first vial was rinsed with toluene (3×0.10 mL) and transferred to the reaction mixture. The vial with the resulting suspension was capped and the solution was stirred on a preheated hot plate at 40 °C over an appropriate time as determined by the NMR spectroscopy yield study (see SI Section II).

The reaction vial was cooled to room temperature and a solution of pinacol (142 mg, 1.20 mmol, 3.00 equiv) in anhydrous Et_3N (0.84 mL, 6.00 mmol, 15.0 equiv) was added. The resulting solution was stirred at 25 °C for 1 h. The vial containing the reaction mixture was then removed from the glovebox. Volatiles were removed in vacuo. The resulting light brown oil was purified by silica gel chromatography using an elution gradient from 100% hexanes to 10% EtOAc in hexanes. Solvents were removed in vacuo to afford the desired

pinacol boronate **4**. All of the pinacol boronates **4a–4j** are missing one carbon signal in their corresponding ^{13}C NMR spectroscopy data. This carbon atom is assigned to the carbon in the newly formed C–B σ -bond. This is expected due to the quadrupolar relaxation of boron.⁵⁵

Pinacol boronate (**4a**) was obtained as colorless oil using C_6D_6 as solvent (81 mg, 85% yield). TLC (20% EtOAc/hexanes): $R_f = 0.71$, visualized by UV absorbance. 1H NMR ($CDCl_3$, 600 MHz): δ 4.28 (t, $J = 9.6$ Hz, 2H), 2.69 (t, $J = 9.0$ Hz, 2H), 2.42 (t, $J = 7.2$ Hz, 2H), 1.52 (sextet, $J = 7.2$ Hz, 2H), 1.25 (s, 12H), 0.90 (t, $J = 7.2$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ 172.5, 82.6, 70.6, 32.0, 29.8, 24.9, 20.9, 13.7. $^{11}B\{^1H\}$ NMR ($CDCl_3$, 192 MHz): δ 30.2 (s). HRMS (ESI-TOF) m/z calcd for $C_{13}H_{24}BO_3$ ($[M+H]^+$) 239.1819, found 239.1824.

Pinacol boronate (**4b**) was obtained as colorless oil using C_6D_6 as solvent (61 mg, 64% yield). TLC (20% EtOAc/hexanes): $R_f = 0.75$, visualized by UV absorbance. 1H NMR ($CDCl_3$, 600 MHz): δ 4.68–4.63 (m, 1H), 2.82 (dd, $J = 14, 9.6$ Hz, 1H), 2.43–2.41 (m, 2H), 2.28 (dd, $J = 14, 7.2$ Hz, 1H), 1.29 (d, $J = 6.6$ Hz, 3H), 1.24 (s, 12H), 1.07 (t, $J = 7.2$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ 173.1, 82.5, 78.6, 39.2, 25.0, 24.9, 22.0, 21.7, 12.4. $^{11}B\{^1H\}$ NMR ($CDCl_3$, 192 MHz): δ 30.1 (s). HRMS (ESI-TOF) m/z calcd for $C_{13}H_{23}BO_3$ ($[M]^+$) 238.1743, found 238.1743.

Pinacol boronate (**4c**) was obtained as colorless oil using toluene as solvent (81 mg, 77% yield). TLC (20% EtOAc/hexanes): $R_f = 0.57$, visualized by UV absorbance. 1H NMR ($CDCl_3$, 600 MHz): δ 4.00–3.99 (m, 1H), 2.78 (t, $J = 11$ Hz, 1H), 2.52–2.51 (m, 1H), 2.44–2.43 (m, 2H), 1.25 (s, 12H), 1.08 (s, 4H), 0.55 (s, 1H), 0.47 (s, 1H), 0.38 (s, 1H), 0.24 (s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ 173.3, 86.5, 82.5, 27.3, 24.98, 24.95, 21.7, 16.0, 12.6, 3.3, 1.3. $^{11}B\{^1H\}$ NMR ($CDCl_3$, 192 MHz): δ 30.1 (s). HRMS (CI-TOF) m/z calcd for $C_{15}H_{25}BO_3$ ($[M]^+$) 264.1900, found 264.1889.

Pinacol boronate (**4d**) was obtained as light yellow oil using toluene as solvent (97 mg, 76% yield). TLC (20% EtOAc/hexanes): $R_f = 0.53$, visualized by UV absorbance. 1H NMR ($CDCl_3$, 600 MHz): δ 7.29 (t, $J = 6.6$ Hz, 2H), 7.02 (t, $J = 8.7$ Hz, 2H), 5.48 (t, $J = 9.3$ Hz, 1H), 3.16 (dd, $J = 14.4, 10.8$ Hz, 1H), 2.66 (dd, $J = 14.4, 7.8$ Hz, 1H), 2.55–2.50 (m, 2H), 1.25 (d, $J = 3.0$ Hz, 12H), 1.15 (t, $J = 7.8$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ 173.1, 163.1, 161.5, 139.4, 127.4, 115.4, 82.7, 82.5, 40.8, 25.0, 21.7, 12.5. $^{11}B\{^1H\}$ NMR ($CDCl_3$, 192 MHz): δ 29.6 (s). $^{19}F\{^1H\}$ NMR ($CDCl_3$, 565 MHz): δ –115.4. HRMS (CI-TOF) m/z calcd for $C_{18}H_{24}BFO_3$ ($[M]^+$) 318.1806, found 318.1804.

Pinacol boronate (**4e**) was obtained as light yellow oil using toluene as solvent (97 mg, 66% yield). TLC (20% EtOAc/hexanes): $R_f = 0.57$, visualized by UV absorbance. 1H NMR (d_8 -toluene, 600 MHz): δ 7.05–7.01 (m, 3H), 6.86 (d, $J = 7.2$ Hz, 1H), 5.38 (dd, $J = 10.2, 8.4$ Hz, 1H), 3.23 (ddd, $J = 15, 10.2, 1.8$ Hz, 1H), 2.87 (ddd, $J = 15, 8.4, 1.8$ Hz, 1H), 2.25 (t, $J = 1.8$ Hz, 1H), 1.09 (d, $J = 6.6$ Hz, 12H). $^{13}C\{^1H\}$ NMR (d_8 -toluene, 150 MHz): δ 168.8, 143.9, 137.9, 128.6, 128.3, 126.6, 123.0, 83.8, 82.5, 41.4, 25.0, 24.9, 21.3, 14.4. $^{11}B\{^1H\}$ NMR (d_8 -toluene, 192 MHz): δ 30.3 (s). HRMS (ESI-TOF) m/z calcd for $C_{18}H_{25}BO_3Na$ ($[M+Na]^+$) 323.1798, found 323.1788.

Pinacol boronate (**4f**) was obtained as light yellow oil using toluene as solvent (125 mg, 82% yield). TLC (20% EtOAc/hexanes): $R_f = 0.54$, visualized by UV absorbance. 1H

NMR (CDCl₃, 600 MHz): δ 7.46 (d, J = 8.4 Hz, 2H), 7.20 (t, J = 8.4 Hz, 2H), 5.46 (t, J = 9.0 Hz, 1H), 3.18 (dd, J = 15, 10.8 Hz, 1H), 2.64 (dd, J = 14.4, 7.8 Hz, 1H), 2.58–2.48 (m, 2H), 1.25 (d, J = 3.6 Hz, 12H), 1.15 (t, J = 7.8 Hz, 3H). ¹³C{¹H}NMR (CDCl₃, 150 MHz): δ 173.0, 142.7, 131.7, 127.4, 121.3, 82.7, 82.3, 40.8, 25.0, 21.6, 12.5. ¹¹B{¹H}NMR (CDCl₃, 192 MHz): δ 30.0 (s). HRMS (CI-TOF) m/z calcd for C₁₈H₂₄BBrO₃ ([M]⁺) 380.0987, found 380.0981.

Pinacol boronate (4g) was obtained as colorless oil using toluene as solvent (102 mg, 72% yield). TLC (20% EtOAc/hexanes): R_f = 0.51, visualized by UV absorbance. ¹H NMR (CDCl₃, 600 MHz): δ 8.01 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.2 Hz, 2H), 5.55 (t, J = 8.4 Hz, 1H), 3.91 (s, 3H), 3.22 (t, J = 12.6 Hz, 1H), 2.66 (dd, J = 14.4, 7.8 Hz, 1H), 2.60–2.51 (m, 2H), 1.24 (d, J = 3.6 Hz, 12H), 1.17 (t, J = 7.8 Hz, 3H). ¹³C{¹H}NMR (CDCl₃, 150 MHz): δ 173.0, 167.1, 148.9, 130.0, 129.3, 125.4, 82.7, 82.4, 52.2, 40.9, 31.7, 25.0, 22.8, 21.7, 14.3, 12.5. ¹¹B{¹H}NMR (CDCl₃, 192 MHz): δ 29.7 (s). HRMS (ESI-TOF) m/z calcd for C₂₀H₂₈BO₅ ([M+H]⁺) 359.2034, found 359.2036.

Pinacol boronate (4h) was obtained as white solid using toluene as solvent (59 mg, 53% yield). TLC (40% DCM/hexanes): R_f = 0.26, visualized by UV absorbance. ¹H NMR (C₆D₆, 500 MHz): δ 7.51 (d, J = 7.5 Hz, 2H), 7.20 (t, J = 7.5 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 4.02 (s, 2H), 3.92 (t, J = 9.5 Hz, 2H), 2.67 (t, J = 9.5 Hz, 2H), 1.12 (s, 12H). ¹³C{¹H}NMR (C₆D₆, 125 MHz): δ 171.4, 139.1, 129.4, 128.6, 126.6, 82.7, 70.8, 35.0, 32.3, 25.0. ¹¹B{¹H}NMR (C₆D₆, 192 MHz): δ 30.5 (s). HRMS (ESI-TOF) m/z calcd for C₁₇H₂₃BO₃Na ([M+Na]⁺) 309.1641, found 309.1645.

Pinacol boronate (4i) was obtained as colorless oil using toluene as solvent (79 mg, 63% yield). TLC (30% EtOAc/hexanes): R_f = 0.52, visualized by UV absorbance. ¹H NMR (C₆D₆, 600 MHz): δ 7.21–7.13 (m, 3H), 6.71 (d, J = 7.8 Hz, 1H), 4.01 (s, 2H), 3.95–3.91 (m, 2H), 3.36 (d, J = 1.8 Hz, 3H), 2.68 (t, J = 9.6 Hz, 2H), 1.13 (d, J = 2.4 Hz, 12H). ¹³C{¹H}NMR (C₆D₆, 150 MHz): δ 171.4, 160.4, 140.6, 129.5, 121.9, 115.4, 112.2, 82.7, 70.8, 54.7, 35.0, 32.3, 25.0. ¹¹B{¹H}NMR (C₆D₆, 192 MHz): δ 30.4 (s). HRMS (ESI-TOF) m/z calcd for C₁₈H₂₅BO₄Na ([M+Na]⁺) 339.1747, found 339.1735.

Pinacol boronate (4j) was obtained as yellow solid using toluene as solvent (91 mg, 66% yield). TLC (40% DCM/hexanes): R_f = 0.22, visualized by UV absorbance. ¹H NMR (C₆D₆, 600 MHz): δ 6.49 (d, J = 2.0 Hz, 2H), 6.32 (t, J = 2.0 Hz, 1H), 4.28 (t, J = 9.5 Hz, 2H), 3.77 (s, 6H), 3.71 (s, 2H), 2.71 (t, J = 9.5 Hz, 2H), 1.28 (s, 12H). ¹³C{¹H}NMR (CDCl₃, 150 MHz): δ 170.2, 160.8, 140.8, 107.0, 98.7, 82.8, 71.0, 55.4, 34.7, 31.8, 25.0. ¹¹B{¹H}NMR (CDCl₃, 192 MHz): δ 30.0 (s). HRMS (ESI-TOF) m/z calcd for C₁₉H₂₇BO₅Na ([M+Na]⁺) 369.1853, found 369.1866.

Gram-scale preparation of 4a. The gram-scale oxyboration reaction was conducted in a 100-mL bomb equipped with a stir bar in a N₂-filled glovebox. A flame-dried 100-mL bomb with a stir bar was charged with alkynol **1a** (0.672 g, 6.00 mmol, 1.00 equiv) together with C₆D₆ (4.6 mL) was added via syringe. To the resulting rapidly stirring suspension was added catecholborane (0.64 mL, 6.0 mmol, 1.0 equiv) via syringe. The bomb was sealed, and the suspension was stirred at room temperature for 30 min. The bomb was removed from the glovebox and placed in a preheated oil bath at 40 °C until full consumption of starting materials was achieved (18 h). This time was chosen based on the time required for conversion on

the NMR scale. The bomb was moved inside the N₂-filled glovebox. Pinacol (2.12 g, 18.0 mmol, 3.00 equiv) was dissolved in anhydrous Et₃N (2.5 mL, 18 mmol, 3.0 equiv). The resulting solution was added to the above reaction mixture via syringe, and the resulting suspension was stirred at 25 °C for 1 h inside the N₂-filled glovebox. The bomb was then removed from the glovebox. Volatiles were removed in vacuo. The resulting light brown oil was purified by silica gel chromatography using an elution gradient from 100% hexanes to 10% EtOAc. Solvents were removed in vacuo to afford the desired pinacol boronate **4a** as a light yellow oil (1.42 g, 75% yield). Spectral data were identical to those previously obtained for this compound.

General Experimental Procedure C for the preparation of 2-alkynyl benzyl and 2'-Alkynyl benzyl alcohols (9a, 9i).⁵⁶ A 100 mL flame-dried and septum-capped round bottom flask was prepared and filled with N₂ on a Schlenk line. Then, 2-iodobenzyl alcohol (1.17 g, 5.00 mmol, 1.00 equiv), PdCl₂(PPh₃)₂ (0.175 g, 0.250 mmol, 5.00 mol %), and CuI (95.0 mg, 0.500 mmol, 10.0 mol %) were quickly placed, respectively, into the 100 mL round bottom flask after the septum was briefly removed. Then, the system was capped with the septum again, followed by vacuumed on high vacuum for ca. 5 min. Then, the system was refilled with N₂ on a Schlenk line. Then, tetrahydrofuran (25 mL) was added via a syringe under N₂ on the Schlenk line to make a homogeneous solution. Then, the N₂ inlet from the Schlenk line was replaced with a N₂-filled balloon, which was kept connected to the reaction round bottom flask until the end of this reaction. To the resulting solution Et₃N (1.4 mL, 10.0 mmol, 2.0 equiv) was added via a syringe. The resulting solution was cooled to 0 °C in an ice bath. At 0 °C, alkyne (7.5 mmol, 1.5 equiv) was added dropwise via a syringe, followed by warming of the resulting solution to 25 °C. The reaction solution was stirred at 25 °C under N₂ for 18 h or until all aryl iodide was consumed as shown by TLC. The reaction was quenched with saturated NH₄Cl(aq) (20 mL), and the resulting organic layer was washed with brine (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over MgSO₄, and then filtered through a Celite® plug (Celite® in a medium glass frit funnel). The filtrate was concentrated in vacuo. The crude product was purified by silica gel flash column chromatography.

(2-(hex-1-yn-1-yl)phenyl)methanol (**9a**): Prepared according to general procedure C, and purified by flash column chromatography (silica, 15% EtOAc in hexane) to afford a brown liquid (0.80 g, 85% yield). ¹H NMR (CDCl₃, 500 MHz): δ 7.44–7.33 (m, 2H), 7.32–7.18 (m, 2H), 4.79 (d, J = 6.3 Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 2.07 (s, 1H), 1.66–1.56 (m, 2H), 1.55–1.44 (m, 2H), 0.96 (t, J = 7.3, 1.2 Hz, 3H). This spectrum is in agreement with previously reported spectral data.⁵⁶

General Experimental Procedure D for the preparation of 2-alkynyl benzyl and 2'-Alkynyl benzyl alcohols (9b–d, 9f).^{56,57} A 100 mL flame-dried and septum-capped round bottom flask containing a stir bar was prepared and filled with N₂ on a Schlenk line. Then 2'-iodoacetophenone (1.0 equiv), PdCl₂(PPh₃)₂ (5 mol%), and CuI (10 mol%) were placed, respectively, to the 100 mL round bottom flask after the septum was briefly removed. Then, the system was capped again with the septum and vacuumed with a high vacuum. Then, the system was refilled with N₂ on a Schlenk line. Tetrahydrofuran (0.2 M) was added under N₂ on the Schlenk line via a syringe. Then, the N₂ inlet from the Schlenk line was replaced with a

N_2 -filled balloon, which was kept connected to the reaction round bottom flask until the end of this reaction. To the resulting solution Et_3N (2.0 equiv) was added. The resulting solution was cooled to $0^\circ C$ in an ice bath. At $0^\circ C$, alkyne (1.5 equiv) was added dropwise, followed by warming of the resulting solution to $25^\circ C$. The reaction solution was stirred at $25^\circ C$ under N_2 for 18 h or until all aryl iodide was consumed as shown by TLC (ca. 10% EtOAc in hexane). The reaction was quenched with saturated $NH_4Cl(aq)$ (20 mL), and the resulting organic layer was washed with brine (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL), and the combined organic layers were dried over $MgSO_4$, and then filtered through a Celite[®] plug (Celite[®] in a medium glass frit funnel). The filtrate was concentrated in vacuo. The crude product was purified by silica gel flash column chromatography to afford 2'-alkynylacetophenones as described separately in the SI. 2'-Alkynylacetophenone (1.0 equiv) was placed into a flame-dried 100 mL round bottomed flask with a stir bar. Then, the round bottom flask was capped with a septum, and the system was vacuumed under high vacuum. Then, the system was refilled with N_2 on a Schlenk line. Under N_2 on the Schlenk line, EtOH was added via a syringe to produce a 0.1 M solution. The resulting solution was cooled to $0^\circ C$. At $0^\circ C$, $NaBH_4$ (2.0–4.0 equiv) was added, and the reaction was stirred at $0^\circ C$ for 10 min. Then, the N_2 inlet from the Schlenk line was replaced with a N_2 -filled balloon, which was kept connected to the reaction round bottom flask until the end of this reaction. The reaction was then warmed to $25^\circ C$ and stirred at this temperature under N_2 18 h before it was quenched with saturated $NH_4Cl(aq)$ (20 mL), and the resulting organic layer was washed with brine (20 mL). Then, the aqueous layer was extracted with EtOAc (3×10 mL), followed by combining all organic layers. The combined organic layers were then dried over $MgSO_4$, and then filtered through a Celite[®] plug (Celite[®] in a medium glass frit funnel), and the filtrate was concentrated in vacuo to afford the crude product, which was then purified by flash column chromatography as described separately for each substrate below.

1-(2-(hex-1-yn-1-yl)phenyl)ethan-1-ol (9b): Prepared according to general procedure D (4.0 equiv $NaBH_4$ used), and purified by flash column chromatography (silica, 10% EtOAc in hexane) to afford a light yellow liquid (0.92 g, 91% yield). 1H NMR ($CDCl_3$, 500 MHz): δ 7.48 (d, $J = 7.9$ Hz, 1H), 7.38 (d, $J = 7.7$ Hz, 1H), 7.30 (t, $J = 7.6$ Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 5.29 (t, $J = 5.7$ Hz, 1H), 2.46 (t, $J = 7.1$ Hz, 2H), 2.19 (d, $J = 4.1$ Hz, 1H), 1.66–1.57 (m, 2H), 1.54–1.44 (m, 5H), 0.96 (t, $J = 7.3$ Hz, 3H). This spectrum is in agreement with previously reported spectral data.⁵⁸

1-(2-(6-chlorohex-1-yn-1-yl)phenyl)ethan-1-one (SI-3c): Prepared according to general procedure D, and purified by flash column chromatography (silica, 15% EtOAc in hexane) to afford an orange oil (0.61 g, 93% yield). The molecular structure was shown in the Supporting Information. 1H NMR ($CDCl_3$, 600 MHz): δ 7.69–7.65 (m, 1H), 7.49 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.41 (td, $J = 7.6$, 1.4 Hz, 1H), 7.35 (td, $J = 7.6$, 1.4 Hz, 1H), 3.74 (t, $J = 6.3$ Hz, 2H), 2.72–2.64 (m, 5H), 2.13–2.05 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 200.7, 141.1, 134.3, 131.3, 128.6, 127.9, 122.1, 94.3, 80.7, 43.8, 31.3, 30.0, 17.3. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{14}ClO$ ($[M+H]^+$) 221.0733, found 221.0738.

1-(2-(6-chlorohex-1-yn-1-yl)phenyl)ethan-1-ol (9c): Prepared according to general procedure D (4.0 equiv $NaBH_4$ used), and purified by flash column chromatography (silica,

20% EtOAc in hexane) to afford a light yellow liquid (0.45 g, 68% yield). 1H NMR ($CDCl_3$, 600 MHz): δ 7.50 (d, $J = 7.8$ Hz, 1H), 7.38 (d, $J = 7.6$, 1H), 7.32 (t, $J = 7.5$, 1H), 7.20 (td, $J = 7.5$, 1.3 Hz, 1H), 5.29 (q, $J = 6.1$ Hz, 1H), 3.72 (t, $J = 6.9$, 2H), 2.66 (t, $J = 6.8$ Hz, 2H), 2.28–1.98 (m, 3H), 1.51 (d, $J = 6.6$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 147.4, 132.5, 128.5, 127.1, 124.7, 120.8, 93.3, 79.4, 68.6, 43.8, 31.5, 24.0, 17.2. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{15}ClO$ ($[M+Na]^+$) 245.0709, found 245.0700.

1-(2-(cyclopropylethynyl)phenyl)ethan-1-one (SI-3d): Prepared according to general procedure D, and purified by flash column chromatography (silica, 10% EtOAc in hexane) to afford a yellow oil (0.34 g, 93% yield). The molecular structure was shown in the Supporting Information. 1H NMR ($CDCl_3$, 500 MHz): δ 7.66 (ddd, $J = 7.5$, 1.5, 0.5 Hz, 1H), 7.48–7.43 (m, 1H), 7.42–7.35 (m, 1H), 7.35–7.24 (m, 1H), 2.70 (s, 3H), 1.50 (tt, $J = 8.2$, 5.0 Hz, 1H), 0.95–0.80 (m, 4H). This spectrum is in agreement with previously reported spectral data.⁵⁹

1-(2-(cyclopropylethynyl)phenyl)ethan-1-ol (9d): Prepared according to general procedure D (2.0 equiv $NaBH_4$ used), and purified by flash column chromatography (silica, 15% EtOAc in hexane) to afford a yellow liquid (0.27 g, 76% yield). 1H NMR ($CDCl_3$, 500 MHz): δ 7.46 (dd, $J = 7.9$, 1.2 Hz, 1H), 7.35 (dd, $J = 7.7$, 0.8 Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.21–7.13 (m, 1H), 5.29–5.21 (m, 1H), 2.16 (d, $J = 4.2$ Hz, 1H), 1.53–1.44 (m, 4H), 0.94–0.85 (m, 2H), 0.87–0.75 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 147.5, 132.5, 128.2, 127.1, 124.7, 121.2, 98.9, 73.5, 68.7, 23.8, 8.9, 0.4. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{14}ONa$ ($[M+Na]^+$) 209.0942, found 209.0937.

2-(hex-1-yn-1-yl)benzaldehyde (SI-5): was prepared according to general procedure D, and purified by flash column chromatography (silica, 10% EtOAc in hexane) to afford a yellow liquid (0.40 g, 86% yield). The molecular structure was shown in the Supporting Information. 1H NMR ($CDCl_3$, 500 MHz): δ 10.54 (s, 1H), 7.89 (d, $J = 7.7$ Hz, 1H), 7.58–7.44 (m, 2H), 7.38 (t, $J = 7.3$ Hz, 1H), 2.49 (t, $J = 7.1$ Hz, 2H), 1.68–1.58 (m, 2H), 1.56–1.44 (m, 2H), 0.97 (t, $J = 7.4$, 1.6 Hz, 3H). This spectrum is in agreement with previously reported spectral data.⁶⁰

2,2,2-trifluoro-1-(2-(hex-1-yn-1-yl)phenyl)ethan-1-ol (9e): Prepared according to a modified reported procedure.⁶¹ In a N_2 -filled glovebox, 2-(hex-1-yn-1-yl)benzaldehyde (SI-5, 0.400 g, 2.15 mmol, 1.0 equiv) was dissolved into DME (10.8 mL, 0.200 M) in a flame-dried 100 mL round bottomed flask, followed by addition of CsF (0.163 g, 1.07 mmol, 0.50 equiv) and a stir bar. Then, the reaction flask was capped with a septum, and removed from the glovebox. The resulting solution was cooled to $0^\circ C$ under N_2 on a Schlenk line. Then, $TMSCF_3$ (0.32 mL, 2.2 mmol, 1.0 equiv) was added dropwise via a syringe, and the reaction was warmed to $25^\circ C$ and stirred under N_2 on the Schlenk line. Upon the full consumption of the starting material (ca. 17 h) as shown by TLC (ca. 10% EtOAc in hexane), the reaction was quenched by adding 10% $HCl(aq)$ (10 mL), and the aqueous layer was extracted with EtOAc (3×10 mL). The organic layers were combined and dried over $MgSO_4$. The drying agent was then removed via filtration through a Celite[®] plug (Celite[®] in a medium glass frit funnel), and the filtrate was concentrated in vacuo. The residue was purified via a flash column chromatography (silica, 10% EtOAc in hexane) to afford a yellow oil (0.37 g, 68% yield). 1H NMR ($CDCl_3$, 500 MHz): δ 7.59–7.53 (m, 1H), 7.45 (dd, J

= 7.0, 2.1 Hz, 1H), 7.39–7.28 (m, 2H), 5.63–5.54 (m, 1H), 2.85 (d, $J = 5.8$ Hz, 1H), 2.45 (t, $J = 7.1$ Hz, 2H), 1.66–1.43 (m, 4H), 0.96 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 135.4, 132.7, 129.2, 128.1, 127.5, 125.6, 123.9, 96.5, 77.7, 71.0 (q, $J = 32$ Hz), 30.8, 22.1, 19.3, 13.7. $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 , 565 MHz): δ -77.74 (d, $J = 6.8$ Hz). HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{O}$ ($[\text{M}-\text{H}]^-$) 255.0997, found 255.0999.

1-(5-fluoro-2-(hex-1-yn-1-yl)phenyl)ethan-1-one (SI-3f): Prepared according to general procedure D, and purified by flash column chromatography (silica, 5% EtOAc in hexane) to afford a brown liquid (0.47 g, 71% yield). The molecular structure was shown in the Supporting Information. ^1H NMR (CDCl_3 , 500 MHz): δ 7.46 (dd, $J = 8.6, 5.5$ Hz, 1H), 7.36–7.33 (m, 1H), 7.12–7.09 (m, 1H), 2.73 (s, 3H), 2.45 (t, $J = 7.1$ Hz, 2H), 1.64–1.52 (m, 2H), 1.54–1.42 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H). This spectrum is in agreement with previously reported spectral data.⁶²

1-(5-fluoro-2-(hex-1-yn-1-yl)phenyl)ethan-1-ol (9f): Prepared according to general procedure D (2.0 equiv NaBH_4 used), and purified by flash column chromatography (silica, 10% EtOAc in hexane) to afford a yellow oil (0.36 g, 76% yield). ^1H NMR (CDCl_3 , 500 MHz): δ 7.34 (dd, $J = 8.5, 5.7$ Hz, 1H), 7.22 (dd, $J = 9.9, 2.8$ Hz, 1H), 6.87 (td, $J = 8.3, 2.7$ Hz, 1H), 5.32–5.22 (m, 1H), 2.44 (t, $J = 7.0$ Hz, 2H), 2.11 (d, $J = 4.0$ Hz, 1H), 1.65–1.55 (m, 2H), 1.55–1.43 (m, 5H), 0.96 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 162.6 (d, $J = 248$ Hz), 150.3 (d, $J = 7$ Hz), 134.1 (d, $J = 8$ Hz), 117 (d, $J = 3$ Hz), 114 (d, $J = 22$ Hz), 112.1 (d, $J = 23$ Hz), 95.3, 77.4, 68.4, 30.9, 23.8, 22.2, 19.30, 13.7. $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 , 565 MHz): δ -111.08– -111.23 (m). HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{17}\text{FONa}$ ($[\text{M}+\text{Na}]^+$) 243.1161, found 243.1167.

4-Chloro-2-iodo-*N*-methoxy-*N*-methylbenzamide (SI-7): was prepared according to a modified reported procedure.⁶³ The molecular structure was shown in the Supporting Information. A 100 mL flame-dried septum-capped round bottom flask containing a stir bar was prepared. Then, 4-chloro-2-iodobenzoic acid (**SI-6**) (1.41 g, 5.00 mmol, 1.0 equiv) was placed in the 100 mL round bottom flask, followed by capping the system with a septum. Then, the system was vacuumed under high vacuum, and refilled with N_2 on a Schlenk line. Then, MeCN (21 mL, 0.2 M) was added under N_2 on the Schlenk line. To the resulting solution, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM; 1.66 g, 6.00 mmol, 1.2 equiv), *N*-methylmorpholine (1.0 mL, 10.0 mmol, 2.0 equiv), and MeO(Me)NH \cdot HCl (0.585 g, 6.0 mmol, 1.2 equiv) were quickly added, respectively, under N_2 on the Schlenk line at 25 °C after the septum was briefly removed. Once the addition of chemicals was done, the septum was quickly returned. Then, the resulting mixture was stirred at 25 °C under N_2 with a N_2 -filled balloon for 18 h. Then, the solvent was removed in vacuo, and the resulting residue was dissolved in EtOAc (20 mL). The new solution was washed with 1 M HCl(aq) (1 \times 20 mL), deionized H_2O (1 \times 15 mL), and brine (1 \times 15 mL). The aqueous phases were combined and extracted with EtOAc (1 \times 15 mL), followed by combining all resulting organic phases. The combined organic phases were then dried over MgSO_4 , and then filtered through a Celite® plug (Celite® in a medium glass frit funnel). The filtrate was concentrated in vacuo to afford the crude product, which was purified by flash column chromatography (40% EtOAc in hexane) to afford a light yellow oil (1.5 g, 93%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.84 (d,

$J = 2.0$ Hz, 1H), 7.37 (dd, $J = 8.2, 2.0$ Hz, 1H), 7.19 (d, $J = 8.2$ Hz, 1H), 4.98–2.47 (m, 6H). This spectrum is in agreement with previously reported spectral data.⁶⁴

4-chloro-2-(hex-1-yn-1-yl)-*N*-methoxy-*N*-methylbenzamide (SI-8): was prepared according to general procedure D from **SI-7**, and purified by flash column chromatography (silica, 30% EtOAc in hexane) to afford a brown oil (1.2 g, 92% yield). The molecular structure was shown in the Supporting Information. ^1H NMR (CDCl_3 , 600 MHz): δ 7.41 (d, $J = 2.0$ Hz, 1H), 7.33–7.20 (m, 2H), 3.41 (br d, $J = 109.2$ Hz, 6H), 2.40 (dd, $J = 7.4, 6.7$ Hz, 2H), 1.61–1.52 (m, 2H), 1.50–1.36 (m, 2H), 0.93 (td, $J = 7.3, 0.7$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 168.5, 136.4, 134.0, 131.2, 127.1, 122.7, 95.1, 76.5, 60.5, 31.8, 30.0, 21.3, 18.5, 13.0. HRMS (ESI-TOF) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{ClNO}_2$ ($[\text{M}+\text{H}]^+$) 280.1104, found 280.1100.

1-(4-chloro-2-(hex-1-yn-1-yl)phenyl)ethan-1-one (SI-9): was prepared according to a modified literature procedure.⁶⁵ The molecular structure was shown in the Supporting Information. To a solution of **SI-8** (1.19 g, 4.25 mmol, 1.0 equiv) in dry THF (21 mL, 0.2 M) in a 100 mL flame-dried septum-capped round bottom flask with a stir bar was added MeMgBr (2.1 mL of a 3.0 M Et_2O solution, 6.37 mmol, 1.5 equiv) dropwise via a syringe at 0 °C under N_2 on a Schlenk line. The resulting solution was warmed to 25 °C, and stirred at this temperature for 2.0 h under N_2 on the Schlenk line. Then, the reaction was quenched with saturated NH_4Cl (aq) (20 mL). The resulting organic layer was washed with brine (20 mL). Then, the aqueous layer was extracted with EtOAc (3 \times 15 mL), followed by combining all organic layers. The combined organic layers were then dried over MgSO_4 , and then filtered through a Celite® plug (Celite® in a medium glass frit funnel), and the filtrate was concentrated in vacuo to afford the crude product, which was then purified by flash column chromatography (10% EtOAc in hexane) to afford a yellow oil (0.73 g, 73%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.63 (d, $J = 8.4$ Hz, 1H), 7.47 (d, $J = 2.1$ Hz, 1H), 7.29 (dd, $J = 8.4, 2.1$ Hz, 1H), 2.70 (s, 3H), 2.46 (t, $J = 7.1$ Hz, 2H), 1.77–1.57 (m, 2H), 1.52–1.41 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 126 MHz): δ 200.0, 139.2, 137.5, 133.8, 130.1, 128.0, 124.5, 98.6, 79.0, 30.5, 30.2, 22.2, 19.5, 13.7. HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{15}\text{ClONa}$ ($[\text{M}+\text{Na}]^+$) 257.0709, found 257.0711

1-(4-chloro-2-(hex-1-yn-1-yl)phenyl)ethan-1-ol (9g): Prepared according to general procedure D from **SI-9** (3.0 equiv NaBH_4 used), and purified by flash column chromatography (silica, 10% EtOAc in hexane) to afford a colorless oil (0.62 g, 84% yield). ^1H NMR (CDCl_3 , 500 MHz): δ 7.43 (d, $J = 8.4$ Hz, 1H), 7.35 (d, $J = 2.3$ Hz, 1H), 7.31–7.21 (m, 1H), 5.25 (qd, $J = 6.4, 3.4$ Hz, 1H), 2.45 (t, $J = 7.1$ Hz, 2H), 2.09 (d, $J = 3.8$ Hz, 1H), 1.69–1.55 (m, 2H), 1.53–1.42 (m, 5H), 0.96 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 126 MHz): δ 145.9, 132.6, 132.0, 128.3, 126.2, 123.0, 97.1, 77.3, 68.2, 30.8, 24.0, 22.2, 19.4, 13.7. HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{17}\text{ClONa}$ ($[\text{M}+\text{Na}]^+$) 259.0865, found 259.0868.

1-(2-(hex-1-yn-1-yl)phenyl)-2-methylpropan-1-ol (9h): Prepared according to reported procedure.⁶⁵ A solution of **SI-5** (0.452 g, 2.43 mmol, 1.00 equiv) in dry THF (4.8 mL, 0.50 M) in a 100 mL flame-dried septum-capped round bottom flask equipped with a stir bar was cooled to 0 °C under N_2 on a Schlenk line. To the cooled solution, $^i\text{PrMgBr}$ (2.9 mL of a 1.0 M THF solution, 2.9 mmol, 1.2 equiv) was added dropwise at 0 °C via a syringe. The resulting solution was warmed to

25 °C, and stirred at this temperature for 2.0 h under N₂. Then, the reaction was quenched with saturated NH₄Cl(aq) (20 mL), and the resulting organic layer was washed with brine (20 mL). Then, the aqueous layer was extracted with EtOAc (3 × 10 mL), followed by combining all organic layers. The combined organic layers were then dried over MgSO₄, and then filtered through a Celite® plug (Celite® in a medium glass frit funnel), and the filtrate was concentrated in vacuo to afford the crude product, which was then purified by flash column chromatography (15% EtOAc in hexane) to afford a yellow oil (0.12 g, 21%). ¹H NMR (CDCl₃, 600 MHz): δ 7.44–7.39 (m, 1H), 7.37 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.32–7.26 (m, 1H), 7.18 (td, *J* = 7.6, 1.4 Hz, 1H), 4.84 (dd, *J* = 6.6, 4.7 Hz, 1H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.18–2.06 (m, 1H), 2.03 (dd, *J* = 4.8, 0.7 Hz, 1H), 1.71–1.56 (m, 2H), 1.53–1.43 (m, 2H), 1.00 (d, *J* = 6.7 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H). ¹³C{¹H}NMR (CDCl₃, 151 MHz): δ 145.6, 132.4, 127.8, 126.9, 126.4, 122.0, 95.6, 78.9, 77.8, 34.7, 31.0, 22.2, 19.7, 19.4, 17.8, 13.8. HRMS (ESI-TOF) *m/z* calcd for C₁₆H₂₂ONa ([M+Na]⁺) 253.1568, found 253.1563.

(2-(phenylethynyl)phenyl)methanol (**9i**): Prepared according to general procedure C, and purified by flash column chromatography (silica, 15% EtOAc in hexane) to afford a light yellow solid, and the resulting solid was further purified with hot hexane (ca. 40–60 °C, ca. 3 mL) to afford a white solid (0.58 g, 56% yield). ¹H NMR (CDCl₃, 500 MHz): δ 7.61–7.45 (m, 4H), 7.42–7.34 (m, 4H), 7.30 (t, *J* = 7.3 Hz, 1H), 4.93 (d, *J* = 6.5 Hz, 2H), 2.07 (t, *J* = 6.4 Hz, 1H). This spectrum is in agreement with previously reported spectral data.⁵⁶

General Experimental Procedure E for the Synthesis of pinacol boronates 12. In a N₂-filled glovebox, to a one-dram vial containing alkynyl benzylic alcohols (0.400 mmol, 1.0 equiv) was added HBcat (42.6 μL, 0.400 mmol, 1.0 equiv), followed by rinsing walls of the vial with 0.05 mL toluene, and the resulting solution was left in the glovebox uncapped to allow the release of H₂ gas at 25 °C for 1.5 h. Then, the resulting substrate solution was transferred to a separate one-dram vial containing IPrAuTFA (7.0 mg, 0.010 mmol, 2.5 mol %) and a stir bar, followed by rinsing the first one-dram vial with 3.5 mL toluene, and the rinse was combined with the reaction solution in the second one-dram vial. The reaction vial was capped. Then, the reaction mixture was heated to 100 °C (or 120 °C for **10e**) with stirring at this temperature for 4 h (18 h for **10e**, and 19 h for **10g**). The resulting solution was cooled to 25 °C, followed by addition of 1,8-diaminonaphthalene (126 mg, 0.800 mmol, 2.0 equiv) and Et₃N (0.84 mL, 6.0 mmol, 15 equiv). The vial used for weighting 1,8-diaminonaphthalene was rinsed with 0.20 mL toluene, and the resulting solution was combined with the reaction solution, followed by capping the reaction vial again. The reaction was stirred at 25 °C for 18 h. Once the isolation reaction was done as determined by TLC (20–40% DCM in hexane), the reaction vial was removed from the glovebox, and the reaction was quenched with saturated NH₄Cl(aq) (5 mL). Then, the resulting organic layer was washed with brine (5 mL). The aqueous layer was then extracted with EtOAc (3 × 5 mL), followed by combining all organic layers. The combined organic layers were then dried over MgSO₄, which was then filtered with a Celite® plug (Celite® in an M glass frit funnel), and the filtrate was concentrated in vacuo to afford the crude product, which was then purified by flash column chromatography.

2-(3-butyl-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (**12a**): Prepared accord-

ing to general procedure E, and purified by flash column chromatography (silica, 35% DCM in hexane) to afford a white foam (0.048 g, 34% yield). ¹H NMR (CDCl₃, 500 MHz): δ 7.23–7.12 (m, 5H), 7.09 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.06–7.01 (m, 1H), 6.35 (dd, *J* = 7.2, 1.1 Hz, 2H), 5.84 (s, 2H), 5.06 (s, 2H), 2.56–2.20 (m, 2H), 1.61 (tt, *J* = 8.9, 6.8 Hz, 2H), 1.40 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H}NMR (CDCl₃, 151 MHz): δ 161.4, 141.3, 136.5, 133.9, 128.3, 127.7, 127.7, 125.9, 124.1, 123.7, 119.9, 117.9, 106.0, 68.6, 34.3, 30.5, 29.8, 22.6, 14.1. ¹¹B{¹H}NMR (CDCl₃, 193 MHz): δ 30.21. HRMS (ESI-TOF) *m/z* calcd for C₂₃H₂₄BN₂O ([M+H]⁺) 355.1986, found 355.1979.

2-(3-butyl-1-methyl-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (**12b**): Prepared according to general procedure E, and purified by flash column chromatography (silica, 25% DCM in hexane) to afford a white solid (0.114 g, 78% yield). ¹H NMR (CDCl₃, 600 MHz): δ 7.20–7.11 (m, 6H), 7.08 (d, *J* = 8.2 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.35 (d, *J* = 7.2 Hz, 2H), 5.83 (s, 2H), 5.20 (q, *J* = 6.5 Hz, 1H), 3.05–2.12 (m, 2H), 1.70–1.58 (m, 5H), 1.49–1.35 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H}NMR (CDCl₃, 151 MHz): δ 159.6, 141.4, 136.5, 133.1, 132.1, 127.9, 127.6, 126.0, 124.0, 123.5, 119.9, 117.9, 106.0, 73.6, 34.5, 30.3, 22.6, 20.0, 14.1. ¹¹B{¹H}NMR (CDCl₃, 193 MHz): δ 30.05. HRMS (ESI-TOF) *m/z* calcd for C₂₄H₂₅BN₂O ([M]⁺) 368.2065, found 368.2066.

2-(3-(3-chloropropyl)-1-methyl-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (**12c**): Prepared according to general procedure E, and purified by flash column chromatography (silica, 25% DCM in hexane) to afford a white solid (0.098 g, 63% yield). ¹H NMR (CDCl₃, 600 MHz): δ 7.23–7.13 (m, 5H), 7.08 (dd, *J* = 15.2, 6.9 Hz, 3H), 6.36 (d, *J* = 7.3 Hz, 2H), 5.93 (s, 2H), 5.22 (q, *J* = 6.6 Hz, 1H), 3.63 (t, *J* = 5.8 Hz, 2H), 2.62–2.50 (m, 2H), 2.19–2.07 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3H). ¹³C{¹H}NMR (CDCl₃, 151 MHz): δ 157.3, 141.3, 136.4, 132.8, 132.1, 128.0, 127.7, 126.4, 124.3, 123.5, 119.9, 117.9, 106.0, 73.7, 44.5, 31.6, 30.3, 19.9. ¹¹B{¹H}NMR (CDCl₃, 193 MHz): δ 30.01. HRMS (ESI-TOF) *m/z* calcd for C₂₃H₂₂BClN₂ONa ([M+Na]⁺) 411.1416, found 411.1403.

2-(3-cyclopropyl-1-methyl-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (**12d**): Prepared according to general procedure E, and purified by flash column chromatography (silica, 25% DCM in hexane) to afford a white foam (0.086 g, 61% yield). ¹H NMR (CDCl₃, 500 MHz): δ 7.22–7.10 (m, 5H), 7.07 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.36 (dd, *J* = 7.3, 1.1 Hz, 2H), 5.94 (s, 2H), 5.09 (q, *J* = 6.5 Hz, 1H), 1.89–1.80 (m, 1H), 1.54 (d, *J* = 6.5 Hz, 3H), 1.03–0.92 (m, 2H), 0.76–0.61 (m, 2H). ¹³C{¹H}NMR (CDCl₃, 151 MHz): δ 158.8, 141.5, 136.5, 133.4, 132.1, 128.0, 127.7, 125.6, 123.5, 123.4, 119.9, 117.9, 106.0, 73.6, 29.9, 19.6, 14.3, 5.9, 5.2. ¹¹B{¹H}NMR (CDCl₃, 193 MHz): δ 30.23. HRMS (ESI-TOF) *m/z* calcd for C₂₃H₂₁BN₂O ([M]⁺) 352.1751, found 352.1741.

2-(3-butyl-1-(trifluoromethyl)-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (**12e**): Prepared according to general procedure E, and purified by flash column chromatography (silica, 25% DCM in hexane) to afford a white foam (0.119 g, 70% yield). ¹H NMR (CDCl₃, 500 MHz): δ 7.23 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.10 (dd, *J* = 9.3, 6.2 Hz, 3H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.29 (d, *J* = 7.4 Hz, 2H), 5.73 (s, 2H), 5.45 (q, *J* = 7.6 Hz, 1H), 2.59–2.15 (m, 2H), 1.79–1.49 (m, 2H), 1.42–1.24 (m, 2H),

0.90 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 157.8, 141.1, 136.4, 133.1, 130.1, 127.8, 127.1, 126.4, 124.9, 123.0, 120.6, 120.0, 118.1, 106.2, 74.5 (q, $J = 32$ Hz), 34.22, 29.87, 22.41, 14.03. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 193 MHz): δ 29.59. ^{19}F NMR (CDCl_3 , 565 MHz): δ -78.48 (d, $J = 7.3$ Hz). HRMS (ESI-TOF) m/z calcd for $\text{C}_{24}\text{H}_{22}\text{BF}_3\text{N}_2\text{O}$ ($[\text{M}]^+$) 422.1782, found 422.1792.

2-(3-butyl-7-fluoro-1-methyl-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (12f): Prepared according to general procedure E, and purified by flash column chromatography (silica, 25% DCM in hexane) to afford a white solid (0.120 g, 77% yield). ^1H NMR (CDCl_3 , 600 MHz): δ 7.17 (td, $J = 7.8, 2.0$ Hz, 2H), 7.14–7.09 (m, 3H), 6.87 (tt, $J = 8.6, 2.3$ Hz, 1H), 6.79 (dt, $J = 9.1, 2.4$ Hz, 1H), 6.37 (dd, $J = 7.2, 1.8$ Hz, 2H), 6.02–5.73 (m, 2H), 5.16 (q, $J = 6.5$ Hz, 1H), 2.40–2.31 (m, 2H), 1.75–1.53 (m, 5H), 1.45–1.37 (m, 2H), 1.00 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 161.3 (d, $J = 245$ Hz), 158.7 (d, $J = 2$ Hz), 141.2, 136.3, 134.1 (d, $J = 7$ Hz), 129.2 (d, $J = 3$ Hz), 127.7, 125.4 (d, $J = 7.6$ Hz), 119.8, 117.9, 114.3 (d, $J = 21$ Hz), 110.7 (d, $J = 23$ Hz), 106.0, 73.1 (d, $J = 2$ Hz), 34.3, 30.2, 22.5, 19.6, 14.2. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 193 MHz): δ 30.29. $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3 , 565 MHz): δ -115.93– -116.15 (m). HRMS (ESI-TOF) m/z calcd for $\text{C}_{24}\text{H}_{24}\text{BFN}_2\text{O}$ ($[\text{M}]^+$) 386.1970, found 386.1966.

2-(3-butyl-6-chloro-1-methyl-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (12g): Prepared according to general procedure E, and purified by flash column chromatography (silica, 25% DCM in hexane) to afford a white solid (0.108 g, 67% yield). ^1H NMR (CDCl_3 , 600 MHz): δ 7.17 (t, $J = 7.8$ Hz, 2H), 7.11 (dd, $J = 7.0, 2.5$ Hz, 4H), 6.96 (d, $J = 8.4$ Hz, 1H), 6.38 (d, $J = 7.2$ Hz, 2H), 5.83 (s, 2H), 5.17 (q, $J = 6.5$ Hz, 1H), 2.35 (tt, $J = 9.9, 5.0$ Hz, 2H), 1.79–1.52 (m, 5H), 1.39 (sext, $J = 7.4$ Hz, 2H), 0.94 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 160.9, 141.2, 136.4, 135.1, 133.6, 130.2, 127.8, 125.7, 124.7, 123.7, 119.9, 118.1, 106.2, 73.3, 34.5, 30.2, 22.5, 19.9, 14.2. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 193 MHz): δ 30.09. HRMS (ESI-TOF) m/z calcd for $\text{C}_{24}\text{H}_{24}\text{BClN}_2\text{O}$ ($[\text{M}]^+$) 402.1674, found 402.1677.

2-(3-butyl-1-isopropyl-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (12h): Prepared according to general procedure E, and purified by flash column chromatography (silica, 25% DCM in hexane) to afford a white solid (0.108 g, 67% yield). ^1H NMR (CDCl_3 , 600 MHz): δ 7.13–7.05 (m, 5H), 7.03 (d, $J = 8.3$ Hz, 2H), 6.93 (d, $J = 7.3$ Hz, 1H), 6.27 (d, $J = 7.2$ Hz, 2H), 5.74 (s, 2H), 4.76 (d, $J = 6.6$ Hz, 1H), 2.33 (td, $J = 7.3, 4.1$ Hz, 2H), 2.27–2.18 (m, 1H), 1.70–1.52 (m, 2H), 1.44–1.29 (m, 2H), 1.07 (d, $J = 6.7$ Hz, 3H), 0.97–0.83 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 159.4, 141.4, 136.4, 133.4, 129.4, 127.8, 127.7, 125.5, 125.3, 124.0, 119.9, 117.8, 106.0, 82.8, 34.7, 31.3, 30.2, 22.6, 19.4, 18.1, 14.1. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 193 MHz): δ 29.93. HRMS (ESI-TOF) m/z calcd for $\text{C}_{26}\text{H}_{30}\text{BN}_2\text{O}$ ($[\text{M}+\text{H}]^+$) 397.2456, found 397.2425.

2-(3-phenyl-1H-isochromen-4-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (12i): Prepared according to general procedure E, and purified by flash column chromatography (silica, 10% EtOAc in hexane) to afford a white solid (0.036 g, 24% yield). ^1H NMR (CDCl_3 , 600 MHz): δ 7.87–7.78 (m, 2H), 7.45 (dd, $J = 7.6, 1.3$ Hz, 1H), 7.42–7.36 (m, 3H), 7.35–26 (m, 3H), 7.25–7.15 (m, 2H), 7.13 (d, $J = 8.2$ Hz, 2H), 6.31 (d, $J = 7.1$ Hz, 2H), 5.83 (s, 2H), 5.29 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 157.9, 141.1, 136.4,

136.3, 134.0, 129.2, 128.5, 128.4, 128.4, 128.2, 127.7, 127.7, 126.7, 124.4, 124.2, 119.8, 117.9, 106.1, 68.9. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 193 MHz): δ 30.30. HRMS (ESI-TOF) m/z calcd for $\text{C}_{25}\text{H}_{19}\text{BN}_2\text{O}$ ($[\text{M}]^+$) 374.1595, found 374.1586.

3-butyl-4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-1H-isochromene (14a): Prepared according to a literature procedure from compound **11a**.⁹ Compound **11a** was prepared according to general procedure E. In a N_2 -filled glovebox, pinacol (0.142 g, 1.20 mmol, 3.0 equiv) was dissolved into Et_3N (0.84 mL, 3.0 mmol, 15 equiv), and the resulting solution was transferred to **11a**. The resulting reaction solution was capped and stirred in the glovebox for 1 h at 25 °C. Then, the reaction vial was removed from the glovebox, and the solvent was removed in vacuo. The resulting residue was purified by flash chromatography (15% DCM in hexane) to afford a yellow oil (0.070 g, 56% yield). ^1H NMR (CDCl_3 , 500 MHz): δ 7.69 (d, $J = 7.8$ Hz, 1H), 7.29–7.21 (m, 1H), 7.15–7.08 (m, 1H), 6.99 (d, $J = 7.4$ Hz, 1H), 4.98 (s, 2H), 2.63 (t, $J = 7.6$ Hz, 2H), 1.67–1.57 (m, 2H), 1.46–1.32 (m, 2H), 1.38 (s, 12H), 0.97 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 126 MHz): δ 170.8, 133.9, 128.1, 127.6, 125.4, 124.6, 123.6, 83.0, 68.9, 33.5, 31.2, 25.0, 22.68, 14.1. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 160 MHz): δ 31.75.

2-(3-butyl-1-methyl-1H-isochromen-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14b): Prepared according to a literature procedure from compound **11b**.⁹ Compound **11b** was prepared according to general procedure E. In a N_2 -filled glovebox, pinacol (70.9 mg, 0.600 mmol, 3.0 equiv) was dissolved into Et_3N (0.42 mL, 3.0 mmol, 15 equiv), and the resulting solution was transferred to **11b**. The resulting reaction solution was stirred in the glovebox for 1 h at 25 °C. Then, the reaction vial was removed from the glovebox, and the solvent was removed in vacuo. The resulting residue was purified by flash chromatography (5% to 100% DCM in hexane) to afford a yellow oil (22.3 mg, 34% yield). ^1H NMR (CDCl_3 , 600 MHz): δ 7.65 (dd, $J = 7.9, 1.1$ Hz, 1H), 7.20 (td, $J = 7.6, 1.4$ Hz, 1H), 7.11 (td, $J = 7.4, 1.2$ Hz, 1H), 6.98 (d, $J = 7.4$ Hz, 1H), 5.09 (q, $J = 6.5$ Hz, 1H), 2.73–2.44 (m, 2H), 1.65–1.53 (m, 5H), 1.44–1.30 (m, 14H), 0.94 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 169.0, 133.2, 132.0, 127.8, 125.5, 124.9, 122.9, 83.0, 74.0, 33.7, 30.9, 25.0, 22.7, 19.6, 14.1. $^{11}\text{B}\{^1\text{H}\}$ NMR (CDCl_3 , 193 MHz): δ 31.37.

1-(2-(hex-1-yn-1-yl)phenyl)ethan-1-one (16): Prepared according to general procedure D, and purified by flash column chromatography (silica, 10% EtOAc in hexane) to afford a brown oil (0.92 g, 92% yield). ^1H NMR (CDCl_3 , 500 MHz): δ 7.68–7.62 (m, 1H), 7.48 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.39 (td, $J = 7.5, 1.5$ Hz, 1H), 7.32 (td, $J = 7.6, 1.4$ Hz, 1H), 2.72 (s, 3H), 2.46 (t, $J = 7.1$ Hz, 2H), 1.66–1.56 (m, 2H), 1.54–1.43 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 151 MHz): δ 201.3, 141.2, 134.1, 131.2, 128.4, 127.7, 122.6, 97.0, 79.8, 30.7, 30.2, 22.2, 19.6, 13.8. HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{16}\text{ONa}$ ($[\text{M}+\text{Na}]^+$) 223.1099, found 223.1096.

Structure elucidation. Oxyboration was performed according to general procedure E, except the isolation portion in the general procedure E was not conducted. Instead, after cyclization, 1 M HCl(aq) (10 mL) was used to quench the reaction and to protodeborate the product in situ. Then, the organic layer was washed with brine (1 × 15 mL), and all aqueous layers were combined and extracted with EtOAc (3 × 5 mL). The organic layers were combined. The combined organic phases were then dried over MgSO_4 , and then filtered through a Celite[®] plug (Celite[®] in a medium glass frit funnel), and the filtrate was concentrated in vacuo to afford the crude product.

An ^1H NMR spectrum of the crude reaction mixture showed only one regioisomer of product. The crude product was then purified by flash column chromatography (15% EtOAc in hexane) to afford a light yellow oil (0.041 g, 50%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.17 (td, $J = 7.4$, 1.3 Hz, 1H), 7.11 (td, $J = 7.5$, 1.4 Hz, 1H), 6.99 (d, $J = 7.3$ Hz, 1H), 6.92 (dd, $J = 7.4$, 1.3 Hz, 1H), 5.61 (s, 1H), 5.20 (q, $J = 6.5$ Hz, 1H), 2.18 (t, $J = 7.5$ Hz, 2H), 1.81–1.49 (m, 5H), 1.46–1.34 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 126 MHz): δ 157.2, 131.8, 131.4, 127.8, 125.8, 123.3, 122.7, 100.3, 74.1, 33.7, 29.2, 22.5, 19.9, 14.1. This spectrum was in agreement with previously reported spectral data for **15** by a different laboratory.¹⁰

For further analysis, likely compound **15** (or perhaps **17**) (0.0408 g, 0.200 mmol, 1.0 equiv) made in the previous step was dissolved in DCM (2.5 mL, 0.08 M) in a one dram vial with a stir bar, and the resulting solution was cooled to -78 °C. Then, O_3 was passed through the cooled solution until the solution became dark blue (ca. 5 min.). To the resulting dark blue solution, a solution of PPh_3 (0.0682 g, 0.260 mmol, 1.3 equiv) in DCM (0.7 mL, 0.4 M) as a quench was added dropwise at -78 °C, and the resulting solution was stirred at 25 °C for 3 h. Then, the solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography (5% EtOAc in hexane) to afford a transparent oil (0.022 g, 47%). ^1H NMR (CDCl_3 , 500 MHz): δ 10.27 (s, 1H), 7.90–7.76 (m, 1H), 7.66–7.54 (m, 2H), 7.46 (ddd, $J = 7.4$, 6.1, 2.5 Hz, 1H), 6.67 (q, $J = 6.6$ Hz, 1H), 2.35 (td, $J = 7.6$, 3.6 Hz, 2H), 1.77–1.49 (m, 5H), 1.44–1.29 (m, 2H), 0.91 (t, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 126 MHz): δ 192.5, 172.9, 144.8, 134.2, 133.1, 132.7, 128.0, 126.1, 68.7, 34.4, 27.1, 22.9, 22.4, 13.8. HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 257.1154, found 257.1154. These spectra indicated the product to be **18**, and ^1H NMR spectral information of both the crude and purified fractions did not match previously reported spectra of **19**¹¹ or **20**¹². It was concluded that the only product was **18**.

Hydroboration-Oxyboration. In a N_2 -filled glovebox, to a one-dram vial containing **16** (0.0801 g, 0.400 mmol, 1.0 equiv) was added HBcat (85.2 μL , 0.800 mmol, 2.0 equiv) and a stir bar. The walls of the vial were rinsed with 0.05 mL toluene, and the vial was capped. Then, the resulting solution was heated at 50 °C for 5.0 h with stirring. Then, the resulting solution was concentrated under high vacuum (ca. 10 mTorr) for 1.5 h at 25 °C in the glovebox. This process completed the hydroboration step.

In a separate one-dram vial in the glovebox, IPrAuTFA (7.0 mg, 0.010 mmol, 2.5 mol %) was dissolved into 0.4 mL toluene, and the resulting catalyst solution was transferred into the substrate vial containing the hydroboration product, and a stir bar was added. The reaction vial was then capped. The reaction mixture was heated to 100 °C with stirring for 4 h. This process completed the oxyboration step.

In order to replace Beat with Bdan , the resulting solution was cooled to 25 °C, followed by addition of 1,8-diaminonaphthalene (126 mg, 0.800 mmol, 2.0 equiv) and Et_3N (0.84 mL, 6.0 mmol, 15 equiv). The vial used for weighting 1,8-diaminonaphthalene was rinsed with 0.20 mL toluene, and the rinse was combined with the reaction solution. The reaction vial was capped again, and the reaction was stirred at 25 °C for 18 h. Once the exchange reaction was done, the reaction vial was removed from the glovebox, and the reaction mixture was quenched with saturated NH_4Cl (aq)

(5 mL). The resulting organic layer was washed with brine (5 mL). Then, the aqueous layer was extracted with EtOAc (3 \times 5 mL), followed by combining all organic layers. The combined organic layers were then dried over MgSO_4 , and then filtered through a Celite[®] plug (Celite[®] in an M glass frit funnel), and the filtrate was concentrated in vacuo to afford the crude product, which was then purified by flash column chromatography (silica, 25% DCM in hexane) to afford a white solid (0.100 g, 68% yield). ^1H NMR spectroscopic data matched that previously obtained from **12b** (see above).

5-propyl-4-(p-tolyl)-2,3-dihydrofuran (22) Compound **3a** was prepared according to the procedure described above, except for the isolation step, and stored in a vial in d_8 -toluene inside the N_2 -filled glovebox without purification. The concentration of the solution of **3a** was calculated by ^1H NMR spectroscopy using an internal standard. Phenanthrene as internal standard (4.5 mg, 0.025 mmol) was dissolved in d_8 -toluene (0.4 mL) in a 1-dram vial. To this solution was added a small aliquot of **3a** in d_8 -toluene (10. μL) using gas-tight syringe. The mixture was then transferred to a J. Young tube and removed from glovebox. The concentration of the stock solution of **3a** was calculated based on the integration ratio between the known phenanthrene and the unknown stock solution using ^1H NMR spectroscopy. This solution was used in the next step.

The cross-coupling procedure was adapted from a literature procedure.⁵⁰ In a N_2 -filled glovebox, to a one-dram vial (“reaction vial”) containing 4-iodotoluene (43.6 mg, 0.200 mmol, 1.0 equiv) was added $\text{CsOH}\cdot\text{H}_2\text{O}$ (100.8 mg, 0.6002 mmol, 3.0 equiv) and **3a** from the stock solution above (0.240 mmol, 1.2 equiv) via gas-tight syringe. XPHOS-Pd-G3 (6.8 mg, 0.0080 mmol, 0.040 equiv) was dissolved in THF (0.1 mL) and transferred via pipet to the reaction vial. The vial containing the Pd catalyst was rinsed with THF (0.1 mL) and the rinse was also added via pipet to the reaction vial. A stir bar was added to the reaction vial. The vial was capped and the solution was stirred at 25 °C for 2.5 d. Then the reaction vial was removed from glovebox and solution was diluted with Et_2O (1 mL). The reaction mixture was filtered through a pad of Celite[®]. The reaction vial and the Celite[®] were rinsed with Et_2O (2 mL). The filtrate was concentrated in vacuo, and purified by flash chromatography (30% DCM in hexane) to afford a colorless oil (31 mg, 77% yield). TLC (40% DCM/hexanes): $R_f = 0.53$, visualized by UV absorbance. ^1H NMR (CDCl_3 , 500 MHz): δ 7.13 (m, 4H), 4.34 (t, $J = 9.0$ Hz, 2H), 3.00 (t, $J = 9.0$ Hz, 2H), 2.36 (t, $J = 8.0$ Hz, 2H), 2.33 (s, 3H), 1.62 (sext, $J = 7.5$ Hz, 2H), 0.96 (t, $J = 7.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 154.1, 134.9, 133.4, 129.1, 126.3, 108.2, 68.0, 34.2, 29.3, 21.2, 20.7, 14.1. HRMS (CI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ ($[\text{M}]^+$) 202.1358, found 202.1355.

5-(2-propyl-4,5-dihydrofuran-3-yl)benzo[d][1,3]dioxole (24): Compound **3a** was prepared according to the procedure described above, except for the isolation step, and stored in a vial in d_8 -toluene inside the N_2 -filled glovebox without purification. The concentration of the solution of **3a** was calculated by ^1H NMR spectroscopy using an internal standard. Phenanthrene as internal standard (4.5 mg, 0.025 mmol) was dissolved in d_8 -toluene (0.4 mL) in a 1-dram vial. To this solution was added a small aliquot of **3a** in d_8 -toluene (10. μL) using gas-tight syringe. The mixture was then transferred to a J. Young tube and removed from glovebox. The concentration of the stock solution of **3a** was calculated based on the integration ratio between the known phenanthrene and the unknown

stock solution using ^1H NMR spectroscopy. This solution was used in the next step.

The cross-coupling procedure was adapted from a literature procedure.⁵⁰ In a N_2 -filled glovebox, to a one-dram vial ("reaction vial") containing **23** (49.6 mg, 0.200 mmol, 1.0 equiv) was added $\text{CsOH}\cdot\text{H}_2\text{O}$ (100.8 mg, 0.6002 mmol, 3.0 equiv) and **3a** from the stock solution above (0.240 mmol, 1.2 equiv) via gas-tight syringe. XPHOS-Pd-G3 (6.8 mg, 0.0080 mmol, 0.040 equiv) was dissolved in THF (0.1 mL) and transferred via pipet to the reaction vial. The vial containing the Pd catalyst was rinsed with THF (0.1 mL) and the rinse was also added via pipet to the reaction vial. A stir bar was added to the reaction vial. The vial was capped and the solution was stirred at 25 °C for 2.5 d. Then the reaction vial was removed from glovebox and solution was diluted with Et_2O (1 mL). The reaction mixture was filtered through a pad of Celite[®]. The reaction vial and the Celite[®] were rinsed with Et_2O (2 mL). The filtrate was concentrated in vacuo and purified by flash chromatography (30% DCM in hexane) to afford a colorless oil (26 mg, 56% yield). TLC (40% DCM/hexanes): R_f = 0.45, visualized by UV absorbance. ^1H NMR (CDCl_3 , 500 MHz): δ 6.78 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 1.5 Hz, 1H), 6.68 (dd, J = 8.0, 1.5 Hz, 1H), 5.94 (s, 2H), 4.32 (t, J = 9.5 Hz, 2H), 2.96 (t, J = 9.5 Hz, 2H), 2.33 (t, J = 7.5 Hz, 2H), 1.60 (sext, J = 7.5 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 154.1, 134.9, 133.4, 129.1, 126.3, 108.2, 68.0, 34.2, 29.3, 21.2, 20.7, 14.1. HRMS (ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{17}\text{O}_3$ ($[\text{M}+\text{H}]^+$) 233.1178, found 233.1181.

1-(4-(3-butyl-1-methyl-1H-isochromen-4-yl)phenyl)ethan-1-one (26): First, intermediate **11b** was prepared according to general procedure E from **9b** (0.040 g, 0.20 mmol, 1.0 equiv) (with the exception that no isolation was performed). Instead of isolation, once **11b** was prepared in the glovebox, the reaction solution was cooled to 25 °C and transferred into a one dram vial ("reaction vial") containing Pd(PPh_3)₄ (23.1 mg, 0.0200 mmol, 10. mol %), Cs_2CO_3 (0.196 g, 0.600 mmol, 3.0 equiv), and a stir bar. Compound 1-(4-iodophenyl)ethan-1-one **25** (0.591 g, 0.240 mmol, 1.2 equiv) was dissolved in 0.15 mL toluene, and the resulting solution was transferred to the reaction vial. Then, the vials for **11b** and **25** were each rinsed with 0.5 mL toluene, and all the rinses were combined into the reaction vial. The reaction vial was capped with a cap with a septum and sealed with black tape before it was taken out from the glovebox. Outside the glovebox, deionized water (4.0 μL , 0.22 mmol, 1.1 equiv) was quickly added via a 10 μL airtight syringe, followed by heating the resulting solution to 100 °C and stirred at this temperature vigorously (to ensure mixing of the water droplet) for 24 h. Then, the reaction was quenched with aqueous saturated NH_4Cl (5 mL). The resulting organic layer was washed with brine (5 mL). Then, the aqueous layer was extracted with EtOAc (3 \times 5 mL), followed by combining all organic layers. The combined organic layers were then dried over MgSO_4 , and then filtered through a Celite[®] plug (Celite[®] in an M glass frit funnel), and the filtrate was concentrated in vacuo to afford the crude product, which was then purified by flash column chromatography (silica, 4% EtOAc in hexane) to afford a light yellow oil (0.042 g, 66%) ^1H NMR (CDCl_3 , 600 MHz): δ 8.02 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 7.12–7.05 (m, 2H), 6.53 (d, J = 7.7 Hz, 1H), 5.27 (q, J = 6.5 Hz, 1H), 2.66 (s, 3H), 2.14–2.03 (m, 2H), 1.67 (d, J = 6.5 Hz, 3H), 1.59–1.42 (m, 2H), 1.31–1.20 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 126 MHz): δ 198.0, 153.8, 142.9, 135.9, 132.4, 131.9, 131.7, 128.7, 127.7, 126.3, 123.2, 122.4,

113.7, 73.6, 31.3, 29.7, 26.8, 22.5, 19.9, 14.0. HRMS (ESI-TOF) m/z calcd for $\text{C}_{22}\text{H}_{24}\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$) 343.1674, found 343.1671.

A mixture of (6-iodo-2,3-dimethoxyphenyl)methanol (**SI-11**) and (5-iodo-2,3-dimethoxyphenyl)methanol (**SI-11'**) was prepared according to a modified literature procedure.^{13,14} In a flame-dried 250 mL round bottom flask, 2,3-dimethoxybenzyl alcohol **27** (0.389 g, 2.30 mmol, 1.0 equiv) and AgTFA (0.508 g, 2.30 mmol, 1.0 equiv) were dissolved in dry CHCl_3 (8 mL) under N_2 on a Schlenk line. To the resulting solution, a solution of I_2 (0.584 g, 2.30 mmol, 1.0 equiv) in 40 mL dry CHCl_3 was added dropwise under N_2 . The resulting mixture was stirred at 25 °C under N_2 for 18 h. Then, the reaction mixture was filtered through a Celite[®] plug (Celite[®] in an M glass frit funnel), and the filtration cake was rinsed with DCM (3 \times 10 mL). Then, all organic solutions were combined, and washed with saturated NaHCO_3 (aq) (1 \times 10 mL) and brine (1 \times 10 mL). Then the combined organic layers were then dried over MgSO_4 , and then filtered through a Celite[®] plug (Celite[®] in an M glass frit funnel), and the filtrate was concentrated in vacuo. The resulting residue was purified by flash column chromatography (silica, 25% EtOAc in hexane) to afford a white solid (0.387 g, 57% yield). The products obtained were a mixture of major product, (6-iodo-2,3-dimethoxyphenyl)methanol (**SI-11**), and minor product (5-iodo-2,3-dimethoxyphenyl)methanol (**SI-11'**). The ratio **SI-11**:**SI-11'** was 2:1 according to ^1H NMR spectroscopy. For the major product, ^1H NMR (CDCl_3 , 500 MHz): δ 7.53 (d, J = 8.7 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 4.81 (d, J = 6.9 Hz, 2H), 3.86–3.83 (m, 6H), 2.29 (t, J = 6.4 Hz, 1H). For the minor product, ^1H NMR (CDCl_3 , 500 MHz): δ 7.33–7.27 (m, 1H), 7.15 (d, J = 2.1 Hz, 1H), 4.64 (d, J = 6.9 Hz, 2H), 3.94–3.88 (m, 6H), 2.07 (t, J = 6.4 Hz, 1H). These spectra are in agreement with previously reported spectral data.¹³

A Mixture of (2,3-dimethoxy-6-(prop-1-yn-1-yl)phenyl)methanol (**28**) and (2,3-dimethoxy-5-(prop-1-yn-1-yl)phenyl)methanol (**28'**) was prepared according to a modified general procedure C: To a 100 mL flame-dried round bottom flask, the mixture of **SI-11** and **SI-11'** (0.387 g, 1.30 mmol, 1.0 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.046 g, 0.066 mmol, 5.0 mol %) and CuI (0.025 g, 0.013 mmol, 10. mol %), Et_3N (2.6 mL, 19. mmol, 2.0 equiv), and a stir bar were mixed under N_2 on a Schlenk line, followed by cooling the resulting mixture to 0 °C. At 0 °C, propyne (2.6 mL of a 1.0 M THF solution, 2.6 mmol, 2.0 equiv) was added via a syringe under N_2 on a Schlenk line. The reaction mixture was warmed to 25 °C, and stirred at 25 °C under N_2 for 18 h. The reaction was quenched with saturated NH_4Cl (aq) (20 mL), and the resulting organic layer was washed with brine (10 mL). The aqueous layer was extracted with EtOAc (3 \times 10 mL), and the combined organic layers were dried over MgSO_4 , and then filtered through a Celite[®] plug (Celite[®] in a medium glass frit funnel), and the filtrate was concentrated in vacuo. The crude product was purified by flash column chromatography (silica, 25% EtOAc in hexane) to afford a brown solid (0.261 g, 97% yield). The ratio **28**:**28'** was 2:1 according to ^1H NMR spectroscopy. For **28**, ^1H NMR (CDCl_3 , 600 MHz): δ 7.15 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 4.85 (d, J = 6.9 Hz, 2H), 3.89–3.86 (m, 6H), 2.52 (t, J = 6.9 Hz, 1H), 2.07 (s, 3H). ^{13}C NMR (CDCl_3 , 126 MHz): δ 152.6, 136.2, 128.6, 124.1, 115.2, 111.8, 88.5, 77.2, 61.5, 59.2, 55.9, 4.6. For **28'**, ^1H NMR (CDCl_3 , 600 MHz): δ 6.99 (d, J = 1.9 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 4.64 (d, J = 6.4 Hz, 2H), 3.87–3.84 (m, 6H), 2.12–2.08 (m, 1H), 2.04 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 126 MHz): δ

152.2, 146.9, 134.5, 119.8, 116.2, 111.8, 85.3, 79.4, 61.1, 59.2, 55.9, 4.5. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{14}O_3Na$ ($[M+Na]^+$) 229.0841, found 229.0841. This mixture was used for the next step without further purification.

7,8-Dimethoxy-3-methylisochroman-4-one (**29**): First, intermediate **SI-11** was prepared according to general procedure E (see SI) to generate the mixture of **28** and **28'** (0.130 g, 0.400 mmol, 1.0 equiv) (with the exception that no isolation was performed). Instead of isolation, once the mixture of **28** and **28'** was prepared, the reaction solution was cooled to 25 °C and transferred into a 25 mL Schlenk tube in the glovebox. A stir bar was also added into the Schlenk tube. Then, this tube was sealed and taken out of the glovebox and attached to a Schlenk line. In order to avoid decomposition of the delicate Bcat product, it was kept under N_2 on the Schlenk line until 0.82 mL NaOH (0.21 mL of a 3.0 M aqueous solution, 0.64 mmol, 1.6 equiv), and H_2O_2 (0.17 mL of a 30. wt % solution in H_2O , 0.64 mmol, 1.6 equiv) were then sequentially and quickly added, and the resulting mixture was stirred at 25 °C for 1.5 h. Once the reaction was done as determined by TLC (ca. 15% EtOAc in hexane), it was quenched with saturated $NH_4Cl(aq)$ (5 mL). The resulting organic layer was washed with brine (5 mL). Then, the aqueous layer was extracted with EtOAc (3 × 5 mL), followed by combining all organic layers. The combined organic layers were then dried over $MgSO_4$, and then filtered through a Celite® plug (Celite® in an M glass frit funnel), and the filtrate was concentrated in vacuo to afford the crude product, which was then purified by flash column chromatography (silica, 15% EtOAc in hexane) to afford a white solid (0.038 g, 64% yield based on the actual amount of **28** present in the reaction, which was calculated based on 1H NMR spectroscopy of the starting material using the ratio of the two regioisomers). 1H NMR ($CDCl_3$, 600 MHz): δ 7.84 (d, $J = 8.7$ Hz, 1H), 6.94 (d, $J = 8.6$ Hz, 1H), 5.13 (d, $J = 15.7$ Hz, 1H), 4.80 (d, $J = 15.7$ Hz, 1H), 4.19 (qd, $J = 6.7$, 1.1 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 1.50 (d, $J = 6.7$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 195.0, 157.0, 143.3, 124.2, 123.3, 111.3, 77.9, 77.4, 63.0, 56.0, 15.8, 7.9. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{14}O_4Na$ ($[M+Na]^+$) 245.0790, found 245.0788. The spectral information is in agreement with previously reported spectral data.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at <http://pubs.acs.org>. Optimization studies and experimental procedures for synthesis of precursors, and 1H , ^{11}B , ^{13}C and ^{19}F NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

* blums@uci.edu

ACKNOWLEDGMENT

We thank the National Science Foundation (CHE-1665202) and the University of California, Irvine (UCI), for funding. We thank Mr. Darius Vrubliauskas (UCI) for assisting the ozonolysis.

REFERENCES

- (1) Godula, K.; Sames, D. C-H Bond Functionalization in Complex Organic Synthesis. *Science* **2006**, *312*, 67–72.
- (2) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Privileged Scaffolds for Library Design and Drug Discovery. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.
- (3) Larsen, M. A.; Hartwig, J. F. Iridium-Catalyzed C–H Borylation of Heteroarenes: Scope, Regioselectivity, Application to Late-Stage Functionalization, and Mechanism. *J. Am. Chem. Soc.* **2014**, *136*, 4287–4299.
- (4) Hirner, J. J.; Faizi, D. J.; Blum, S. A. Alkoxyboration: Ring-Closing Addition of B–O σ Bonds across Alkynes. *J. Am. Chem. Soc.* **2014**, *136*, 4740–4745.
- (5) Chong, E.; Blum, S. A. Aminoboration: Addition of B–N σ Bonds across C–C π Bonds. *J. Am. Chem. Soc.* **2015**, *137*, 10144–10147.
- (6) Tu, K. N.; Hirner, J. J.; Blum, S. A. Oxyboration with and without a Catalyst: Borylated Isoxazoles via B–O σ -Bond Addition. *Org. Lett.* **2016**, *18*, 480–483.
- (7) Faizi, D. J.; Issaian, A.; Davis, A. J.; Blum, S. A. Catalyst-Free Synthesis of Borylated Lactones from Esters via Electrophilic Oxyboration. *J. Am. Chem. Soc.* **2016**, *138*, 2126–2129.
- (8) Faizi, D. J.; Davis, A. J.; Meany, F. B.; Blum, S. A. Catalyst-Free Formal Thioboration to Synthesize Borylated Benzothiophenes and Dihydrothiophenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 14286–14290.
- (9) Issaian, A.; Tu, K. N.; Blum, S. A. Boron–Heteroatom Addition Reactions via Borylative Heterocyclization: Oxyboration, Aminoboration, and Thioboration. *Acc. Chem. Res.* **2017**, *50*, 2598–2609.
- (10) Warner, A. J.; Lawson, J. R.; Fasano, V.; Ingleson, M. J. Formation of $C(Sp^2)\square$ Boronate Esters by Borylative Cyclization of Alkynes Using BCl_3 . *Angew. Chem. Int. Ed.* **2015**, *54*, 11245–11249.
- (11) Warner, A. J.; Churn, A.; McGough, J. S.; Ingleson, M. J. BCl_3 -Induced Annulative Oxo- and Thioboration for the Formation of C3-Borylated Benzofurans and Benzothiophenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 354–358.
- (12) Kikuchi, T.; Takagi, J.; Isou, H.; Ishiyama, T.; Miyaura, N. Vinyl C–H Borylation of Cyclic Vinyl Ethers with Bis(Pinacolato)Diboron Catalyzed by an Iridium(I)-Dtbpy Complex. *Chem. Asian J.* **2008**, *3*, 2082–2090.
- (13) Kikuchi, T.; Takagi, J.; Ishiyama, T.; Miyaura, N. Iridium-Catalyzed Vinyl C–H Borylation of Cyclic Vinyl Ethers by Bis(Pinacolato)Diboron. *Chem. Lett.* **2008**, *37*, 664–665.
- (14) Green, S. Antineoplastic Activity of Aflatoxin B1. *Nature* **1968**, *220*, 931–932.
- (15) Jacobi, P. A.; Selnick, H. G. Total Synthesis of (+)-Gnididione and (+)-Isognididione. *J. Org. Chem.* **1990**, *55*, 202–209.
- (16) Koike, T.; Takai, T.; Hoashi, Y.; Nakayama, M.; Kosugi, Y.; Nakashima, M.; Yoshikubo, S.; Hirai, K.; Uchikawa, O. Synthesis of a Novel Series of Tricyclic Dihydrofuran Derivatives: Discovery of 8,9-Dihydrofuro[3,2-*c*]pyrazolo[1,5-*a*]pyridines as Melatonin Receptor (MT_1/MT_2) Ligands. *J. Med. Chem.* **2011**, *54*, 4207–4218.
- (17) Kilroy, T. G.; O'Sullivan, T. P.; Guiry, P. J. Synthesis of Dihydrofurans Substituted in the 2-Position. *Eur. J. Org. Chem.* **2005**, *2005*, 4929–4949.
- (18) Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; et al. Novel 2,3-Dihydrobenzofuran-2-Carboxylic Acids: Highly Potent and Subtype-Selective PPAR α Agonists with Potent Hypolipidemic Activity. *J. Med. Chem.* **2005**, *48*, 5589–5599.
- (19) Freire, C. P. V.; Ferreira, S. B.; de Oliveira, N. S. M.; Matsuura, A. B. J.; Gama, I. L.; da Silva, F. de C.; de Souza, M. C. B. V.; Lima, E. S.; Ferreira, V. F. Synthesis and Biological Evaluation of Substituted α - and β -2,3-Dihydrofuran Naphthoquinones as Potent Anticandidal Agents. *Medchemcomm* **2010**, *1*, 229–232.
- (20) Matsuya, Y.; Suzuki, N.; Kobayashi, S.-Y.; Miyahara, T.; Ochiai, H.; Nemoto, H. Synthesis and Anti-Influenza Virus Activity of Dihydrofuran-Fused Perhydrophenanthrenes with a Benzyloxy-Type Side-Chain. *Bioorg. Med. Chem.* **2010**, *18*, 1477–1481.
- (21) Lipshutz, B. H. Five-Membered Heteroaromatic Rings as Intermediates in Organic Synthesis. *Chem. Rev.* **1986**, *86*, 795–819.
- (22) Mancuso, R.; Mehta, S.; Gabriele, B.; Salerno, G.; Jenks, W. S.; Larock, R. C. A Simple and Mild Synthesis of 1 *H* - Isochromenes and (*Z*)-1-Alkylidene-1,3-Dihydroisobenzofurans by the Iodocyclization of 2-(1-

- Alkynyl)Benzylic Alcohols. *J. Org. Chem.* **2010**, *75*, 897–901.
- (23) Varela-Fernández, A.; González-Rodríguez, C.; Varela, J. A.; Castedo, L.; Saá, C. Cycloisomerization of Aromatic Homo- and Bis-Homopropargylic Alcohols via Catalytic Ru Vinylidenes: Formation of Benzofurans and Isochromenes. *Org. Lett.* **2009**, *11*, 5350–5353.
- (24) Qian, H.; Huang, W. L.; Wu, X. M.; Zhang, H. Bin; Zhou, J. P.; Ye, W. C. A New Isochroman-4-One Derivative from the Peel of *Musa Sapientum* L. and Its Total Synthesis. *Chin. Chem. Lett.* **2007**, *18*, 1227–1230.
- (25) Tomás-Mendivil, E.; Starck, J.; Ortuno, J.-C.; Michelet, V. Synthesis of Functionalized 1*H*-Isochromene Derivatives via a Au-Catalyzed Domino Cycloisomerization/Reduction Approach. *Org. Lett.* **2015**, *17*, 6126–6129.
- (26) Wang, W.; Li, T.; Milburn, R.; Yates, J.; Hinnant, E.; Luzzio, M. J.; Noble, S. A.; Attardo, G. Novel 1,3-Disubstituted-5,10-Dihydro-5,10-Dioxo-1*H*-Mbenzo[*g*]isochromene-3-Carboxamides as Potent Antitumor Agents. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1579–1584.
- (27) Harborne, J. B.; Giriya, A. R.; Devi, H. M.; Lakshmi, N. K. M. Anthochlor Pigments from the Petals of *Mussaenda Hirsutissima* and *Zinnia Linearis*. *Phytochemistry* **1983**, *22*, 2741–2742.
- (28) Kanokmedhakul, S.; Kanokmedhakul, K.; Nasomjai, P.; Louangsouphanh, S.; Soyong, K.; Isobe, M.; Kongsaree, P.; Prabpai, S.; Suksamrarn, A. Antifungal Azaphilones from the Fungus *Chaetomium Cupreum* CC3003. *J. Nat. Prod.* **2006**, *69*, 891–895.
- (29) Wang, C.; Wei, G.; Yang, X.; Yao, H.; Jiang, J.; Liu, J.; Shen, M.; Wu, X.; Xu, J. First Total Synthesis of Antihypertensive Natural Products S-(+)-XJP and R-(-)-XJP. *Org. Biomol. Chem.* **2014**, *12*, 7338–7344.
- (30) Fu, R.; Yan, T.; Wang, Q.; Guo, Q.; Yao, H.; Wu, X.; Li, Y. Suppression of Endothelial Cell Adhesion by XJP-1, a New Phenolic Compound Derived from Banana Peel. *Vascul. Pharmacol.* **2012**, *57*, 105–112.
- (31) Fu, R.; Wang, Q.; Guo, Q.; Xu, J.; Wu, X. XJP-1 Protects Endothelial Cells from Oxidized Low-Density Lipoprotein-Induced Apoptosis by Inhibiting NADPH Oxidase Subunit Expression and Modulating the PI3K/Akt/ENOS Pathway. *Vascul. Pharmacol.* **2013**, *58*, 78–86.
- (32) Fu, R.; Chen, Z.; Wang, Q.; Guo, Q.; Xu, J.; Wu, X. XJP-1, a Novel ACEI, with Anti-Inflammatory Properties in HUVECs. *Atherosclerosis* **2011**, *219*, 40–48.
- (33) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483.
- (34) Roy, D.; Uozumi, Y. Recent Advances in Palladium-Catalyzed Cross-Coupling Reactions at Ppm to Ppb Molar Catalyst Loadings. *Adv. Synth. Catal.* **2018**, *360*, 602–625.
- (35) Faizi, D. J.; Nava, N. A.; Al-Amin, M.; Blum, S. A. Oxyboration: Synthesis of Borylated Benzofurans. *Org. Synth.* **2016**, *93*, 228–244.
- (36) Wishart, D. S.; Knox, C.; Guo, A. C.; Cheng, D.; Shrivastava, S.; Tzur, D.; Gautam, B.; Hassanali, M. DrugBank: A Knowledgebase for Drugs, Drug Actions and Drug Targets. *Nucleic Acids Res.* **2008**, *36*, D901–D906.
- (37) Yuan, Y.; Lee, R. E.; Besra, G. S.; Belisle, J. T.; Barry, C. E. Identification of a Gene Involved in the Biosynthesis of Cyclopropanated Mycolic Acids in *Mycobacterium Tuberculosis*. *Proc. Natl. Acad. Sci.* **1995**, *92*, 6630–6634.
- (38) George, K. M.; Yuan, Y.; Sherman, D. R.; Barry, C. E. The Biosynthesis of Cyclopropanated Mycolic Acids in *Mycobacterium Tuberculosis*. *J. Biol. Chem.* **1995**, *270*, 27292–27298.
- (39) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529–2591.
- (40) Salaün, J. Cyclopropane Derivatives and Their Diverse Biological Activities. In *Small ring compounds in organic synthesis VI*; Springer, 2000; pp 1–67.
- (41) Talele, T. T. The “Cyclopropyl Fragment” Is a Versatile Player That Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59*, 8712–8756.
- (42) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. Palladium-Catalyzed Cross-Coupling Reaction of Bis(Pinacolato)Diboron with 1-Alkenyl Halides or Triflates: Convenient Synthesis of Unsymmetrical 1,3-Dienes via the Borylation-Coupling Sequence. *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006.
- (43) Issaian, A.; Faizi, D. J.; Bailey, J. O.; Mayer, P.; Berionni, G.; Singleton, D. A.; Blum, S. A. Mechanistic Studies of Formal Thioboration Reactions of Alkynes. *J. Org. Chem.* **2017**, *82*, 8165–8178.
- (44) Nogushi, H.; Hojo, K.; Suginome, M. Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki–Miyaura Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 758–759.
- (45) Yuan, K.; Wang, S. *Trans*-Aminoboration across Internal Alkynes Catalyzed by B(C₆F₅)₃ for the Synthesis of Borylated Indoles. *Org. Lett.* **2017**, *19*, 1462–1465.
- (46) Geri, J. B.; Szymczak, N. K. Recyclable Trifluoromethylation Reagents from Fluoroform. *J. Am. Chem. Soc.* **2017**, *139*, 9811–9814.
- (47) Männig, D.; Nöth, H. Catalytic Hydroboration with Rhodium Complexes. *Angew. Chem. Int. Ed.* **1985**, *24*, 878–879.
- (48) Terada, M.; Li, F.; Toda, Y. Chiral Silver Phosphate Catalyzed Transformation of *Ortho*-Alkynylaryl Ketones into 1*H*-Isochromene Derivatives through an Intramolecular-Cyclization/Enantioselective-Reduction Sequence. *Angew. Chem. Int. Ed.* **2014**, *53*, 235–239.
- (49) Maluenda, I.; Navarro, O. Recent Developments in the Suzuki–Miyaura Reaction: 2010–2014. *Molecules* **2015**, *20*, 7528–7557.
- (50) Thomas, A. A.; Zahrt, A. F.; Delaney, C. P.; Denmark, S. E. Elucidating the Role of the Boronic Esters in the Suzuki–Miyaura Reaction: Structural, Kinetic, and Computational Investigations. *J. Am. Chem. Soc.* **2018**, *140*, 4401–4416.
- (51) Perrin, D. D.; Armarego, W. L. F. Purification of Organic Chemicals. In *Purification of Laboratory Chemicals*; Elsevier, 2017; pp 95–634.
- (52) Iafe, R. G.; Chan, D. G.; Kuo, J. L.; Boon, B. A.; Faizi, D. J.; Saga, T.; Turner, J. W.; Merlic, C. A. Cyclization Strategies to Polyenes Using Pd(II)-Catalyzed Couplings of Pinacol Vinylboronates. *Org. Lett.* **2012**, *14*, 4282–4285.
- (53) Qian, M.; Negishi, E. I. Palladium-Catalyzed Cross-Coupling Reaction of Alkynylzincs with Benzylic Electrophiles. *Tetrahedron Lett.* **2005**, *46*, 2927–2930.
- (54) Li-Jun, Z.; Xue-Sheng, M.; Yao-Zeng, H. On Pentaoarylstiborane: III. Regio- and Diastereoselective Additions of Acetylenic and Allenic Organoantimony Compounds to Aldehydes. *J. Organomet. Chem.* **1994**, *471*, 77–85.
- (55) Akitt, J. W. Quadrupole Relaxation of Boron-11 and Boron-10 Nuclei. *J. Magn. Reson.* **1970**, *3*, 411–414.
- (56) Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. Cyclization Reactions of 2-Alkynylbenzyl Alcohol and 2-Alkynylbenzylamine Derivatives Promoted by Tetrabutylammonium Fluoride. *Tetrahedron* **2001**, *57*, 9697–9710.
- (57) Schulte, B.; Fröhlich, R.; Studer, A. Atroposelective Radical Aryl Migration Reactions from Sulfur to Carbon. *Tetrahedron* **2008**, *64*, 11852–11859.
- (58) Wang, C.; Yang, J.; Cheng, X.; Li, E.; Li, Y. Molecular Iodine Mediated Cyclization Reactions of 2-(1-Alkynyl)Benzylic Alcohols to Substituted Indenones. *Tetrahedron Lett.* **2012**, *53*, 4402–4404.
- (59) Mora-Radó, H.; Bialy, L.; Czechtizky, W.; Méndez, M.; Harrity, J. P. A. An Alkyne Diboration/6π-Electrocyclization Strategy for the Synthesis of Pyridine Boronic Acid Derivatives. *Angew. Chem. Int. Ed.* **2016**, *55*, 5834–5836.
- (60) Yanada, R.; Hashimoto, K.; Tokizane, R.; Miwa, Y.; Minami, H.; Yanada, K.; Ishikura, M.; Takemoto, Y. Indium(III)-Catalyzed Tandem Reaction with Alkynylbenzaldehydes and Alkynylanilines to Heteroaromatic Compounds. *J. Org. Chem.* **2008**, *73*, 5135–5138.
- (61) Fan, Y. C.; Kwon, O. Phosphine/Palladium-Catalyzed Syntheses of Alkylidene Phthalans, 3-Deoxyisochracinic Acid, Isochracinic Acid, and Isochracinol. *Org. Lett.* **2012**, *14*, 3264–3267.
- (62) Das, A.; Liao, H.-H.; Liu, R.-S. Platinum-Catalyzed Chemoselectively Hydrative Dimerization of 2-Alkynyl-1-Acetylbenzenes for One-Pot Facile Synthesis of Chrysene Derivatives. *J. Org. Chem.* **2007**, *72*, 9214–9218.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- (63) Nakao, A.; Hayakawa, M. Preparation of Heterocycle-Containing Cyclic Amine Compounds as Calcium Receptor Antagonists. *Jpn. Kokai Tokkyo Koho* **2013**, *JP 2013-21*, 17 Oct 2013.
- (64) Jithunsa, M.; Ueda, M.; Miyata, O. Copper(II)Chloride-Mediated Cyclization Reaction of *N*-Alkoxy-*Ortho*-Alkynylbenzamides. *Org. Lett.* **2011**, *13*, 518–521.
- (65) Zhang, F.; Qin, Z.; Kong, L.; Zhao, Y.; Liu, Y.; Li, Y. Metal/Benzoyl Peroxide (BPO)-Controlled Chemoselective Cycloisomerization of (*o*-Alkynyl)Phenyl Enaminones: Synthesis of α -Naphthylamines and Indeno[1,2-*c*]Pyrrolones. *Org. Lett.* **2016**, *18*, 5150–5153.

Insert Table of Contents artwork here

