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Carboxyboration: The Catalyst-Free Synthesis of Borylated Lactones and Isocoumarins From Esters

THESIS

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by

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Professor Elizabeth R. Jarvo

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Abstract of This Thesis

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Professor Suzanne A. Blum, Chair

Catalyst-free formation of isocoumarins and α-pyrones from the corresponding alkynyl esters is realized. The resulting γ- and δ-lactones are isolated as the pinacolboronic esters, boronic acids or potassium trifluoroborate salts, which provide a variety of methods for downstream functionalization of the newly formed B−C σ bond. Reaction conditions have been optimized and a substrate table has been constructed to show tolerance of various functional groups incompatible with other borylation techniques. A mechanism has been proposed as a result of mechanistic studies and downstream functionalization is in progress to show the versatility of the methodology.[1]

Please note that this project was completed in collaboration with graduate student Darius J. Faizi and undergraduate student Ashlee J. Davis. For clarity of credits, my work is shown in blue in this manuscript.

Introduction

Lactones are privileged scaffolds that are found in a variety of biologically active compounds with diversified structures from 4−60 membered rings, exhibiting a wide range of biological properties.[2] Isocoumarins and α-pyrones are among the important classes of naturally occurring lactones.[3] The pharmacological functions of these structural subunits such as anti-inflammatory,[4] antibiotic,[5] phytotoxic,[6] antifungal[7] and anti-allergic[8] activities have sparked an interest in the fields of pharmaceutical and medicinal chemistry.[3, 9] In fact, the most recent Nobel Prize in Physiology or Medicine was awarded to the discovery of a new function for Artemisinin,[10] an α-pyrone derivative that has decreased death rates from malaria since the beginning of its use in standard anti-malarial procedures.[11]

Substantial efforts have been made in developing different methods for the synthesis of isocoumarins[12] and α-pyrones. [13, 14] Among these methods, several compelling approaches to electrophilic cyclizations to produce isocoumarins and other lactone derivatives were recently reported. [14, 15] Examples of these electrophiles include various halide derivatives, such as iodine, which are useful as they provide a handle for downstream functionalization of the newly formed products. [3, 9, 14]

Organoboron reagents are one of the most commonly used classes of compounds for downstream functionalization.[16] Boronic acids and their derivatives are especially versatile reagents in medicinal chemistry and drug discovery since they can be functionalized through the C−B σ bond.[17] In addition, the remnant electrophilic reactivity of organoboron compounds, even under physiological conditions, has allowed their incorporation in a growing number of bioactive

molecules for pharmaceutical applications.[18] An example of this is the first proteasome inhibitor anticancer drug, Bortezomib, which contains a boronic acid unit central for its function.[19]

Thus, a method to synthesize isocoumarins and α-pyrones that contain a C−B σ bond would furnish an important substrate class with a newly formed synthetic handle for further functionalization. Some of the borylation techniques that are currently known include lithiation/electrophilic trapping and transition metal catalyzed reactions.[16] Our group has pioneered borylation strategies that are predicated on preformation of the desired heteroatom−boron bond using gold (I) catalysis. [20, 21]

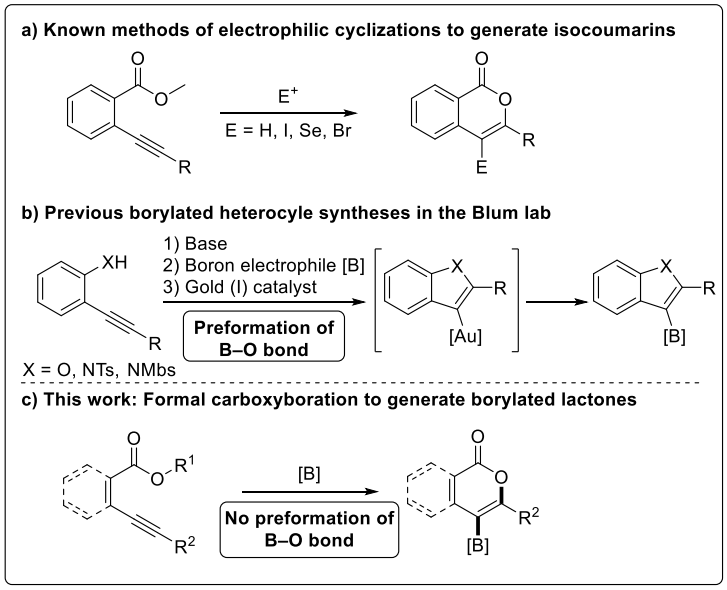


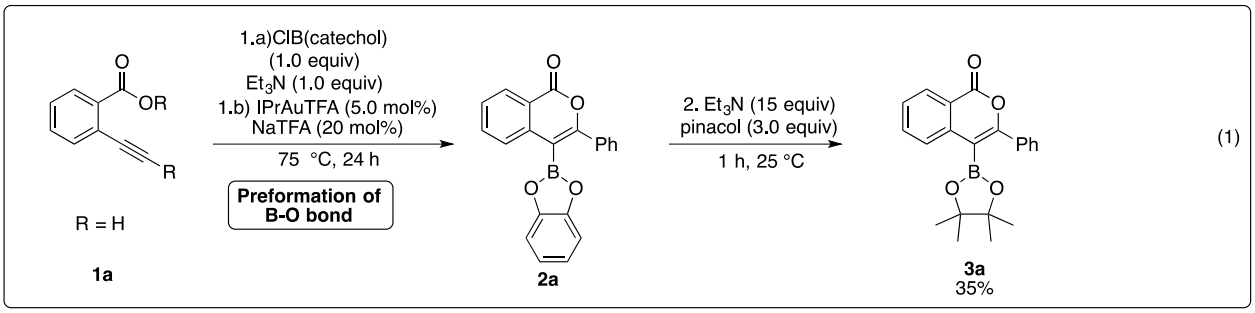
Figure 1. (a) Previous work developing electrophilic cyclizations with different electrophiles. (b) Previous work of the Blum group demonstrating addition of B−O bonds across alkynes. (c) This work representing electrophilic cyclizations to create carboxyboration products.

Herein we report a formal carboxyboration reaction across alkynes to furnish borylated iscoumarins and α-pyrones. This method is catalyst free and affords the formation of both a C−O σ bond and a C−B σ bond in one synthetic step without requiring the preformation of the B−O σ bond. The borylated lactones are then primed for downstream functionalization through the

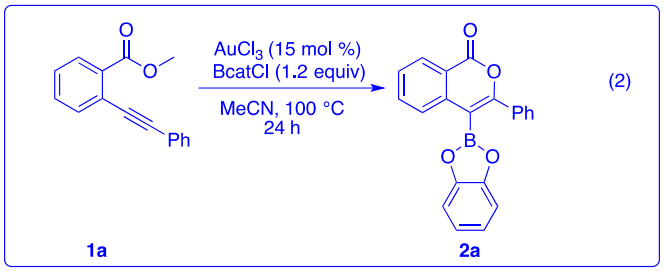
realization of the newly formed C−B σ bond. The reaction transforms easily accessible esters as starting materials to borylated isocoumarins and α-pyrones that provide complementary regioselectivity and functional group tolerance of the existing borylation strategies. The procedure is operationally simple in that it takes place in one pot and does not require the isolation of the reaction intermediates.

Results and Discussion

A preliminary study by Darius J. Faizi, a senior graduate student in the Blum group, showed that 2-alkynyl benzoic acid **1a** undergoes cyclization through a preformed C–B bond and gold (I)-catalyzed mechanism to form the borylated lactone **2a**, which is then transesterified to afford column-stable product **3a** in 35% yield (eq 1).



This reaction, however, did not prove to be efficient for reasons such as competitive thermal cyclization of **1a** and protodeboronation in the second step. In addition, preformation of the B–O σ bond was not a clean reaction and resulted in byproducts that decreased the overall yield of the reaction. Therefore, inspired by gold (I) catalyzed synthesis of lactones by van de Weghe et al.,[22] we decided to test our borylation techniques using methyl 2-alkynyl benzoates as starting materials.



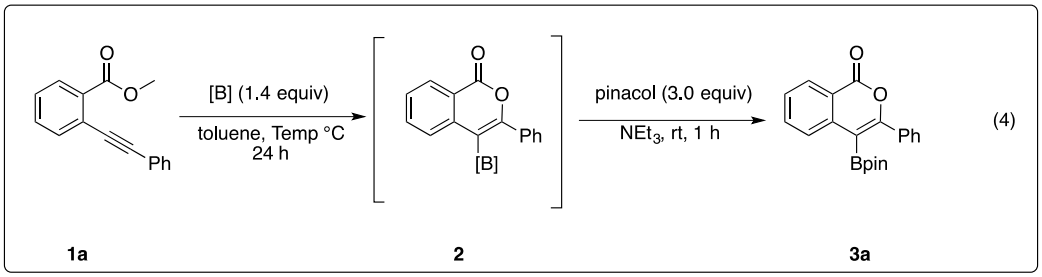
Methyl 2-(phenylethynyl)benzoate **1a** was synthesized from the corresponding commercially available 2-iodobenzoate **SI-1** through standard Pd- and Cu- catalyzed Sonogashira cross coupling reactions in good yields. Subsequent treatment of **1a** with gold (III) chloride and

B-chlorocatecholborane in acetonitrile at 100 °C afforded **2a** by ^{11}B Nuclear Magnetic Resonance (NMR) spectroscopy (eq 2). Monitoring eq 2 by ^{11}B NMR spectroscopy showed the coordination of acetonitrile with boron immediately and consistently. As a result, the first step in eq 2 was carried out in d_8-toluene as a non-coordinating solvent. Upon affording **2a**, subsequent screenings were performed in toluene.

Next, several different catalysts, as well as lower catalyst loadings, were screened in an attempt to optimize the carboxyboration reaction conditions (SI, eq 3). The results obtained from this set of experiments showed 5.0 mol % PPh_3AuOTf to be the optimal catalyst under the initial conditions (SI, Table 1). Consequently, the temperature and the concentration were screened for further optimization. These results yielded the highest product formation at 100 ^{o}C, and no reaction at room temperature. Moreover, increasing the concentration indicated that the reaction can proceed through a catalyst-free route (entry 12) at 1M followed by a lower reaction time (see SI, Table 2). It is noteworthy that even though under the aforementioned conditions the reaction reached completion at 16 hours, allowing the reaction to run for 24 hours did not afford any decomposition or side products. Therefore, the remaining optimizations of various equivalents of *B*-chlorocatecholborane were performed without a catalyst (SI, Table 3).

We hypothesized that an increase in electrophilicity at the boron center would reduce reaction times and temperatures. Moreover, highly electrophilic boron species have been recently used to affect various borylation cyclization strategies. Therefore, we next set out to optimize the electrophile used to facilitate this carboxyboration technique (Table 4).

Table 4. Boron Electrophile Screen



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

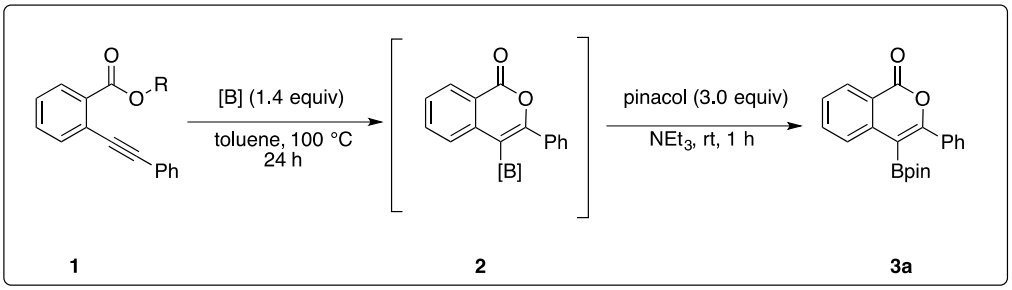
[a]isolated yield. [b]1.0 M solution in DCM.

Unexpectedly, however, both trihalogenated boron sources BBr_3 (entry 1) and BCl_3 (entry 2) failed to yield any desired borylated isocoumarin **3a**, but instead formed the demethylated alkynylbenzoic acid. The *B*-catecholborane (Bcat) haloderivatives (entries 3, 4, and 5), on the other hand, provided the borylated isocoumarin in yields of 25%, 75% and 48%, respectively. The mass balance of entry 5 was the demethylated alkynylbenzoic acid, confirming the higher dealkylation rate of bromide compared to chloride in these systems, investigated in previous studies.[23] Synthesis of the *B*-chloropinacolborane (BpinCl) electrophile proved to be challenging, and the lack of stability (decomposition above -30 °C) reduced its synthetic practicality, and was therefore not tested. [24]

Next, we set out to test various *O*-alkyl esters for compatibility with the carboxyboration method (Table 5). The carboxyboration reaction tolerates methyl and ethyl groups in similar yields (entries 1 and 2, respectively), but a slightly diminished yield is realized when the *O*-alkyl group is changed to isopropyl (entry 3). Moreover, the *tert*-butyl ester did not furnish any desired

borylated product, and only starting material was recovered (entry 4). We attribute this to the steric hindrance of the *tert*-butyl center, preventing the nucleophile from attacking in the dealkylation process, as this step is believed to proceed through an S_N2 type mechanism. [23, 25] We also hypothesize that a decrease in conversion rate is observed when the physical state of the resulting chloroalkane byproduct changes from a gas (entries 1 and 2) to an entropically disfavored liquid (entry 3).

Table 5. *O*-Alkyl Group Tolerance of the Carboxyboration Reaction

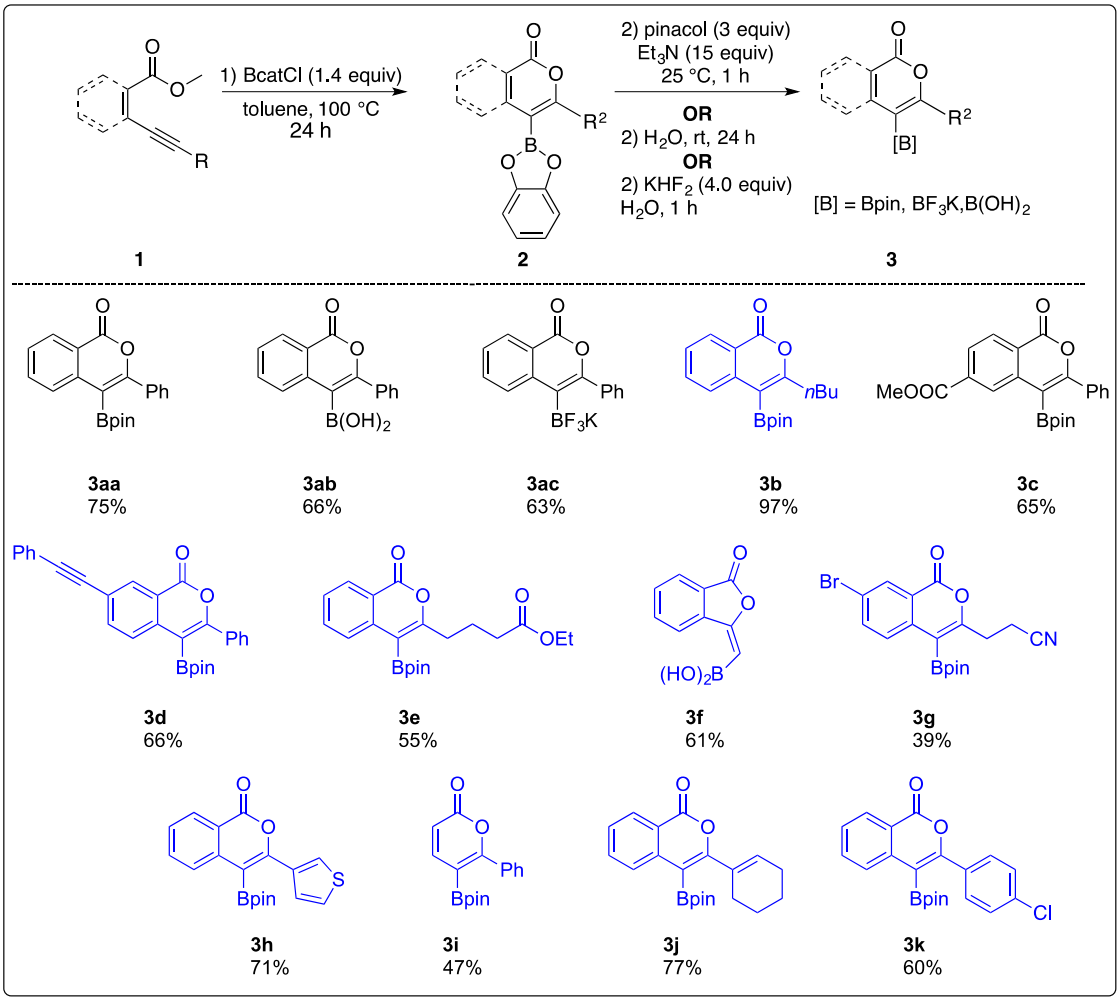


Entry	R	Yield (%)[a] **3a**
1	Me	81
2	Et	68
3	*i*Pr	60
4	*t*Bu	0

[a]Yield determined by HNMR using mesitylene as an internal standard.

Our carboxyboration strategy provides access to borylated lactones and isocoumarins with complementary regiochemisrty and functional groups that are incompatible with alternative synthetic routes (Table 6).

Table 6. Synthesis of Borylated Isocoumarins and α-pyrones via Carboxyboration Reaction[a]



[a]Isolated yield.

Various functional groups can be tolerated with this methodology, including esters, cyanides, aryl bromides and chlorides, thiophenes and alkynes. In addition, the reaction has broad applicability to furnish more than just borylated isocoumarins since there is no need for an aromatic backbone to enforce a certain ring bias (**3i**), although lower yielding. It is also noteworthy that because of the strong electrophilicity of *B*-chlorocatecholborane, certain Lewis acid-sensitive groups, such as ethers, furans and ketones, led to decomposition of the starting material and could not be tolerated under these conditions. For synthetic ease, the borylated products can be isolated three different ways with each method providing unique advantages:

as the boronic acid, the pinacolboronic ester, or the potassium organotrifluoroborate. The boronic acid, although not air and moisture stable for an extended period of time, is generally the preferred transition metal-catalyzed cross coupling partner.[26] The pinacolboronic ester isolation method is stable on silica gel for column chromatography and can be cross-coupled under basic conditions.[27] Lastly, the potassium organotrifluoroborate, although the lowest yielding of the three isolation methods, provides extended stability and its simple workup procedure makes it amenable for large-scale reactions (See SI).[28] Since pinacolboronic ester (**3aa**) proved to be highest yielding when probing these different isolation techniques, the majority of the borylated products were isolated using this protocol. Product **3g** was not silica gel stable and was isolated as the boronic acid. Single-crystal X-ray diffraction analysis of **3aa** allowed for the unambiguous identification of the carboxyboration product (Figure 2).

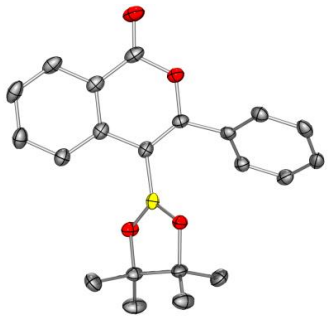
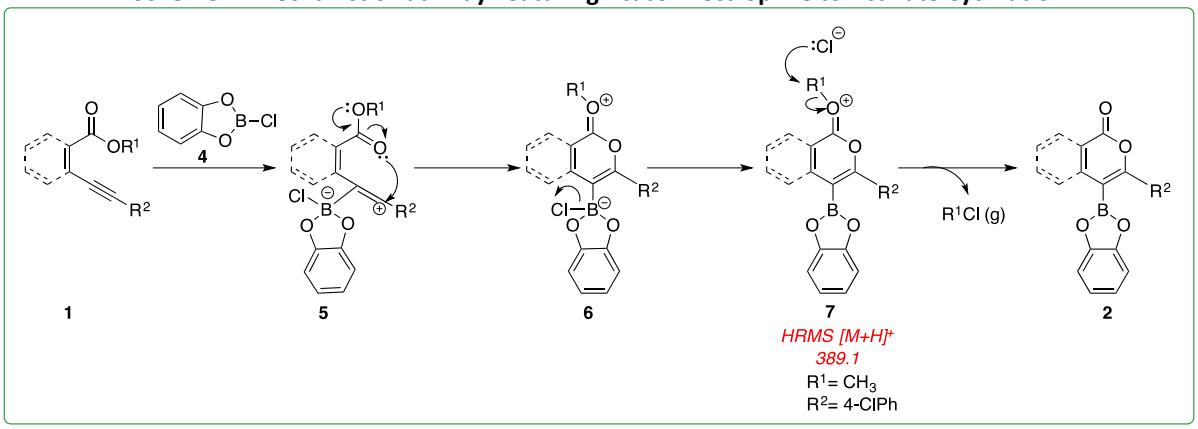


Figure 2. X-ray structure of **3aa** with thermal ellipsoid set at 50% probability level (B, yellow; C, gray; H, white; O, red).

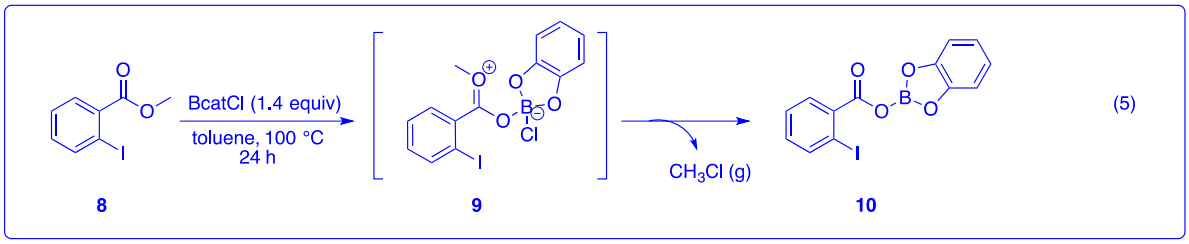
Several cyclization mechanisms have been proposed,[16] though not with boron electrophiles. We propose the following mechanism for the carboxyboration reaction (Scheme 1). *B*-chlorocatecholborane (**4**) coordinates to the alkyne of **1** to form the chloroboronate **5**, which then facilitates ring-closing nucleophilic attack by the ester, generating the oxocarbenium and ejecting the chloride in **5** and **6**, respectively. Demethylation by the chloride yields the desired borylated product **2**. The steric bulk of the *B*-chlorocatecholborane predominantly

promotes the *6-endo-dig* pathway. However, a more stable carbocation is formed for the *5-exo-dig* pathway for the unsubstituted alkyne (R=H), hence the regioselectivity for **3f**.

Scheme 1. Mechanistic Pathway Featuring BcatCl Electrophile to Activate Cyclization



A competing mechanistic pathway in which the oxophilic *B*-chlorocatecholborane first demethylates the ester **1** to form the boric ester **5**, followed by cyclization to intermediate **6** was also considered. We tested this hypothesis by subjecting **8** to the carboxyboration conditions (eq 5).

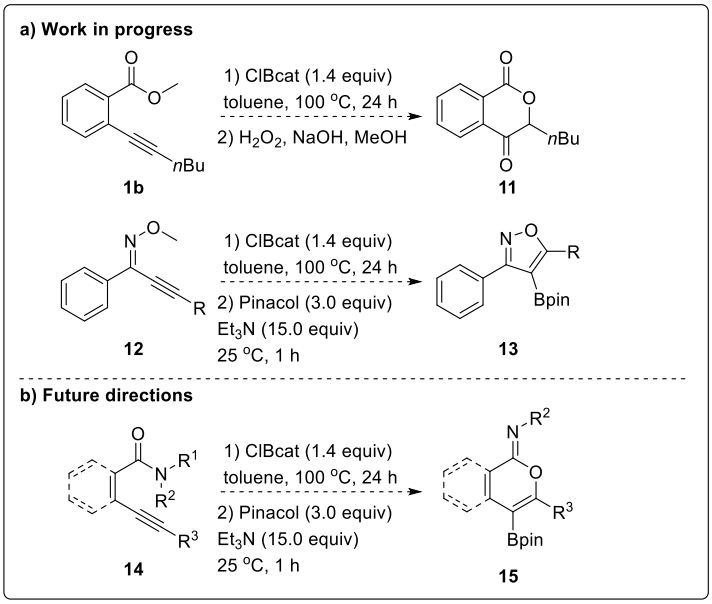


The demethylation resulted in less than 10% conversion in 24 hours, which further confirmed the plausibility of our proposed mechanism.

Summary and Conclusion

In this methodology, efficient syntheses of a variety of substituted isocoumarins and α-pyrones have been established. This strategy accommodates different alkynyl esters and affords the anticipated corresponding isocoumarins and α-pyrones. The resulting borylated products can be readily elaborated to more complex products by using known coupling reactions.

Scheme 2. Work in Progress and Proposed Future Work Incorporating Carboxyboration Methodology



Downstream functionalization reactions for some of our isolated products are in progress to develop a chromium-free route for isochroman-1,4-dione (**11**) formation as precursors in a variety of natural products (Scheme 2a).[29] In the future, we will extend our carboxyboration methodology to synthesize different borylated heterocycles, such as isoxazoles (**13**) and isochromen-1-imines (**15**) and produce products that are not compatible with other borylation techniques presently known (Scheme 2a and 2b respectively).

References

1) Faizi, D. J.; Issaian, A.; Davis, A. J.; Blum, S. A. *J. Am. Chem. Soc.* **2016**, *138*, 2126. (https://pubs.acs.org/doi/10.1021/jacs.5b1298)

2) Janecki, T., Ed. *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*; John Wiley-VCH: Weinheim, Germany, **2014**; pp. 147–192.

3) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1128–1135.

4) Pochet, L.; Frederick, R. Masereel, B. *Curr. Pharm. Des.* **2004**, *10*, 3781–3796.

5) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.; Nakajima, S. *Chem. Pharm. Bull.* **1981**, *29*, 2689–2691.

6) Sato, H.; Konoma, K.; Sakamura, S. *Agric. Biol. Chem.* **1981**, *45*, 1675.

7) (a) Simon, A.; Dunlop, R. W.; Ghisalberti, E. L. Sivasithamparam, K. *Soil Biol. Biochem.* **1988**, *20*, 263. (b) Claydon, N.; Asllan, M.; Hanson, J. R.; Avent, A. G. *Trans. Br. Mycol. Soc.* **1987**, *88*, 503. (c) Culter, H. G.; Cox, R. H.; Crumley, F. G.; Cole, P. O. *Agric. Biol. Chem.* **1986**, *50*, 2943.

8) Kurume, A.; Kamata, Y.; Yamashita, M.; Wang, Q.; Matsuda, H.; Yoshikawa, M.; Kawasaki, I.; Ohta, S. *Chem. Pharm. Bull.* **2008**, *56*, 1264–1269.

9) Pal, S.; Chatare, V.; Pal, M. *Current Organic Chemistry* **2011**, *15*, 782–800.

10) Nobelprize.org, Sweden. The Official Web site of the Nobel Prize – 2015 (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2015).

11) Tu, Y.Y. *Nat. Med.* **2011**, *17*, 1217–1220.

12) (a) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem*. **1977**, *42*, 1329. (b) Batu, G.; Stevenson, R. *J. Org. Chem.* **1980**, *45*, 1532. (c) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274. (d) Izumi, T.; Nishimoto, Y.; Kohei, K.; Kasahara, A. *J. Heterocycle. Chem*. **1997**, *27*, 1783. (e) Liao, H, -Y.; Cheng, C. -H. *J. Org. Chem.* **1995**, *60*, 3711. (f) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145. (g) Sashida, H.; Kawamukai, A. *Tetrahedro*n **2000**, *56*, 4777. (h) Napolitano, E. *Org. Prep. Proced. Int.* **1997**, *29*, 631. (i) Rossi, R.; Bellina, F.; Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett.* **2000**, *41*, 5281.

13) (a) Henry, W.; Hughes, R. P. *J. Am. Chem. Soc*. **1986**, *108*, 7876. (b) Inoue, Y.; Itoh, Y.; Kazama, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 3329. (c) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795. (d) Pavlik, J. W.; Patten, A. D.;

Bolin, D. R.; Bradford, K. C.; Clennan, E. L. *J. Org. Chem.* **1984**, *49*, 4523. (e) Ishibe, N.; Yutaka, S. *J. Org. Chem.* **1978**, *43*, 2138. (f) Ishibe, N.; Sunami, M.; Odani, M. *J. Am. Chem. Soc*. **1973**, *95*, 463. (g) Takata, T.; Tajima, R.; Ando, W. *Chem. Lett*. **1985**, 665. (h) Ho, T. L.; Hall, T. W.; Wong, C. M. *Synth. Commun*. **1973**, *3*, 79. (i) Hayasi, Y.; Nozaki, H. *Tetrahedron* **1971**, *27*, 3085. (j) Kotrestou, S. I.; Georgiadis, M. P. *Org. Prep. Proced. Int*. **2000**, *32*, 161. (k) Tsuda, T.; Morikawa, S.; Saegusa, T. *Chem. Commun*. **1989**, 9. (l) Liebeskind, L. S.; Wang, J. *Tetrahedron* **1993**, *49*, 5461. (m) Cerezo, S.; Moreno-Mañ as, M.; Pleixats, R. *Tetrahedron Lett*. **1998**, *54*, 7813. (n) Fringuelli, F.; Piermatt, O.; Pizzo, F. *Heterocycles* **1999**, *50*, 611. (o) Tominaga, Y. *Yuki Gosei Kagaku Kyokaishi* **1989**, *47*, 413.

14) Yao, T,; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936–5942.

15) (a) Oliver, M. A.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 558. (b) Yao, T,; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 7401. (c) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067–2081.

16) Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine, and Materials*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2011.

17) Burke, M. d.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095–14104.

18) Petasis, N. A. *Aust. J. Chem.* **2007**, *60*, 795–798.

19) Chen, D.; Frezza, M.; Schmitt, S.; Kanwar, J.; Dou, Q. P. *Curr. Cancer Drug Targets* **2011**, *11*, 239–253.

20) Hirner, J. J.; Faizi, D. J.; Blum, S. A. *J. Am. Chem. Soc*. **2014**, *136*, 4740–4745.

21) Chong, E.; Blum, S. A. *J. Am. Chem. Soc.* **2015**, *137*, 10144–10147.

22) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979–9990.

23) King, P. F.; Stroud, S. G. *Tetrahedron Lett*. **1985**, *26*, 1415–1418.

24) Cui, Y.; Li, W.; Sato, T.; Yamashira, Y.; Kobayashi, S. *Adv. Synth. And Cat.* **2013**, *355*, 1193–1205.

25) Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411–1414.

26) Kirckoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, F. C. *J. Am. Chem. Soc*. **2002**, *124*, 13662–13663.

27) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N. *J. Am. Chem. Soc*. **2002**, *124*, 390–391.

28) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286.

29) Hobson, J. S.; Parkin, A.; Marquez, R. *Org. Lett.* **2008**, *10*, 2813–2816.

Experimental

All chemicals were used as received from commercial sources unless otherwise noted. Toluene, Et_3N tetrahydrofuran, and dichloromethane were purified by passage through an alumina column under argon pressure on a push-still solvent system. Toluene-d_8 was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. All manipulations were conducted in a glovebox under nitrogen atmosphere or using standard Schlenk techniques unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using Merck F_{250} plates. Plates were visualized under UV irradiation (254 nm) and/or using a basic aqueous solution of potassium permanganate. Flash chromatography was conducted using a Teledyne Isco Combiflash® Rf 200 Automated Flash Chromatography System, and Teledyne Isco Redisep® 35–70 μm silica gel. All proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker DRX-400 spectrometer, Bruker DRX-500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE-600 spectrometer. All boron nuclear magnetic resonance (^{11}B NMR) spectra were recorded on a Bruker AVANCE-600 spectrometer. All fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker DRX-400. All chemical shifts (δ) are reported in parts per million (ppm) downfield of tetramethylsilane, and referenced to the residual protiated solvent peak (δ = 7.26 ppm for $CDCl_3$, δ = 2.05 ppm for d_6-acetone, or δ = 1.94 ppm for CD_3CN in ^{1}H NMR spectroscopy experiments; δ = 77.2 ppm for $CDCl_3$, δ = 29.8 ppm and 206.3 ppm for d_6-acetone, or δ = 1.34 ppm for CD_3CN in ^{13}C NMR spectroscopy experiments). ^{11}B and ^{19}F NMR spectroscopy experiments are referenced to the absolute frequency of 0 ppm in the ^{1}H dimension according to the Xi scale. High-resolution mass spectrometry data were obtained at the University of California, Irvine.

Screening for Methodology

General Procedure

This screen was carried out in a nitrogen-filled glove box. A 4 mL vial was charged with the corresponding catalyst, **1a** (0.50 mmol, 1.0 equiv) and 0.5 mL d_8-toluene, and the mixture was stirred at room temperature for 20 mins. In a separate vial, *B*-chlorocatecholborane (0.6 mmol, 1.2 equiv) was added. The content in the initial reaction vial were then transferred to the boron-containing vial via pipette, stirred for homogeneity, and transferred into a J-Young tube. The vial was capped and heated to 100 ^{o}C for 24 h. At this time, the reaction mixture was cooled down to room temperature, and ^{1}H NMR and ^{11}B NMR were taken in d_8-toluene to monitor conversion from **1a** to **2a**.

General Procedure (Isolation as *B*-pinacolborane)

This screen was carried out in a nitrogen-filled glove box. A 4 mL vial was charged with the corresponding catalyst, **1a** (0.50 mmol, 1.0 equiv) and 0.5 mL d_8-toluene, and the mixture was stirred at room temperature for 20 mins. In a separate vial, *B*-chlorocatecholborane (0.6 mmol, 1.2 equiv) was added. The content in the initial reaction vial was then transferred to the boron-containing vial via pipette, stirred for homogeneity, and transferred into a J-Young tube. The tube was sealed and heated to 100 ^{o}C for 24 h. At this time, the reaction mixture was cooled down to room temperature, and 1H NMR and ^{11}B NMR was taken in d_8-toluene to monitor conversion from **1a** to **2a**.

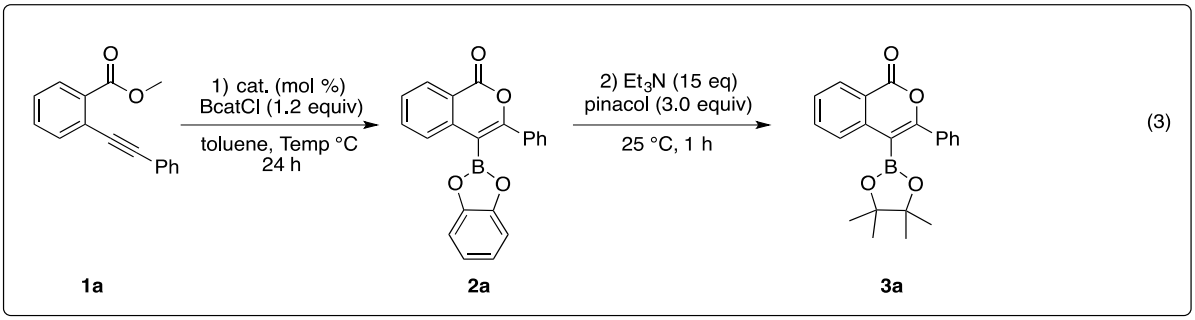
In a separate vial, pinacol (0.18 g, 1.5 mmol, 3 equiv) is dissolved in Et_3N (1.0 mL, 7.5 mmol, 15 equiv). This solution is then added to the reaction mixture via pipette. The resulting solution was then stirred for 1 h at room temperature. The solution was then concentrated in vacuo. ^{1}H NMR was then taken of each crude mixture in $CDCl_3$ and a yield was obtained.

General Procedure (Preparation of PPh_3AuOTf)

This reaction was carried out in a nitrogen-filled glove box. A 4 mL vial was charged with PPh_3AuCl and AgOTf (1.0 equiv) and 0.5 mL d_8-toluene. The resulting mixture was, then, filtered through celite into a 4 mL vial charged with **1a (**0.5 mmol, 1.0 equiv).

In a separate vial, *B*-chlorocatecholborane (0.6 mmol, 1.2 equiv) was added. The content in the initial reaction vial was then transferred to the boron-containing vial via pipette, stirred for homogeneity, and transferred into a J-Young tube. The tube was sealed and heated to 100 ^{o}C for 24 h. At this time, the reaction mixture was cooled down to room temperature, and 1H NMR and ^{11}B NMR was taken in d_8-toluene to monitor conversion from **1a** to **2a**.

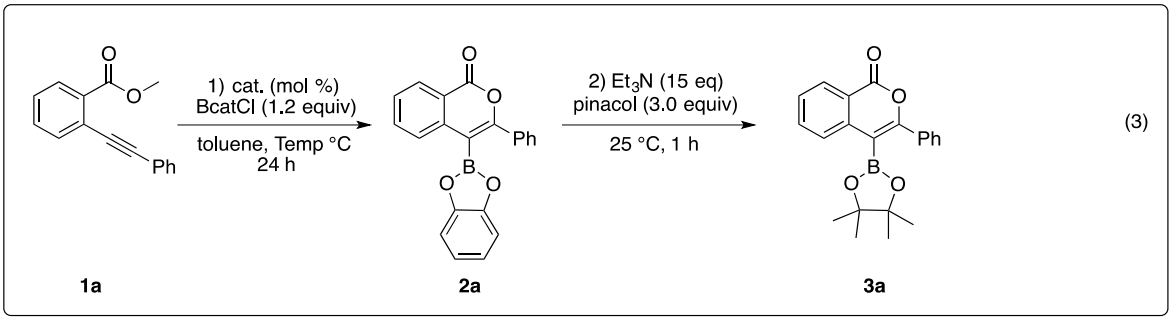
Table 1. Catalyst and Catalyst Loading Screen.



Entry	Catalyst	Catalyst Loading (mol %)	Temp (°C)	Concentration (M)	Reaction Time (h)	%Conversion to 2a[a]
1	AuCl	15	100	0.5	24	93
2	$AuCl_3$	15	100	0.5	24	94
3	$(PPh_3)_2PdCl_2$	15	100	0.5	24	94
4	PPh_3AuOTf	15	100	0.5	24	95
5	-	-	100	0.5	24	50
6	AuCl	5	100	0.5	24	93
7	$AuCl_3$	5	100	0.5	24	94
9	PPh_3AuOTf	5	100	0.5	24	95
10	iPrAuTFA	5	100	0.5	24	86
11	CuOTf	5	100	0.5	24	61[b]
12	$(PPh_3)_2PdCl_2$	5	100	0.5	24	64
13	CuI	5	100	0.5	24	65

[a]Determined by ^1H NMR. [b]isolated yield of **3a**.

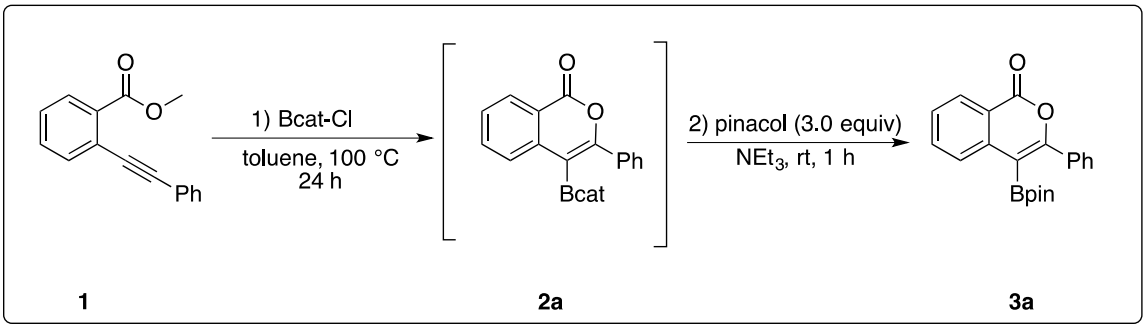
Table 2. Temperature and Concentration Screen



Entry	Catalyst	Catalyst Loading (mol %)	Temp (°C)	Concentration (M)	Reaction Time (h)	%Conversion to 2a[a]
1	PPh_3AuOTf	5	100	0.5	24	95[b]
2	PPh_3AuOTf	5	90	0.5	24	80[b]
3	PPh_3AuOTf	5	75	0.5	24	57[b]
4	PPh_3AuOTf	5	60	0.5	24	43[b]
5	PPh_3AuOTf	5	50	0.5	24	20[b]
6	PPh_3AuOTf	5	25	0.5	24	NR
7	PPh_3AuOTf	5	100	0.7	21	95
8	PPh_3AuOTf	5	100	0.9	18	95
9	PPh_3AuOTf	5	100	1.0	16	95
10[c]	PPh_3AuOTf	5	100	1.3	-	-
11[c]	PPh_3AuOTf	5	100	1.5	-	-
12	-	-	100	1.0	24	95

[a]Determined by ^1H NMR. [b]Calculated % yield using mesitylene as internal standard. [c]Solubility issues generated by high concentrations.

Table 3. *B*-chlorocatecholborane Equivalents Screen

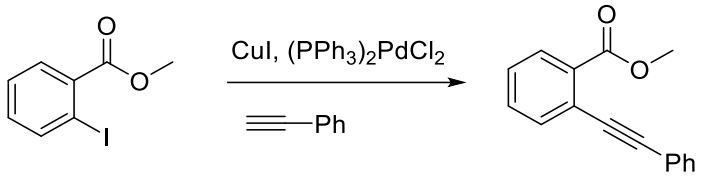


Entry	Boron Electrophile [B]	Electrophile Equivalents	Temp (°C)	Concentration (M)	Reaction Time (h)	Yield (%)
1	BCatCl	1.0	100	1.0	24	53[b]
2	BCatCl	1.2	100	1.0	24	65[b]
3	BCatCl	1.2	100	1.0	24	74[b]
4	BCatCl	1.3	100	1.0	24	86[b]
5	BCatCl	1.4	100	1.0	24	95[b]
6	BCatCl	1.5	100	1.0	24	91[b]
7	BCatCl	2.0	100	1.0	24	70[b]

[a]1.0 M solution in DCM. [b]Determined by ^{1}H NMR using mesitylene as internal standard.

Synthetic Procedures

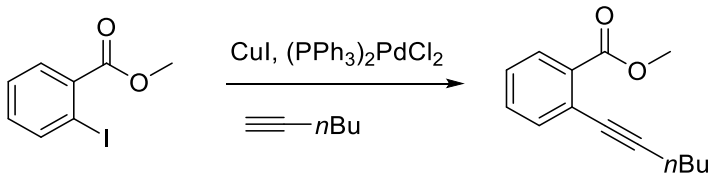
A. Preparation of Esters 1a–1k



SI-1 **1a**

Methyl 2-(phenylethynyl)benzoate (1a). A flask was charged with compound **SI-1** (3.0 mL, 20. mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.28 g, 0.40 mmol, 0.020 equiv), and CuI (0.15 g, 0.80 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 40 mL of acetonitrile and Et_3N (22 mL, 160 mmol, 8.0 equiv) were added. Phenylacetylene (2.4 mL, 22 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (5% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 200 mL EtOAc and washed with NH_4Cl (1 × 45 mL), water (1 × 45 mL), brine (1 × 45 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 5% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1a** as a light yellow oil (4.2 g, 88% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.59 – 7.57 (m, 2H), 7.59 – 7.57 (m, 1H), 7.40 – 7.35 (m, 4H), 3.97 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]

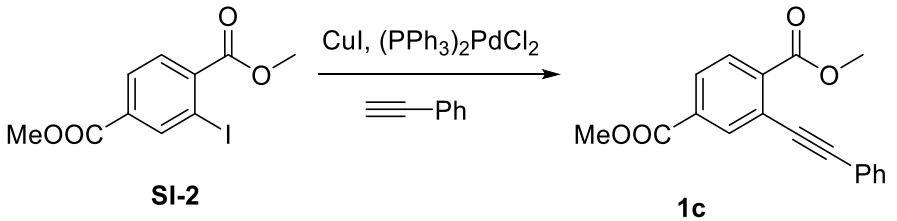


SI-1 **1b**

Methyl 2-(hex-1-yn-1-yl)benzoate (1b). A flask was charged with compound **SI-1** (0.73 mL, 5.0 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.070 g, 0.10 mmol, 0.020 equiv), and CuI (0.038 g, 0.20 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 10 mL of acetonitrile and Et_3N (5.6 mL, 40. mmol, 8.0 equiv) were added. 1-hexyne (0.63 mL, 5.5 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 100 mL EtOAc and washed with NH_4Cl (1 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Product-containing fractions were combined and

concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1b** as a light yellow oil (0.80 g, 74% yield).

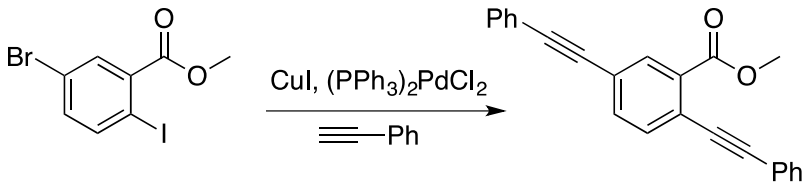
^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.88 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.41 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (td, *J* = 7.6, 1.0 Hz, 1H), 3.91 (s, 3H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.64 – 1.60 (m, 2H), 1.54-1.48 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[1]



SI-2 **1c**

Methyl 4-acetoxy-2-(phenylethynyl)benzoate (1c). A flask was charged with $(PPh_3)_2PdCl_2$ (0.022 g, 0.030 mmol, 0.020 equiv), and CuI (0.011 g, 0.060 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 4 mL of NEt_3 was added. The reaction mixture was then sparged for 5 minutes before **SI-2** (0.50 g, 1.6 mmol, 1.0 equiv) was added. Phenylacetylene (0.21 mL, 1.9 mmol, 1.2 equiv) was then added via syringe, and the reaction mixture was heated to 55 °C in an oil bath and stirred for 16 h under dynamic N_2. At this time, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 100 mL DCM and washed with water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1c** as a yellow solid (0.44 g, 95% yield).

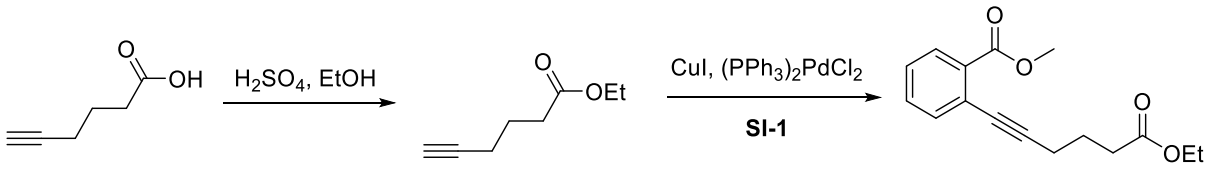
^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.26 (s, 1H), 8.00 – 7.96 (m, 2H), 7.57 – 7.56 (m, 2H), 7.35 – 7.34 (m, 3H), 3.96 (s, 3H), 3.92 (s, 3H). This spectrum is in agreement with previously reported spectral data.[2]



SI-3 **1d**

Methyl 2,5-bis(phenylethynyl)benzoate (1d) A flask was charged with $(PPh_3)_2PdCl_2$ (0.017 g, 0.24 mmol, 0.040 equiv), and CuI (0.016 g, 0.12 mmol, 0.020 equiv). The flask was then evacuated and refilled with N_2 three times before 4 mL of NEt_3 was added. The reaction mixture was then sparged for 5 minutes before **SI-3** (2.00 g, 5.87 mmol, 1.0 equiv) was added. Phenylacetylene (0.70 mL, 6.45 mmol, 1.1 equiv) was then added via syringe, and the reaction mixture was heated to 55 °C in an oil bath and stirred for 16 h under dynamic N_2. At this time, analysis by TLC (5% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 100 mL DCM and washed with water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 5% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1d** as a white solid (0.168 g, 11% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.15 (s, 1H), 7.60 – 7.54 (m, 4H), 7.38 – 7.36 (m, 6H), 4.0 (s, 3H). This spectrum is in agreement with previously reported spectral data.[3]



SI-4 **SI-5** **1e**

Ethyl hex-5-ynoate (SI-5) was prepared according to a literature procedure in 87% yield.[4] ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.14 (q, *J* = 7.1 Hz, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.27 (dt, *J* = 7.0, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.85 (quin, *J* = 7.2 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[4]

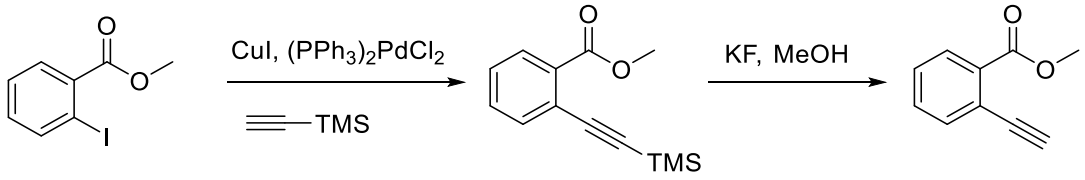
Methyl 2-(6-ethoxy-6-oxohex-1-yn-1-yl)benzoate (1e). A flask was charged with compound **SI-1** (0.50 g, 1.8 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.0.038 g, 0.054 mmol, 0.030 equiv), and CuI (0.031 g, 0.16 mmol, 0.090 equiv). The flask was then evacuated and refilled with N_2 three times before 4 mL of acetonitrile and Et_3N (0.25 mL, 1.8 mmol, 8.0 equiv) was added. **SI-5** (0.38 g, 2.7 mmol, 1.5 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 125 mL EtOAc and washed with NH_4Cl (1 × 45 mL), water (1 × 45 mL), brine (1 × 45 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Product-containing fractions were combined and

concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1a** as a light yellow oil (0.42 g, 80% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.88 (d, *J* = 9.4 Hz, 1H), 7.5 (d, *J* = 9.1 Hz, 1H), 7.42 (t, *J* = 8.9 Hz, 1H), 7.31 (t, *J* = 9.0 Hz, 1H), 4.13 (q, *J* = 8.4 Hz, 2H), 3.91 (s, 3H), 2.56-2.52 (m, 4H), 1.95 (quin, *J* = 8.5 Hz, 2H), 1.25 (t, *J* = 8.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 166.9, 134.3, 132.0, 131.6, 130.2, 127.4, 124.2, 94.4, 80.1, 60.4, 52.2, 33.2, 33.0, 29.7, 23.9, 23.5, 18.7, 14.3.

HRMS (ESI+): Calculated for $C_{16}H_{18}O_4Na$ ([M+Na]$^+$), 297.1103; found 297.1096.



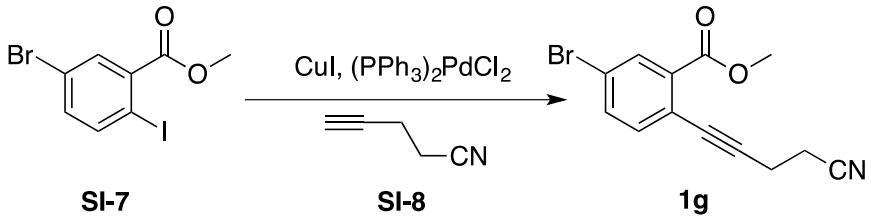
SI-1 **SI-6** **1f**

Methyl 2-((trimethylsilyl)ethynyl)benzoate (SI-6). A flask was charged with compound **SI-1** (5.2 mL, 38 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.53 g, 1.5 mmol, 0.020 equiv), and CuI (0.29 g, 1.5 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 76 mL of acetonitrile and Et_3N (40 mL, 300 mmol, 8 equiv) were added. TMS acetylene (5.9 mL, 42 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (5% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 300 mL Et_2O and washed with NH_4Cl (1 × 50 mL), water (1 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 5% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **SI-6** as a yellow oil (7.0 g, 79% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.90 (app d, *J* = 7.6 Hz, 1H), 7.58 (app d, *J* = 7.5 Hz, 1H), 7.44 (td, *J* = 7.6, 0.8 Hz, 1H), 7.36 (app t, *J* = 7.6 Hz, 1H), 3.92 (s, 3H), 0.27 (s, 9H). This spectrum is in agreement with previously reported spectral data.[5]

Methyl 2-ethynylbenzoate (1f). A flask was charged with compound **SI-6** (2.9 g, 13 mmol, 1.0 equiv), 63 mL methanol, and potassium fluoride (2.6 g, 44 mmol, 3.5 equiv). The flask was then sealed with a ground glass stopper and heated to 40 °C while stirring for 3 h. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 200 mL Et_2O and washed with water (4 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo at ~10 Torr and 25 °C [warning: product is volatile], yielding a dark yellow/red liquid (1.7 g, 84% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.94 (dd, *J* = 9.5, 1.1 Hz, 1H), 7.62 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.47 (td, *J* = 9.1, 1.6 Hz, 1H), 7.40 (td, *J* = 9.2, 1.5 Hz, 1H), 3.93 (s, 3H), 3.40 (s, 1H). This spectrum is in agreement with previously reported spectral data.[6]



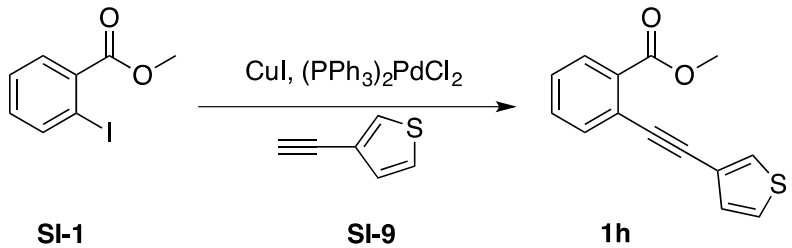
SI-7 **SI-8** **1g**

Methyl 5-bromo-2-(4-cyanobut-1-yn-1-yl)benzoate (1g). A flask was charged with compound **SI-7** (0.34 g, 1.0 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.014 g, 0.020 mmol, 0.020 equiv), and CuI (0.008 g, 0.04 mmol, 0.04 equiv). The flask was then evacuated and refilled with N_2 three times before 2 mL of acetonitrile and Et_3N (1.1 mL, 8.0 mmol, 8.0 equiv) were added. **SI-8** (0.10 mL, 1.1 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 150 mL EtOAc and washed with NH_4Cl (1 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1g** as a light yellow solid (0.25 g, 86% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.06 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 3.92 (s, 3H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.2, 135.7, 134.9, 133.4, 122.3, 122.0, 118.3, 91.7, 81.0, 52.6, 17.5, 17.2.

HRMS (CI+): Calculated for $C_{13}H_{14}BrN_2O_2$ ($[M+NH_4]^+$), 309.0239; found 309.0230.



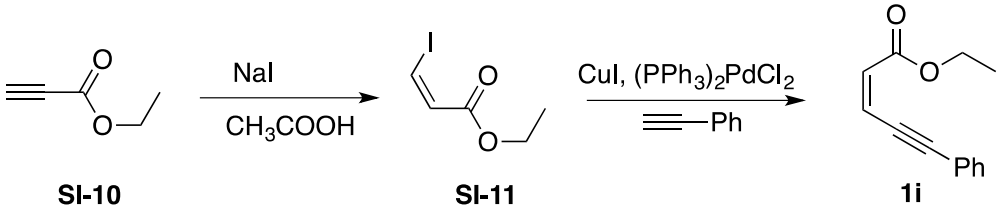
SI-1 **SI-9** **1h**

Methyl 2-(thiophen-3-ylethynyl)benzoate (1h). A flask was charged with compound **SI-1** (0.22 mL, 1.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.021 g, 0.030 mmol, 0.020 equiv), and CuI (0.011 g, 0.060 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 3 mL of acetonitrile and Et_3N (1.7 mL, 12 mmol, 8.0 equiv) was added. **SI-9** (0.17 mL, 1.7 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 150 mL EtOAc and washed with NH_4Cl (1 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1h** as a light yellow solid (0.37 g, 78% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.00 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.61 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.57 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.1 Hz, 1H), 7.29 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.23 (dd, *J* = 5.0, 1.1 Hz, 1H), 3.93 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.7, 134.0, 131.8, 131.7, 130.5, 130.0, 129.2, 127.9, 125.5, 123.8, 122.5, 89.7, 87.9, 52.2.

HRMS (CI+): Calculated for $C_{14}H_{10}SO_2$ ($[M]^+$), 242.0401; found 242.0390.



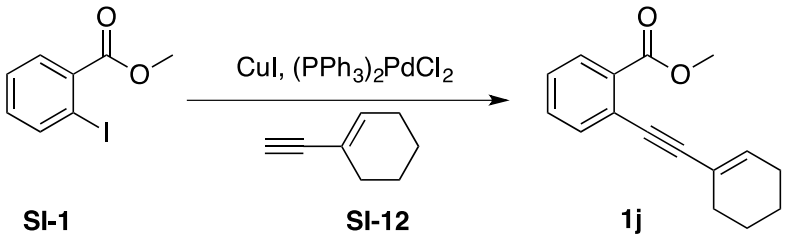
SI-10 **SI-11** **1i**

Ethyl (Z)-3-iodoacrylate (SI-11) was prepared according to a literature procedure in 67% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.43 (d, *J* = 8.9 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[7]

Ethyl (Z)-5-phenylpent-2-en-4-ynoate (1i). A flask was charged with compound **SI-11** (0.50 g, 2.2 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.12 g, 0.17 mmol, 0.080 equiv), and CuI (0.015 g, 0.081 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 5 mL of Et_3N was added. Phenylacetylene (0.29 mL, 2.6 mmol, 1.2 equiv) was then syringed into the reaction mixture which was then heated to 50 °C and stirred for 18 h under dynamic N_2. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 150 mL Et_2O and washed with NH_4Cl (1 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo,

and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1i** as a viscous light yellow oil (0.28 g, 63% yield).

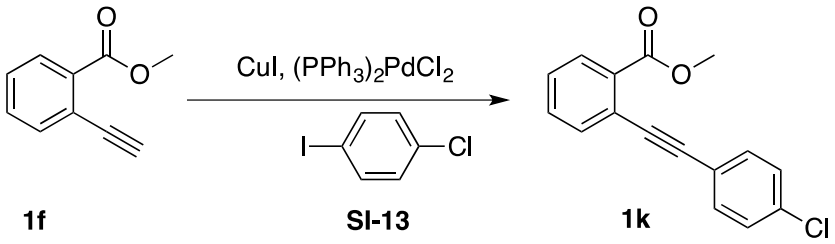
^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.53 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.36 – 7.33 (m, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[2]



SI-1 **SI-12** **1j**

Methyl 2-(cyclohex-1-en-1-ylethynyl)benzoate (1j). A flask was charged with compound **SI-1** (0.22 mL, 1.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.021 g, 0.030 mmol, 0.020 equiv), and CuI (0.011 g, 0.060 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 3 mL of acetonitrile and Et_3N (1.7 mL, 12 mmol, 8.0 equiv) was added. **SI-12** (0.20 mL, 1.7 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 150 mL Et_2O and washed with NH_4Cl (1 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 5% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1j** as a light yellow oil (0.35 g, 96% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.92 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.43 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (td, *J* = 7.7, 1.2 Hz, 1H), 6.28 – 6.26 (m, 1H), 3.92 (s, 3H), 2.28 – 2.25 (m, 2H), 2.18 – 2.14 (m, 2H), 1.71 – 1.67 (m, 2H), 1.64 – 1.61 (m, 2H). This spectrum is in agreement with previously reported spectral data.[8]



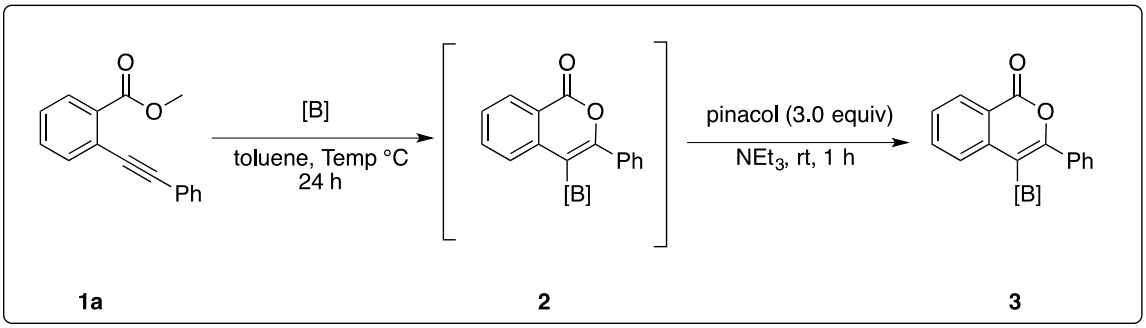
1f **SI-13** **1k**

Methyl 2-((4-chlorophenyl)ethynyl)benzoate (1k). A flask was charged with compound **SI-13** (0.36 g, 1.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.021 g, 0.030 mmol, 0.020 equiv), and CuI (0.012 g, 0.060 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 3 mL of acetonitrile and Et_3N (1.7 mL, 12 mmol, 8.0 equiv) was added. **1f** (0.27 g, 1.7 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At

this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 150 mL Et_2O and washed with NH_4Cl (1 × 40 mL), water (1 × 40 mL), brine (1 × 40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1k** as a light yellow liquid that solidified upon standing at room temperature (0.34 g, 84% yield).

^{1}H NMR ($CDCl_3$, 500MHz): δ 7.99 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.64 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.52 – 7.49 (m, 3H), 7.40 (td, *J* = 7.7, 1.3 Hz, 1H), 7.35 – 7.33 (m, 2H), 3.96 (s, 3H). This spectrum is in agreement with previously reported spectral data.[9]

B. [B] Electrophile Screen



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

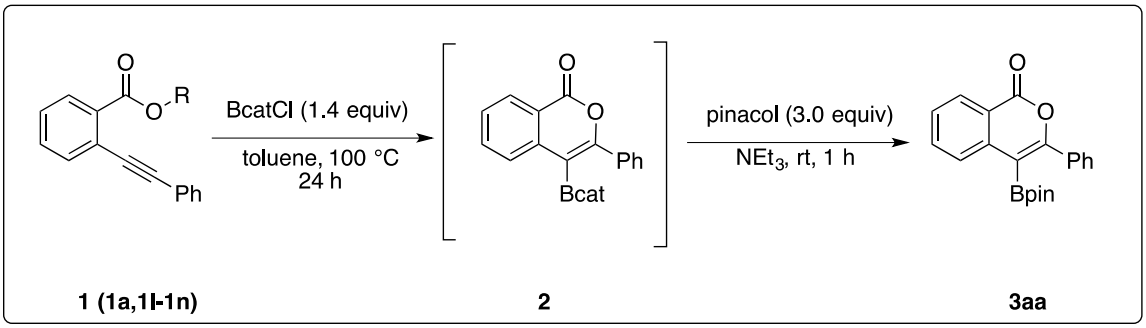
General Procedure: Entries 1 and 2

This screen was carried out in a nitrogen-filled glove box. A 4 mL vial was charged with **1a** (0.118 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. 0.6 mL (1.2 equiv) of a 1M solution of either BBr_3 or BCl_3 was then added to the vial, and the vial was sealed and heated to 45 °C for 24 h. At this time, the reaction mixture was cooled down to room temperature. In a separate vial, pinacol (0.18 g, 1.5 mmol, 3 equiv) was dissolved in Et_3N (1.0 mL, 7.5 mmol, 15 equiv). This solution was then added to the reaction mixture. The resulting solution was stirred for 1 h at room temperature. The solution was eventually concentrated in vacuo. ^1H NMR spectroscopy (600 MHz, $CDCl_3$) and ^{11}B NMR spectroscopy (126 MHz, $CDCl_3$) confirmed that the desired product **3aa** was not produced.

General Procedure: Entries 3–5

This screen was carried out in a nitrogen-filled glove box. A 4 mL vial was charged with **1a** 0.50 mmol, 1.0 equiv) and 0.5 mL toluene. In a separate vial, *B*-chlorocatecholborane (0.7 mmol, 1.4 equiv) or *B*-bromocatecholborane (0.7 mmol, 1.4 equiv) was added. The initial reaction vial was then transferred to the boron-containing vial via pipette, and this vial was sealed and heated to the specified temperature for 24 h. At this time, the reaction mixture was cooled down to room temperature. In a separate vial, pinacol (0.18 g, 1.5 mmol, 3 equiv) was dissolved in Et_3N (1.0 mL, 7.5 mmol, 15 equiv). This solution was then added to the reaction mixture. The resulting solution was stirred for 1 h at room temperature. The solution was eventually concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3aa** as a light yellow oil, which solidified upon standing. The ^1H NMR spectrum of each product was then compared to the authentic sample (See section D, product **3aa**) to establish purity and identity.

C. Synthesis of *O*-Alkyl Esters and Screen

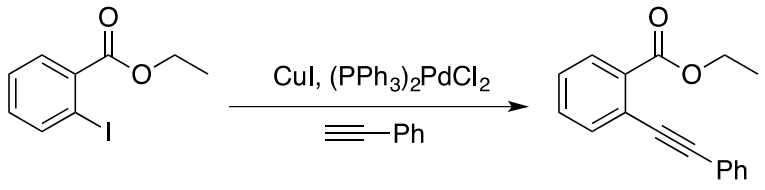


1 (1a,1l-1n) **2** **3aa**

Entry	R	Yield (%)[a] **3aa**
1	Me (**1a**)	81
2	Et (**1l**)	68
3	*i*Pr (**1m**)	60
4	*t*Bu (**1n**)	0

General Procedure

This screen was carried out in a nitrogen-filled glove box. A 4 mL vial was charged with the desired *O*-alkyl ester (**1a**, **1l-1n**) **(**0.50 mmol, 1.0 equiv) and 0.5 mL toluene. In a separate vial, *B*-chlorocatecholborane (0.7 mmol, 1.4 equiv) was added. The initial reaction vial was then transferred to the boron-containing vial via pipette, and this vial was sealed and heated to 100 ^{o}C for 24 h. At this time, the reaction mixture was cooled down to room temperature. In a separate vial, pinacol (0.18 g, 1.5 mmol, 3 equiv) is dissolved in Et_3N (1.0 mL, 7.5 mmol, 15 equiv). This solution is then added to the reaction mixture via pipette. The resulting solution was then stirred for 1 h at room temperature. The solution was then concentrated in vacuo. 1H NMR was then taken of each crude mixture in $CDCl_3$ and compared against mesitylene as the internal standard to determine the yield of the desired borylated isocoumarin **3aa**.

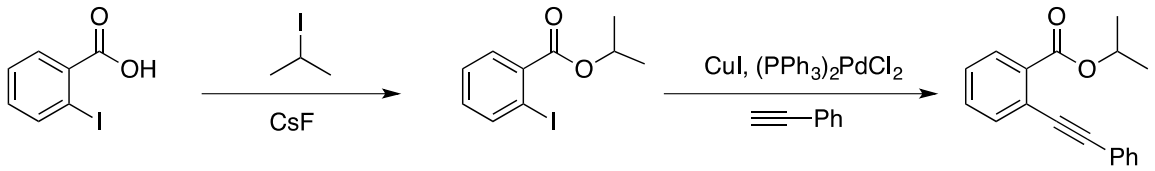


SI-14 **1l**

Ethyl 2-(phenylethynyl)benzoate (1l). A flask was charged with compound **SI-14** (0.96 g, 3.50 mmol, 1.00 equiv), $(PPh_3)_2PdCl_2$ (0.049 g, 0.070 mmol, 0.020 equiv), and CuI (0.027 g, 0.140 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 7 mL of acetonitrile and Et_3N (3.8 mL, 28 mmol, 8.0 equiv) was added. Phenylacetylene (0.42 mL, 3.8 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of

starting material. The reaction mixture was diluted with 200 mL EtOAc and washed with NH_4Cl (1 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 5% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1l** as a light yellow oil (0.68 g, 78% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.99 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.65 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.60 – 7.58 (m, 2H), 7.47 (app t, *J* = 7.6 Hz, 1H), 7.38 – 7.34 (m, 4H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[10]

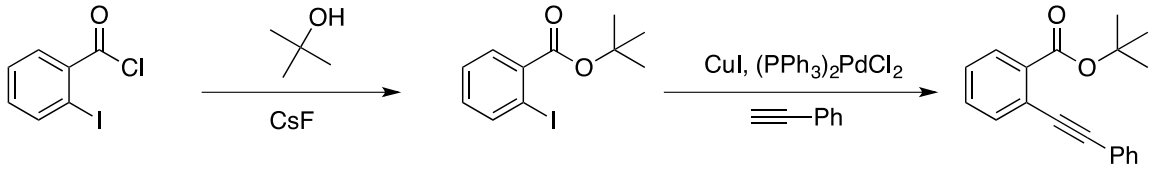


SI-15 **SI-16** **1m**

Isopropyl 2-iodobenzoate (SI-16) was prepared according to a literature procedure in 56% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.68 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.37 (td, *J* = 7.7, 1.0 Hz, 1H), 7.10 (td, *J* = 7.9, 1.7 Hz, 1H), 5.24 (hept, *J* = 6.2 Hz, 1H), 1. 39 (d, *J* = 6.2 Hz, 6H). This spectrum is in agreement with previously reported spectral data.[11]

Isopropyl 2-(phenylethynyl)benzoate (1m). A flask was charged with compound **SI-16** (0.50 g, 1.7 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.024 g, 0.034 mmol, 0.020 equiv), and CuI (0.013 g, 0.070 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 4 mL of acetonitrile and Et_3N (1.9 mL, 14 mmol, 8.0 equiv) was added. Phenylacetylene (0.21 mL, 1.9 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (15% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 200 mL EtOAc and washed with NH_4Cl (1 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 5% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1m** as a light yellow oil (0.39 g, 85% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.95 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.65 – 7.63 (m, 1H), 7.58 – 7.56 (m, 2H), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H), 7.39 – 7.34 (m, 4H), 5.30 (hept, *J* = 6.2 Hz, 1H), 1.38 (d, *J* = 6.2 Hz, 6H). This spectrum is in agreement with previously reported spectral data.[12]



SI-17 **SI-18** **1n**

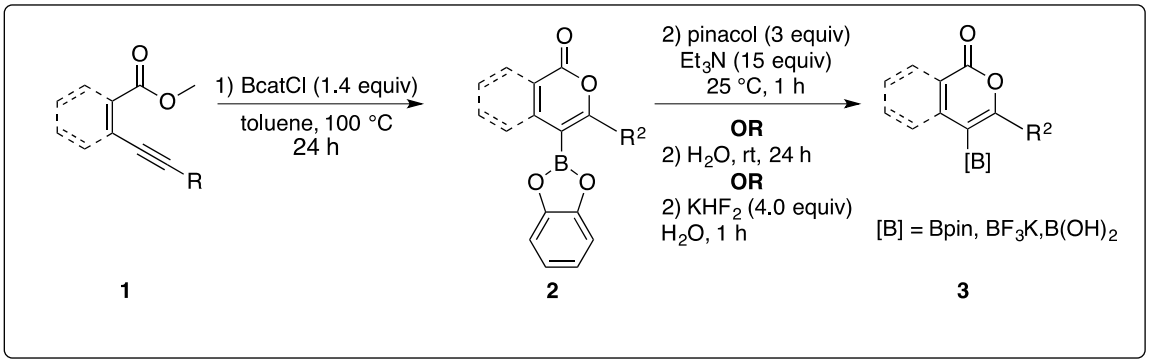
***tert*-Butyl 2-iodobenzoate (SI-18)** was prepared according to a literature procedure in 75% yield.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.94 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.68 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.37 (td, *J* = 7.7, 1.0 Hz, 1H), 7.10 (td, *J* = 7.9, 1.7 Hz, 1H), 1.6 (s, 29H). This spectrum is in agreement with previously reported spectral data.[13]

***tert*-Butyl 2-(phenylethynyl)benzoate (1n)**. A flask was charged with compound **SI-18** (0.49 g, 1.6 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.022 g, 0.032 mmol, 0.020 equiv), and CuI (0.012 g, 0.064 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 3 mL of acetonitrile and Et_3N (1.8 mL, 13 mmol, 8.0 equiv) was added. Phenylacetylene (0.20 mL, 1.8 mmol, 1.1 equiv) was then syringed into the reaction mixture which stirred for 18 h under dynamic N_2. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 200 mL EtOAc and washed with NH_4Cl (1 × 25 mL), water (1 × 25 mL), brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient from 100% hexanes to 5% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **1n** as a light yellow oil (0.40 g, 90% yield).

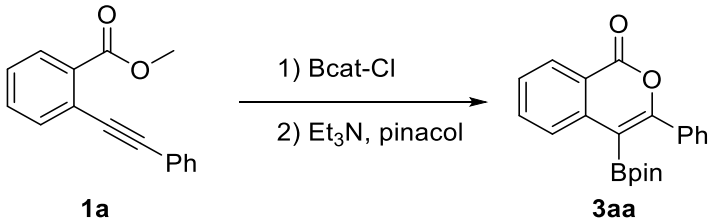
^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.86 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.56 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.51 (dd, *J* = 8.1, 1.9 Hz, 2H), 7.39 (td, *J* = 7.7, 1.3 Hz, 1H), 7.32 – 7.28 (m, 4H), 1.56 (s, 9H). This spectrum is in agreement with previously reported spectral data.[2]

A. Synthesis and Isolation of Carboxyboration Products 3aa–3k



General Remarks

For synthetic ease, these reactions were carried out in a nitrogen-filled glovebox unless specified otherwise. *B*-Chlorocatecholborane is water-reactive and should be stored cool (0 °C or lower) in a desiccator or glovebox when not in use.



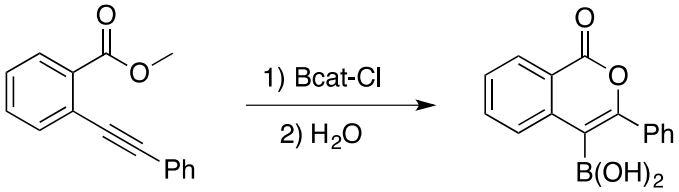
3-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3aa). A vial was charged with **1a** (0.118 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3aa** as a yellow oil (0.13 g, 75% yield).

^{1}H NMR (toluene-d_8, 600 MHz): δ 8.32 (app dd, J = 7.9, 1.0 Hz, 1H), 7.92 (app dd, J = 7.9, 0.4 Hz, 1H), 7.52 – 7.50 (m, 2H), 7.27 (ddd, J = 15.3, 6.5, 1.5 Hz, 1H), 7.12 – 6.99 (m, 4H), 0.99 (s, 12H).

^{13}C NMR (toluene-d_8, 125 MHz): δ 161.4, 160.9, 129.1, 128.7, 128.1, 128.1, 127.8, 125.3, 124.9, 84.0, 24.7, 20.7, 20.6, 20.3, 20.1.

^{11}B NMR (toluene-d_8, 193 MHz): δ 31.5.

HRMS (ESI+): Calculated for $C_{21}H_{21}BO_4Na$ ($[M+Na]^+$), 371.1435; found 371.1434.



1a **3ab**

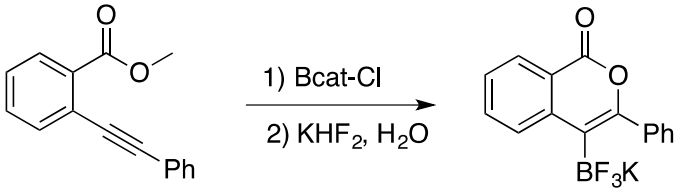
(1-oxo-3-phenyl-1*H*-isochromen-4-yl)Boronic acid (3ab). A vial was charged with **1a** (0.118 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and transferred to a vial containing 1 mL of water, and the resulting mixture stirred vigorously for 18 h at room temperature. The solution was then filtered through a medium porosity fritted funnel. The solid was then rinsed with cold (~0 °C) water (3 × 3 mL). The solid was dried in vacuo c.a. 10 mTorr for 18 h to afford **3ab** as a light purple solid (0.088 g, 66% yield).

^{1}H NMR (CD_3CN, 600 MHz): δ 8.27 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.81 (ddd, *J* = 15.2, 7.2, 1.4 Hz, 1H), 7.76 – 7.75 (m, 2H), 7.65 (app d, *J* = 7.7 Hz, 1H), (ddd, *J* = 15.2, 7.9, 0.5 Hz, 1H), 7.53 – 7.49 (m, 3H), 6.51 (s, 2H).

^{13}C NMR (CD_3CN, 125 MHz): δ 162.2, 155.2, 139.4, 135.0, 134.9, 129.9, 128.7, 128.2, 127.5, 127.0.

^{11}B NMR (CD_3CN, 193 MHz): δ 30.0.

HRMS (ESI-): Calculated for $C_{15}H_{11}BO_4Cl$ ([M+Cl]$^-$), 301.0442; found 301.0441.



1a **3ac**

3-Phenyl-4-(trifluoro-λ^4-boranyl)-1*H*-isochromen-1-one, potassium salt (3ac). A vial was charged with **1a** (0.118 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and dissolved in 1 mL acetone and concentrated in vacuo. The content of the flask was then transferred into a 10mL flask with KHF_2 (0.137g, 1.80 mmol, 3.50 equiv) and 1.5 mL H_2O in it. The resulting mixture was stirred for 1 h then concentrated on the vacuo. The volatiles were removed at c.a. 10 mTorr for 1 h. The product then filtered through a medium porosity fritted funnel. The solid was then rinsed with cold (~0 °C) water (3 × 3 mL) and ether (3 x 3 mL). The solid was dried in vacuo c.a. 10 mTorr for 18 h to afford **3ac** as a white solid (0.103 g, 63% yield).

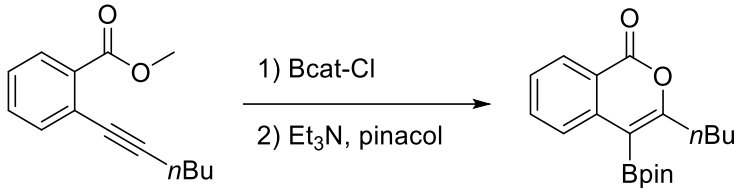
^{1}H NMR ($(CD_3)_2CO$, 600 MHz): δ 8.37 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 6.4 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.31 – 7.30 (m, 3H).

^{13}C NMR ($(CD_3)_2CO$, 600 MHz): δ 168.5, 160.0, 148.8, 143.2, 138.2, 138.1, 135.4, 135.3, 135.2, 132.9, 131.9, 131.2, 126.3.

^{11}B NMR ($(CD_3)_2CO$, 193 MHz): δ 2.9.

^{19}F NMR ($(CD_3)_2CO$, 376 MHz): δ -131.6.

HRMS (ESI-): Calculated for $C_{15}H_9BF_3O_2$ ($[M-K]^-$), 289.0651; found 289.0640.



1b **3b**

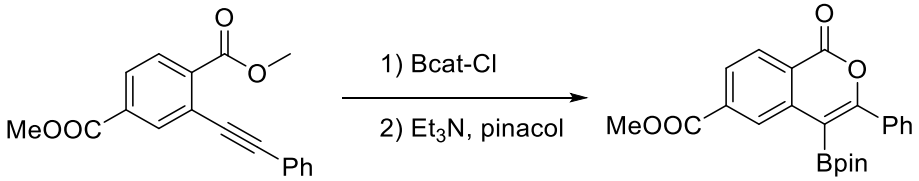
3-Butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3b). A vial was charged with **1b** (0.108 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3b** as a yellow oil (0.16 g, 97% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.24 (d, *J* = 9.5 Hz, 1H), 8.04 (d, *J* = 9.9 Hz, 1H), 7.65 (td, *J* = 9.5, 1.5 Hz, 1H), 7.42 – 7.38 (m, 1H), 2.80 (t, *J* = 9.3 Hz, 2H), 1.72 – 1.66 (m, 2H), 1.39 – 1.38 (m, 14H), 0.92 (t, *J* = 8.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.6, 162.9, 139.8, 134.7, 129.2, 127.2, 126.6, 119.9, 84.0, 33.7, 30.9, 24.9, 22.5, 13.9.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 31.6.

HRMS (ESI+): Calculated for $C_{19}H_{25}BO_4K$ ($[M+K]^+$), 367.1487; found 367.1481.



1c **3c**

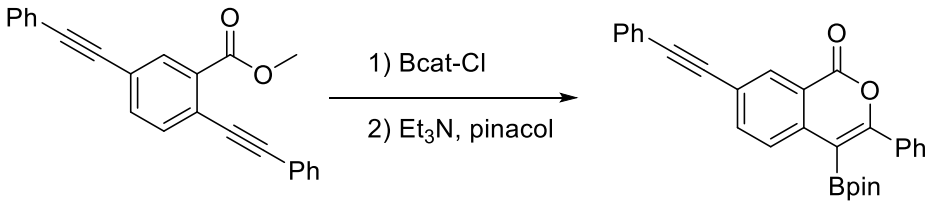
Methyl 1-oxo-3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromene-6-carboxylate (3c). A vial was charged with **1c** (0.147 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3c** as a yellow solid (0.13 g, 65% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.60 (d, *J* = 1.1 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.71 – 7.70 (m, 2H), 7.49-7.43 (m, 3H), 3.99 (s, 3H), 1.35 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.0, 161.8, 160.3, 139.7, 135.4, 134.2, 130.4, 129.9, 128.8, 128.4, 128.3, 128.1, 123.1, 84.8, 52.7, 24.8.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 31.7.

HRMS (ESI+): Calculated for $C_{23}H_{23}BO_6Na$ ($[M+Na]^+$), 429.1490; found 429.1499.



1d **3d**

3-Phenyl-7-(phenylethynyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3d). A vial was charged with **1d** (0.168 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo

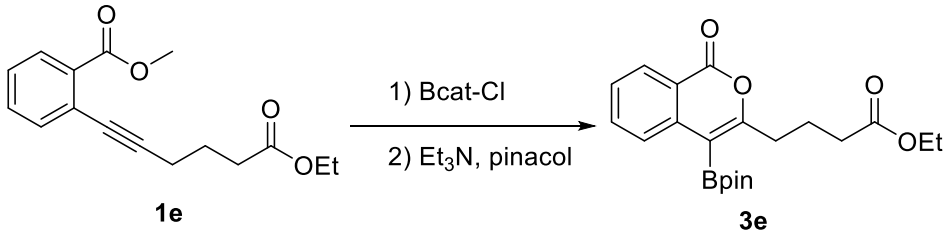
and purified by column chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3d** as a yellow solid (0.15 g, 66% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.50 (s, 1H), 7.85 – 7.81 (m, 2H), 7.68 (app d, *J* = 7.5 Hz, 2H), 7.56 – 7.54 (m, 2H), 7.47 – 7.45 (m, 1H), 7.43 – 7.41 (m, 2H), 7.38 – 7.35 (m, 3H), 1.29 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.7, 160.5, 139.2, 137.3, 134.5, 132.7, 131.8.9, 130.3, 128.9, 128.8, 128.5, 128.2, 126.6, 123.1, 122.8, 120.3, 91.5, 88.3, 84.6, 24.9.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 31.3.

HRMS (ESI+): Calculated for $C_{29}H_{25}BO_4Na$ ($[M+Na]^+$), 471.1749; found 471.1759.



1e **3e**

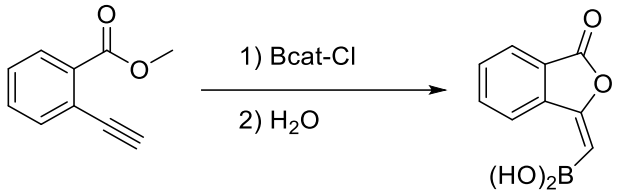
Ethyl 4-(1-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-3-yl)butanoate (3e). A vial was charged with **1e** (0.064 g, 0.233 mmol, 1.00 equiv) and 0.23 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.050 g, 0.33 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.23 mL toluene. A separate vial was then charged with pinacol (0.083 g, 0.70 mmol, 3.0 equiv) and Et_3N (0.5 mL, 3.8 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3e** as a yellow solid (0.050 g, 55% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.25 (app d, *J* = 8.0 Hz, 1H), 8.08 (app d, *J* = 8.2 Hz, 1H), 7.66 (ddd, *J* = 11.8, 5.9, 1.1 Hz, 1H), 7.42 (app t, *J* = 7.6 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.36 (t, *J* = 7.6 Hz, 2H), 2.05 (tt, *J* = 14.8, 7.5 Hz, 2H), 1.38 (s, 12H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.1, 165.2, 162.7, 139.5, 134.7, 129.3, 127.5, 126.8, 120.0, 84.2, 60.4, 33.6, 33.1, 24.9, 23.7, 14.3.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 31.3.

HRMS (ESI+): Calculated for $C_{21}H_{27}BO_6Na$ ($[M+Na]^+$), 409.1802; found 409.1808.



1f **3f**

(E)-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)Boronic acid (3f). A vial was charged with **1f** (0.080 g, 0.50 mmol, 1.0 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 20 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then transferred to a vial containing 10 mL of water, and the resulting mixture stirred vigorously for 3 h at room temperature. The solution was then filtered through a medium porosity fritted funnel. The solid was then rinsed with cold (0 °C) water (3 × 3 mL). The solid was dried in vacuo c.a. 10 mTorr for 18 h to afford **3f** as a light brown solid (0.058 g, 61% yield).

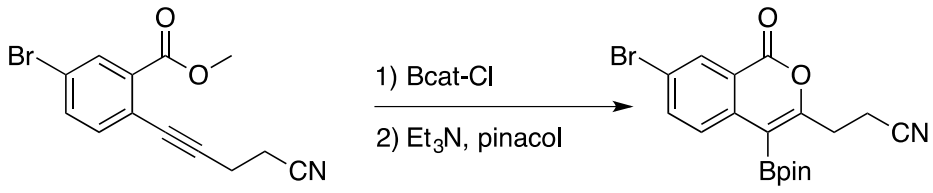
^{1}H NMR (CD_3CN, 600 MHz): δ 8.60 (d, *J* = 9.6 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.79 (app t, *J* = 9.2 Hz, 1H), 7.65 (app t, *J* = 9.0 Hz, 1H), 6.34 (s, 2H), 5.48 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 157.2, 139.3, 135.6, 131.8, 127.5, 125.99, 125.4, 118.3.

^{11}B NMR (CD_3CN, 193 MHz): δ 28.1.

HRMS (ESI-): Calculated for $C_9H_7BO_4Cl$ ($[M+Cl]^-$), 225.0128; found 225.0121.

Note: An HMQC determined the H–C correlation of the compound, such that the non-aromatic C–H peak coordinated with a carbon peak that is not visible in the ^{13}C NMR because of broadening. This analysis determined the regiochemistry to be a 5-membered ring.



1g **3g**

3-(7-bromo-1-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-3-yl)propanenitrile (1g). A vial was charged with **1g** (0.146 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this

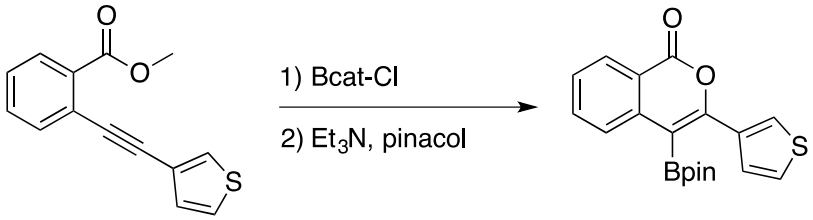
vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 25% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3g** as a white solid (0.079 g, 39% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.37 (d, *J* = 2.2 Hz, 1H), 8.18 (d, *J* = 8.7 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.26 (t, *J* = 7.4 Hz, 2H), 2.76 (t, *J* = 7.4 Hz, 2H), 1.40 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.3, 160.7, 138.1, 137.7, 131.8, 129.4, 121.8, 121.8, 118.3, 84.6, 29.7, 25.0, 16.2.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 30.6.

HRMS (ESI+): Calculated for $C_{18}H_{19}BBrNO_4Na$ ([M+Na]$^+$), 426.0492; found 426.0486.



1h **3h**

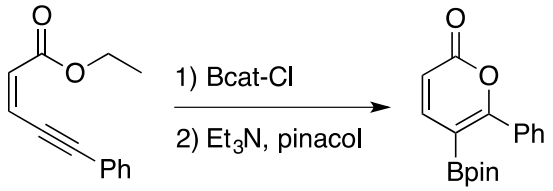
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(thiophen-3-yl)-1H-isochromen-1-one (3h). A vial was charged with **1h** (0.177 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3h** as a white solid (0.13 g, 71% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.31 (app d, *J* = 7.9 Hz, 1H), 7.78 – 7.76 (m, 1H), 7.74 (dd, *J* = 8.0, 0.3 Hz, 1H), 7.69 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 7.46 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 7.43 – 7.42 (m, 1H), 7.35 – 7.33 (m, 1H), 1.34 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.3, 154.5, 139.6, 135.9, 134.8, 129.7, 127.9, 127.7, 127.2, 126.4, 125.8, 120.2, 84.7, 25.1.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 31.8.

HRMS (ESI+): Calculated for $C_{21}H_{19}BO_4SNa$ ([M+Na]$^+$), 377.0999; found 377.0995.



1i **3i**

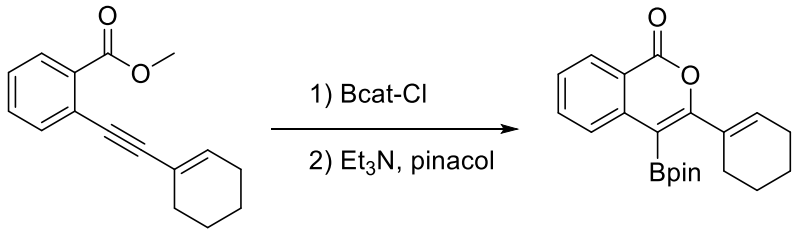
6-Phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-pyran-2-one (3i). A vial was charged with **1i** (0.070 g, 0.35 mmol, 1.0 equiv) and 0.4 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.075 g, 0.49 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.4 mL toluene. A separate vial was then charged with pinacol (0.124 g, 1.05 mmol, 3.00 equiv) and Et_3N (0.70 mL, 5.3 mmol, 15 equiv). This mixture was added to the reaction mixture drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 25% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3i** as a yellow crystalline solid (0.049 g, 47% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.65 – 7.63 (m, 3H), 7.47 (app t, *J* = 7.4 Hz, 1H), 7.39 (app t, *J* = 7.7 Hz, 2H), 6.27 (d, *J* = 9.3 Hz, 1H), 1.25 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.6, 162.1, 148.9, 133.3, 131.0, 129.5, 127.9, 113.0, 84.5, 24.7.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 30.8.

HRMS (ESI+): Calculated for $C_{17}H_{19}BO_4Na$ ($[M+Na]^+$), 321.1277; found 321.1283.



1j **3j**

3-(cyclohex-1-en-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3j). A vial was charged with **1j** (0.120 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction

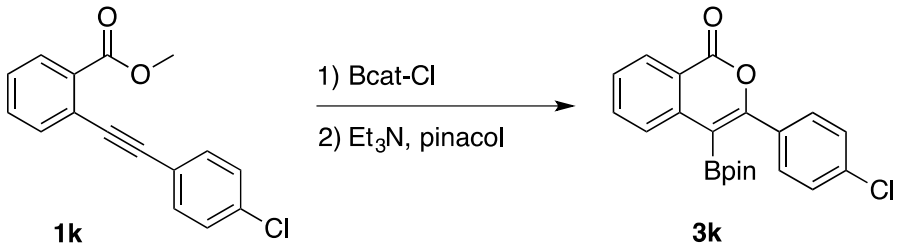
mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3j** as a yellow oil (0.14 g, 77% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.25 (app d, *J* = 7.8 Hz, 1H), 7.72 (app d, *J* = 8.0 Hz, 1H), 7.64 (app td, *J* = 7.6, 1.2 Hz, 1H), 7.41 (app td, *J* = 7.6, 1.0 Hz, 1H), 2.41 – 2.39 (m, 2H), 7.43 – 7.42 (m, 2H), 2.14-2.12 (m, 2H), 1.74 – 1.70 (m, 2H), 1.65 – 1.61 (m, 2H), 1.35 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.0, 162.7, 139.8, 134.6, 134.6, 132.0, 129.5, 127.5, 126.2, 120.2, 84.2, 26.3, 25.5, 25.0, 22.2, 21.7.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 31.3.

HRMS (ESI+): Calculated for $C_{21}H_{25}BO_4Na$ ($[M+Na]^+$), 375.1747; found 375.1744.



3-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3k). A vial was charged with **1k** (0.135 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added drop wise over c.a. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added drop wise over c.a. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at c.a. 10 mTorr for 18 h to afford **3k** as a white solid (0.11 g, 60% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.73 (app t, *J* = 7.7 Hz, 1H), 7.64 – 7.62 (m, 2H), 7.52 (app t, *J* = 7.7 Hz, 1H), 7.41 – 7.39 (m, 2H), 1.31 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.3, 158.8, 139.5, 136.3, 135.0, 133.2, 130.4, 129.8, 128.5, 128.3, 126.6, 120.3, 84.7, 25.0.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 31.4.

HRMS (ESI+): Calculated for $C_{21}H_{20}BClO_4Na$ ($[M+Na]^+$), 405.1045; found 405.1048.

References

1) Hashmi, A. S. K.; Lothschuetz, C.; Doepp, R.; Ackermann, M.; De Buck Becker, J.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Cat.* **2012**, *354*, 133–147.

2) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936–5942.

3) Droz, S. A.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Act.* **2001**, *84*, 2243–2289.

4) Hirner, J. J.; Faizi, D. J.; Blum, S. A. *J. Am. Chem. Soc*. **2014**, *136*, 4740–4745.

5) Estelle, M.; Philippe, U.; Beatrice, L.; Loic, T.; Weghne, P. *Tetrahedron* **2007**, *63*, 9979–9990.

6) Pearson, A. J.; Kim, J. B. Tetrahedron Lett. **2003**, *44*, 8525–8527.

7) Spino, C.; Rezaei, H.; Dupont-Guadet, K.; Belanger, F. *J. Am. Chem. Soc*. **2004**, *126*, 9926–9927.

8) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc*. **1993**, *115*, 2637–2647.

9) Malik, H.; Bourguignon, J. J.; Bihel, F. J. –J. *Tetrahedron Lett.* **2008**, *49*, 62–65.

10) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **2009**, *351*, 2827–2832.

11) Anderson, N. G.; Maddaford, S. O.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556–9559.

12) Kusama, H.; Funami, H.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2004**, *6*, 605–608.

13) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681–7684.