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IRVINE

Borylative Heterocyclizations

DISSERTATION

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DOCTOR OF PHILOSOPHY

in Chemistry

by

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Publications

8. "Catalyst-Free Formal Thioboration to Synthesize Borylated Benzothiophenes and Dihydrothiophenes." **Faizi, D. J.**; Davis, A. J.; Meany, F. B.; Blum, S. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 14286–14290.

7. "Oxyboration: Synthesis of Borylated Benzofurans." **Faizi, D.J.**; Nava, N. A.; Al-Amin, M.; Blum, S. A. *Org. Synth.* **2016**, *93*, 228–244.

6. "Catalyst-Free Synthesis of Borylated Lactones from Esters via Electrophilic Oxyboration." **Faizi, D. J.**; Issaian, A.; Davis, A. J.; Blum, S. A. *J. Am. Chem. Soc.* **2016**, *138*, 2126–2129.

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3. “Alkoxyboration: Ring-Closing Addition of B–O σ Bonds Across Alkynes.” Hirner, J. J.; **Faizi, D. J.**; Blum, S. A. *J. Am. Chem. Soc.* **2014**, *136*, 4740–4745.

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Abstract of the Dissertation

Borylative Heterocyclizations

By

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Doctor of Philosophy in Chemistry

University of California, Irvine, 2017

Associate Professor Suzanne A. Blum, Chair

The syntheses of borylated *S*- and *O*- heterocycles are reported via mechanistically distinct borylative cyclizations. These methods can proceed with a Au(I) catalyst (direct borylation, formation of B–X bond) or without (formal borylation). Commercially-available *B*-chlorocatecholborane was the boron source used in these studies. The borylated products furnished from these methods provide complementary functional group tolerance to existing borylation methods, as well as complementary regioselectivity. Borylated benzofurans, dihydrofurans, isocoumarins, α-pyrones, benzothiophenes, and dihydrothiophenes were synthesized using this borylative cyclization methodology. In the direct borylative cyclization pathway (chapter 2), the mechanism is proposed to proceed via Au(I)-induced cyclization via a boric ester, follow by transmetalation of the organogold intermediate to furnish the desired borylated heterocycle. In the formal borylative cyclization pathway (chapters 3–5), mechanistic studies revealed that *B*-chlorocatecholborane preferentially coordinated with the C–C π system instead of the heteroatom to induce cyclization. These methods generate borylated building blocks that can be further functionalized through various C–B σ-bond transformations.

Chapter 1

Introduction to Borylative Heterocyclizations

Abstract: This chapter provides a brief introduction to the synthesis of borylated building blocks and electrophilic heterocyclizations. The context of work in the Blum group and this thesis in relation to the field is also discussed.

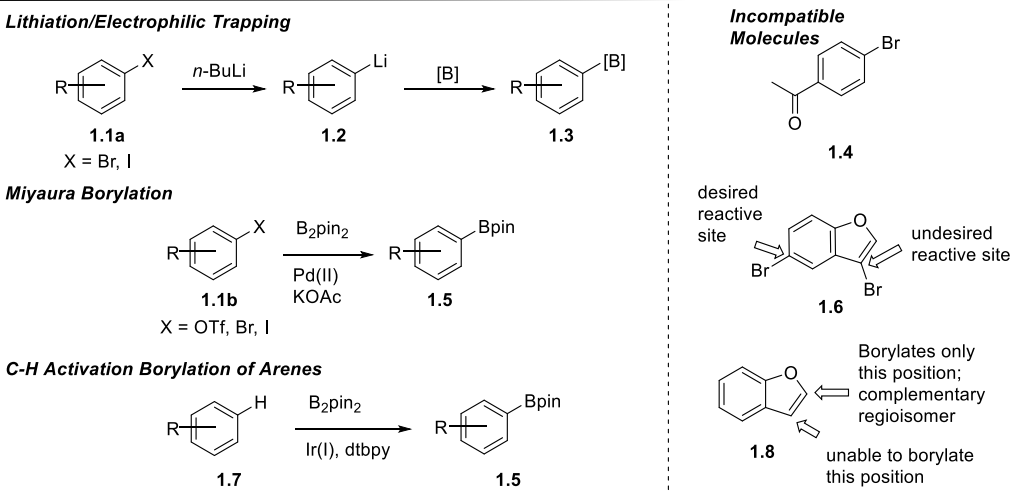
Introduction

Boronic acids and their ester derivatives have emerged as one of the preferred downstream functionalization partners in organic synthesis due to their versatility and low toxicity.[1] The C–B σ bonds in these compounds generate new C–C bonds via a variety of downstream functionalization reactions, most notably the Suzuki cross-coupling reaction.[2] With a need to rapidly build complexity in molecular scaffolds for drug discovery, it is of interest to develop new methods to install boron functional groups.

There are currently several methods to install this useful functional group. One way to install a B–C σ bond is through traditional functional group transformations. Three of the most common methods are lithiation/electrophilic trapping,[3] Miyaura borylation,[4] and Hartwig-Ishiyama borylation (Scheme 1.1).[5] In the lithiation/electrophilic trapping method, either an acidic proton or a halogen (via lithium/halogen exchange) is required to produce the desired lithiate species **1.2**. This nucleophilic species can then attack an electrophilic boron source (e.g. $B(OMe)_3$) to generate the desired boronic ester **1.3**. One advantage of this method is its simplicity in using generally available organic reagents (*n*-BuLi and $B(OMe)_3$ are commercially available), but a significant drawback of this system is the sensitivity to carbonyl-containing functional groups, additional acidic positions, and other

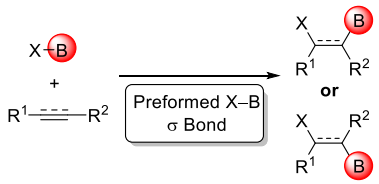
halogens (e.g., compound **1.4**). A milder borylation method was developed by Miyaura; this reaction removed the need for strong organolithium reagents, instead replacing the metalation step with catalytic palladium. For example, triflate- or halogen-containing compound **1.1b** is subjected to Miyaura borylation conditions to furnish borylated compound **1.5**. These conditions are mechanistically distinct from lithiation/electrophilic trapping; Miyaura borylation proceeds through a Pd(0) to Pd(II) cycle, requiring an oxidative addition into the carbon–halogen/triflate bond. Variants of this method use other transition metals, such as nickel.[6] One drawback of this method is the sensitivity to functional groups that could compete for oxidative addition of the Pd(0) species (e.g., as shown in compound **1.6**). The last major method to install C–B σ bonds is through C–H activation using Ru(I) (for alkyl variants)[7] or Ir(I) (for aryl variants).[8] Both transition metal systems employ boron dimers (B_2pin_2 or B_2cat_2); in the proposed mechanism, the weak B–B σ bond is a prime oxidative addition candidate which yields borylated compound **1.5**. Although reaction conditions are mild for these systems, the regioselectivity of this reaction is less controlled and can result in a mixture of regioisomers or only provide synthetic access to the complementary regioisomer (**1.8**).[9]

Scheme 1.1. Methods to synthesize C–B σ bonds without requiring a site of unsaturation.



Another method is by a *direct* borylation (this terminology was developed in our group); this involves preformation of a B–X bond (Figure 1.1). This element–boron bond can then be added to a site of unsaturation (e.g., an alkyne or alkene) to generate a new C–X σ bond as well as a C–B bond. One of the most common examples of a *direct* borylation is hydroboration;[10,11] a B–H bond is added across an alkyne to generate a boronic ester. Other B–X direct additions have been developed, such as X = C,[12,13] Si,[14–16] Sn,[14,17] S,[18] B,[14,19] Cl,[20] Br,[21] and I.[21] Most of these other direct additions require the use of a catalyst and proceed via oxidative addition into the B–X bond.

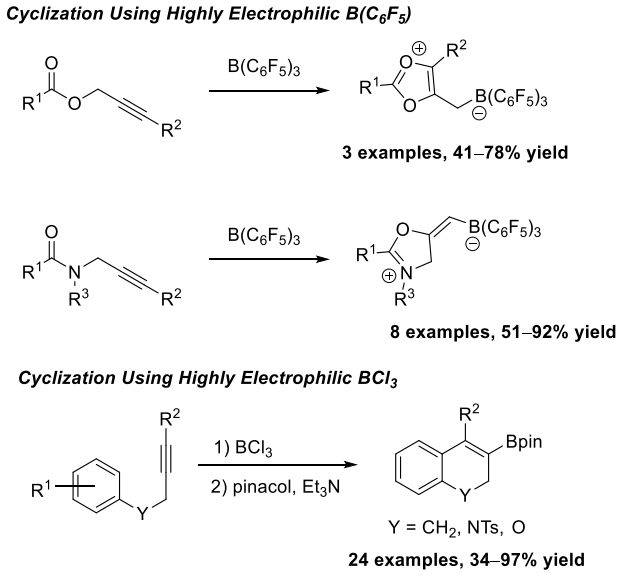
Figure 1.1. General reaction for direct borylation.



Although installing B–C σ bonds is a well-developed field via direct functional group transformations and direct borylations, there is little information about constructing a B–C σ bond during an electrophilic cyclization step (known as a borylative cyclization). In contrast, the ability to install a downstream handle as well as effect an electrophilic cyclization has been well developed using electrophiles such as ICl, I_2, Br_2, and Cl_2.[22–25] Early examples of borylative cyclizations of alkynes involved the use of highly electrophilic $B(C_6F_5)_3$ to synthesize a variety of zwitterionic intermediates (Scheme 1.2).[26–28] Despite the novelty, one drawback of these electrophilic cyclizations is the inability to further elaborate the C–B σ bond in a subsequent downstream functionalization step, as the zwitterions are unreactive to such transformations. One of the first borylative cyclizations that resulted in the formation of a usable C–B σ bond that served as a downstream handle

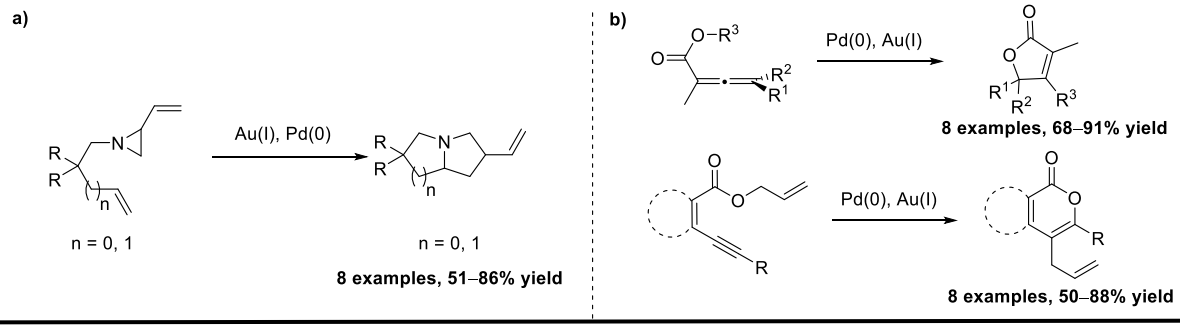
was a carboboration discovered by Ingleson and coworkers wherein electrophilic BCl_3 was required and proceeded through an electrophilic aromatic substitution pathway.[29]

Scheme 1.2. Early examples of borylative cyclizations.



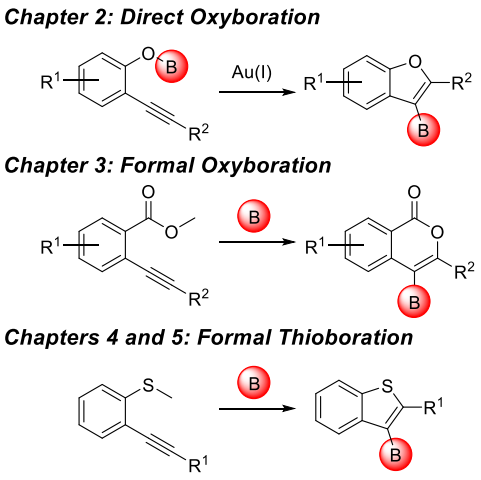
Previous work in the Blum group focused on using Au(I)/Pd(0) dual catalysis to effect unique functional group transformations (Scheme 1.3).[30–32] Gold(I) is a well-known carbophilic Lewis acid that can induce heterocyclizations.[33] The standard in the field is to protodeaurate the resulting vinyl- or arylgold species to generate the desired heterocycle. Instead of protodeauration, research in the Blum group devised strategies to elaborate the C–Au bond in Au/Pd systems to generate new C–C bonds via Pd(II)-catalyzed π-allyl cross-coupling reactions.[30,34]

Scheme 1.3. Previous work in the Blum group to synthesize **a)** *N*-heterocycles and **b)** *O*-heterocycles using Au(I) chemistry.



Building off this research, the following chapters discuss efforts towards the synthesis of borylated building blocks via borylative heterocyclization chemistry (Scheme 1.4). These transformations were effected not only via Au(I) catalysis using a direct borylation method (Chapter 2) to furnish borylated benzofurans, but also through formal borylation methods using electrophilic *B*-chlorocatecholborane (ClBcat) to synthesize borylated isocoumarins and α-pyrones (Chapter 3) as well as borylated benzothiophenes and dihydrothiophenes (Chapter 4). In contrast to direct borylations, formal borylations proceed through a mechanistically distinct pathway that does not require preformation of a B–X bond, but the final product will resemble that of a direct borylation reaction. In this terminology, formal borylation is the net addition of a heteroatom and boron to the C-C π bond. Preliminary mechanistic studies were conducted on the formal thioboration reaction to better understand the rules that govern reactivity in these formal heterocyclization reactions (Chapter 5). These reactions represent the first methods to synthesize *O*- and *S*-heterocyclic building blocks using *B*-chlorocatecholborane, a reagent that was predominantly used as a reagent to remove protecting groups[35] prior to the work reported in this dissertation.

Scheme 1.4. Preview of the work in this dissertation.



The reactions developed in this thesis are valuable for several reasons. The methods developed herein not only synthesize heterocycles, but also furnish B–C σ bond handles for further downstream functionalization reactions in the same synthetic step. Moroever, the mechanistic studies detailed in this thesis provide fundamental knowledge of the reactivity for direct and formal borylation methods that can serve as a springboard for future reaction design.

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Chapter 2

Oxyboration: Ring-Closing Addition of B–O σ Bonds Across Alkynes

Abstract: For nearly 70 years, the addition of boron–X σ bonds to carbon–carbon multiple bonds has been employed in the preparation of organoboron reagents. However, the significantly higher strength of boron–oxygen bonds has thus far precluded their activation for addition, preventing a direct route to access a potentially valuable class of oxygen-containing organoboron reagents for divergent synthesis. We herein report the realization of an oxyboration reaction, the addition of boron–oxygen σ bonds to alkynes. *O*-Heterocyclic boronic acid derivatives are produced using this transformation. Our results demonstrate activation of a boron–oxygen σ bond using a gold catalysis strategy that is fundamentally different from that used previously for other boron–element addition reactions. This project was initiated by graduate student Joshua J. Hirner. I served as second author on its publication.[1] For scientific clarity, the full story is shared here; our respective contributions are noted in the experimental section.

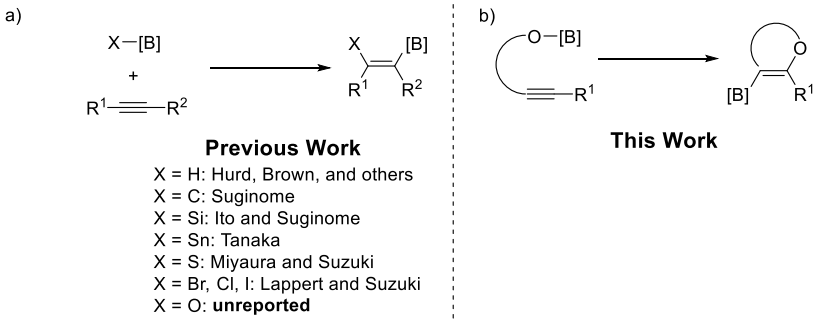
Introduction

Boronic acids and their derivatives are versatile reagents in modern organic synthesis, and the hydroboration reaction is a well-established method for generating these building blocks through the addition of B–H bonds across C–C multiple bonds.[2] First described by Hurd[3] in 1948 and later developed in detail by Brown,[4] this reaction has inspired many catalyzed variants.[5,6] Recently, several compelling examples of related B–X bond addition reactivity have been reported for X = C,[7,8] Si,[6,9,10] Sn,[6,11] S,[12] B,[6,13] Cl,[14] Br,[15] and I[15] (Scheme 2.1a). Many of these transformations proceed through the oxidative addition of a catalytic transition metal such Ni(0), Pd(0), or Pt(0) into the B–X σ bond.

Despite this progress, the corresponding activation of B–O bonds and subsequent addition to C–C multiple bonds—oxyboration—has remained elusive for 65 years.[16,17]

This striking dearth of B–O bond activation reactivity may be due to the extremely high strength of the B–O bond, ~136 kcal/mol, compared to less than 105 kcal/mol for all others entries in the series.[18] This high stability may render the B–O bond unreactive towards oxidative addition, thus preventing the successful application of Ni, Pd, or Pt catalysis[7–12] in an oxyboration reaction. Organoboron reagents are the building blocks of choice for medicinal chemistry and drug discovery.[19] Given that ethers are found in many diverse classes of natural products[20] and in nearly 25% of the top-grossing pharmaceuticals in the United States for 2012,[21] the development of such a transformation allows for the preparation of oxygen-containing building blocks useful in drug discovery and materials science.[21,22]

Scheme 2.1. a) Previous work on B–X direct additions. b) This work demonstrating the first B–O σ-bond addition across alkynes.



Results and Discussion

Herein we report the realization of an oxyboration reaction of alkynes (Scheme 2.1b), through which new *O*-heterocyclic organoboronate coupling partners are available for downstream functionalization. The high functional group tolerance of this reaction enables downstream divergent synthesis of functionalized benzofurans—the ability to accesses multiple downstream products from one bench stable precursor. In contrast,

current methods for synthesizing benzofurans often rely on harsh conditions that limit compatibility with functional groups desirable for divergent synthesis.[23]

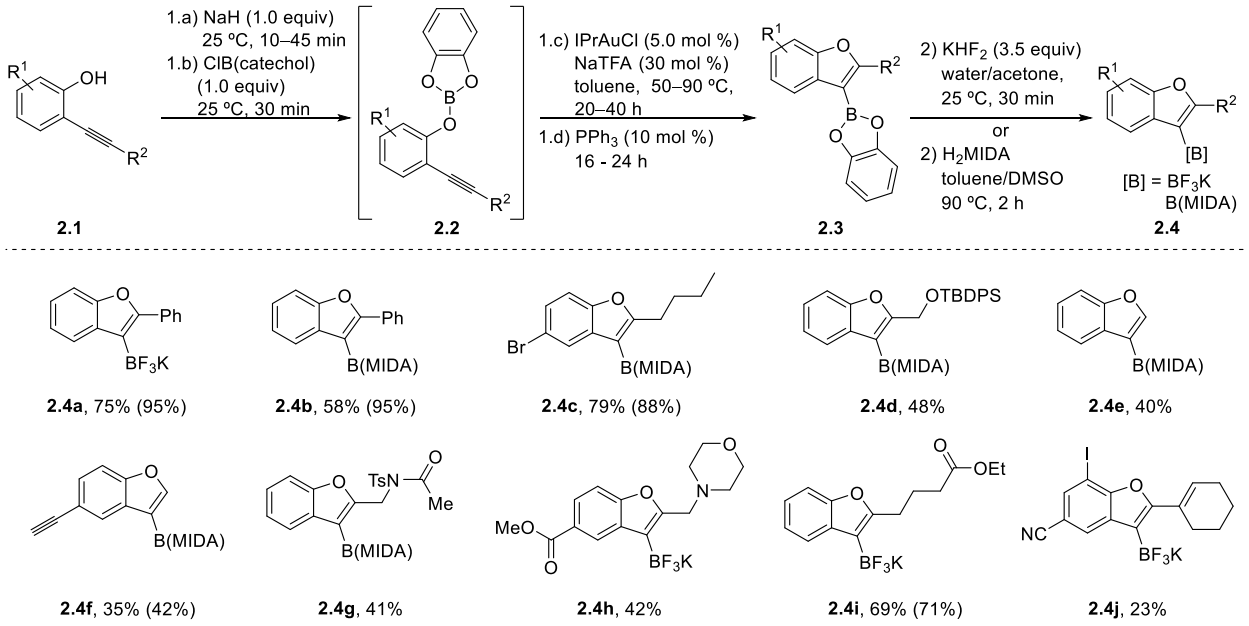
We envisioned that the desired oxyboration reactivity could be promoted through an activation pathway employing a bifunctional Lewis acidic/Lewis basic catalyst, which could simultaneously activate both the alkyne and the B–O σ bond partners. We anticipated that this unique strategy could allow for the *anti* addition of B–O bonds across alkynes by circumventing the previous problematic strategy of oxidative cleavage of the B–O bond.

Our optimized one-pot procedure begins with 2-alkynyl phenols (**2.1**), which are converted into the requisite boric ester intermediate **2.2** using the readily available reagent *B*-chlorocatecholborane (Table 2.1). Treatment of this intermediate with the commercially available Lewis acidic gold(I) precatalyst IPrAuCl and sodium trifluoroacetate (NaTFA) affords oxyboration product **2.3** in good to excellent conversion as determined by the ERETIC method.[24] Interestingly, our screen of alternative π-Lewis acidic transition metal catalysts revealed no other active catalysts aside from Au(I).[25] For synthetic ease, the catechol boronic ester oxyboration product **2.3** was converted into either the organotrifluoroborate[26] or *N*-methyliminodiacetic acid (MIDA) boronate[27] derivative, **2.4**, both of which are air stable indefinitely.

Organotrifluoroborate **2.4a** is readily isolated in high yield using a chromatography-free purification method, making this derivatization method particularly amenable to applying the oxyboration reaction on preparative scale. The corresponding MIDA derivative (**2.4b**) provides an option for purification by silica gel chromatography, but this

comes at the cost of slightly diminished yield. Single-crystal X-ray diffraction analysis of **2.4b** allowed for the unambiguous identification of the oxyboration product.

Table 2.1. Functionalized borylated benzofurans available through the oxyboration reaction.



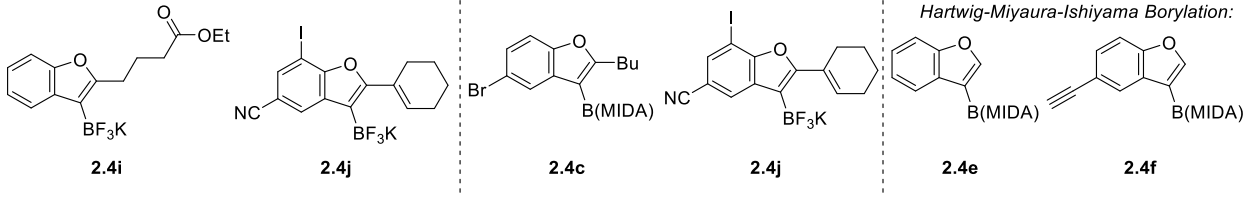
Values represent isolated yields of organotrifluoroborate or MIDA boronate products **2.4**. Values in parentheses represent ^{1}H NMR yields of the corresponding catecholboronic ester **2.3** versus an external mesitylene standard using the ERETIC method.

The oxyboration reaction is tolerant of a variety of functional groups suitable for downstream reactivity. Aryl bromide **2.4c**, silyl-protected alcohol **2.4d**, terminal alkyne **2.4f**, amide **2.4g**, esters **2.4h** and **2.4i**, and the functionally-dense iodonitrile **2.4j** are compatible with the reaction conditions. Many of these oxyboration reactions proceed smoothly at 50 °C, although the reactions generating **2.4d**, **2.4g**, **2.4h**, and **2.4j** required heating to 90 °C in order to effect full conversion. We attribute the relatively slow formation of **2.4d** to the high steric encumbrance from the silyl ether at the 2-position of the benzofuran. The cyclization of substrates containing Lewis basic nitrogen atoms (forming **2.4g**, **2.4h**, and **2.4j**) was likely retarded by reversible N–B coordination that was

observed by ^{11}B nuclear magnetic resonance (NMR) spectroscopy. For all substrates, the mass balance was largely attributable to gold-catalyzed protonolysis of the product C–B bond.

Notably, many of these products contain functional groups incompatible with commonly employed methods of benzofuran synthesis, including via other borylation techniques (Figure 2.1). In one frequently used borylation technique, an aryl lithium intermediate is trapped by a boron electrophile (Method 1); thus electrophiles such as carbonyl or nitrile groups and enolizable protons are not generally tolerated due to the highly nucleophilic and basic nature of the requisite organolithium intermediate.[28] Aryl halides may also suffer from undesired lithium/halogen exchange. The Miyaura borylation is a milder alternative that is compatible with electrophilic functional groups (Method 2), but aryl halides are borylated through this Pd(0)-catalyzed reaction[29] and are therefore not spectator functional groups under these conditions. Finally, the Ir-catalyzed C–H activation/borylation reaction[30] is an effective means of accessing aryl boronic acid derivatives (Method 3). This reaction, however, is regioselective for either 2- or 7-borylation; 3-borylated benzofurans such as those available through the oxyboration reaction cannot be synthesized regioselectively through C–H activation/borylation.[31]

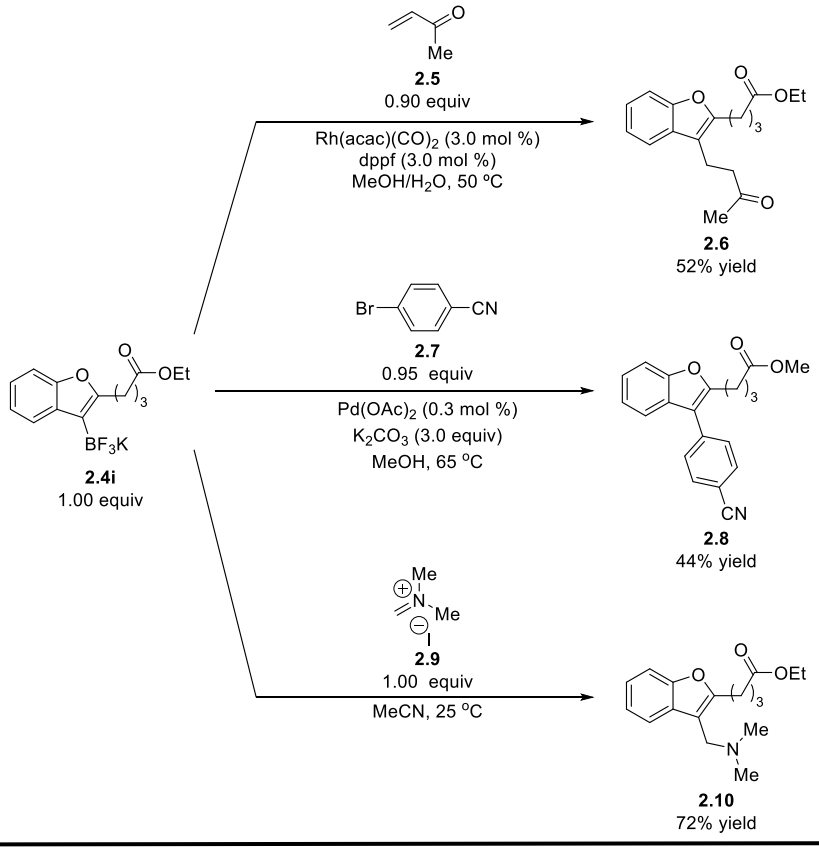
Figure 2.1. Benzofuran boronic acid derivatives inaccessible using conventional borylation methods but newly accessible using the oxyboration reaction.



We set out to demonstrate the utility in divergent synthesis of the oxyboration products enabled through this synthesis in subsequent divergent functionalization steps

(Scheme 2.2). Rh-catalyzed conjugate addition of **2.4i** into methyl vinyl ketone using the method developed by Batey[32] provided *β*-benzofuranyl ketone **2.6** in moderate yield. Subjection of the same benzofuran trifluoroborate to Suzuki-Miyaura coupling conditions described by Molander and Biolatto[33] afforded 3-arylated benzofuran **2.8** with concomitant methanolysis of the ethyl ester. Finally, addition of **2.4i** to an iminium ion was used to prepare aminated benzofuran **2.10**. Thus, a single bench-stable oxyboration product can be functionalized a variety of ways, which is important in diversity oriented syntheses to develop compound catalogs for drug discovery.[19]

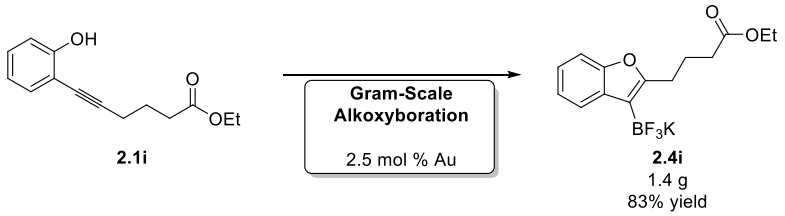
Scheme 2.2. Versatility of an oxyboration product in diversity-oriented synthesis.



We next explored the scalability of the oxyboration reaction. Ester-containing phenol **2.1i** was successfully converted to more than 1 g of organotrifluoroborate **2.4i** on

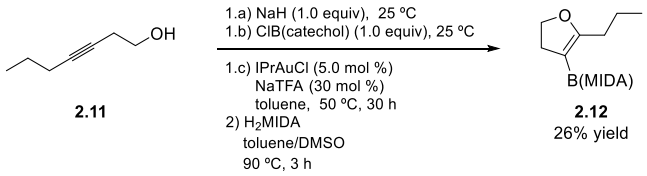
a 5 mmol scale with 2.5% gold catalyst (Figure 2.2). Full conversion of starting material was effected even with this lower Au catalyst loading. This convenient scalability demonstrates that quantities of *O*-heterocyclic boronic acid derivatives sufficient for multistep synthesis may be prepared using the oxyboration method.

Figure 2.2. Gram scale reactivity of the oxyboration reaction.



Having demonstrated the utility of this transformation in generating members of the benzofuran class of *O*-heteroaryl boronic acid derivatives, we explored its application to the synthesis of a non-aromatic oxygen-containing heterocycle (Figure 2.3). Simple and commercially available homopropargyl alcohol **2.11** was subjected to standard oxyboration reaction conditions to prepare dihydrofuran product **2.12**. A large number of unidentifiable trace coproducts were detected in this reaction, possibly consistent with intermolecular reactivity. This proof-of-concept result suggests the potential for generality in the oxyboration reaction: The reaction features low labor “setup cost” by employing simple, commercially available starting materials to generate highly value-added *O*-heterocyclic organoboronate compounds in one synthetic step, and the cyclization proceeds without requiring the gain of product aromaticity or the need for a fused ring system that enforces a conformational bias towards cyclization.

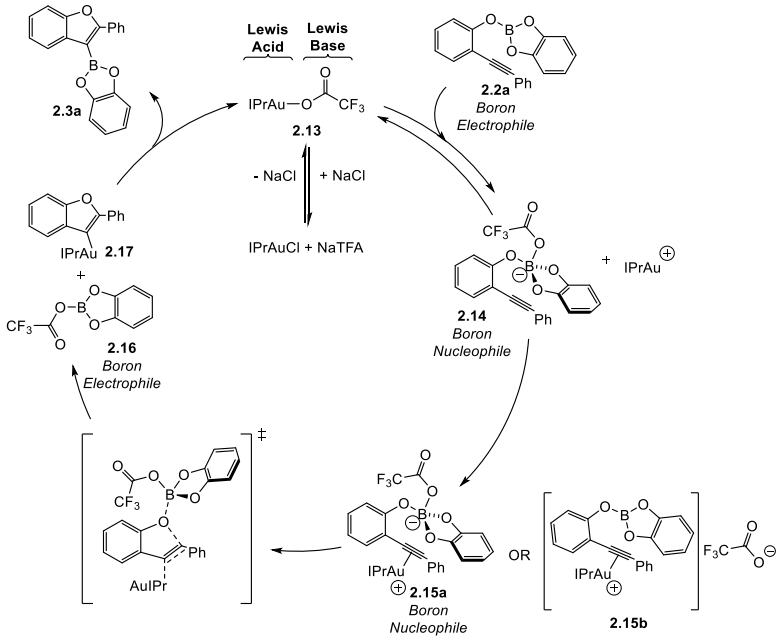
Figure 2.3. Extension of the oxyboration method to synthesize borylated dihydrofurans.



Several late transition metal catalysts have developed for the addition of oxygen–electrophile bonds across alkynes.[34] Inspired by the general mechanistic profile of these transformations, we originally proposed the catalytic cycle shown in Scheme 2.3 featuring bifunctional Lewis acidic/Lewis basic substrate activation. The bifunctional catalyst IPrAuTFA could be generated *in situ* from IPrAuCl and NaTFA. Reaction of the Lewis basic trifluoroacetate moiety with electrophilic boric ester **2.2a** would give nucleophilic borate **2.14**. The resulting Lewis acidic Au(I) cation may then bind to the alkyne (**2.15a**), increasing its electrophilicity. Nucleophilic attack on the alkyne–Au π complex by the phenol B–O bond would provide neutral intermediates: boron electrophile **2.16** and organogold nucleophile **2.17**, which could recombine to regenerate **2.13** with concomitant formation of the observed oxyboration product **2.3a**. Thus, the $IPrAu^+$ moiety of the catalyst activates the alkyne for nucleophilic attack, and the TFA counter ion could allow for reversible tuning from a boron electrophile to a nucleophilic borate adduct. Later kinetics and detailed mechanistic studies in our group refined the mechanism in that binding of the counter ion is no longer required for activation (**2.15b**).[35] This reaction manifold is fundamentally unique from the metal-catalyzed addition of B–C, B–Si, B–Sn, and B–S addition reactions, which often proceed through oxidative addition of a low-valent metal catalyst into the B–X bond. We believe that the new activation strategy employed in the oxyboration reaction could be extended to other types of B–X bonds to provide additional reactivity complementary to preexisting methods. Notably, this

approach also suggests a new generalizable mechanism for Au catalyst turnover by trapping with electrophilic boron to generate other previously inaccessible organoboron building blocks.

Scheme 2.3. Proposed mechanism for the oxyboration reaction.



Further Reaction Optimization and Large Scale Synthesis for *Organic Syntheses*

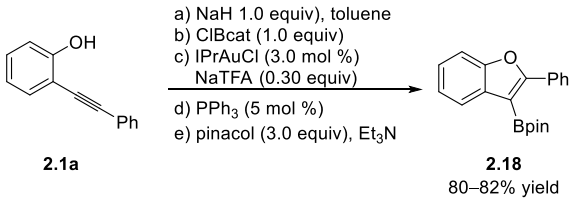
Following our first report of the oxyboration reaction, we set out to further optimize the borylation reaction to enhance the applicability of the method. The goal of this project was to develop a peer-reviewed, scalable, and robust synthetic method. This procedure was reviewed and repeated in the laboratory of Prof. Neil K. Garg at the University of California, Los Angeles, and was published in *Organic Syntheses*.[36]

We first set out to increase the reaction scale and optimize the isolation conditions of the oxyboration reaction (Figure 2.4). Ultimately 2-alkynylphenol **2.1a** was converted to borylated benzofuran **2.18** in 80–82% yield (two runs on the 7.2 g scale). This improvement in yield during scale up further demonstrated the synthetic utility of the

oxyboration reaction. Moreover, the $IPrAu^+$ catalyst quenching step (addition of PPh_3) was optimized by reducing the total reaction time. Finally, the transesterification step was expanded to include pinacol boronic esters using a procedure adapted from Ingleson.[37] The pinacol boronic esters are valuable because they are well-established cross-coupling partners and Michael addition partners in transition metal chemistry.[38]

Several challenges were overcome during scale up of the oxyboration reaction that were not encountered on the smaller scale. One major issue was dealing with the stoichiometric byproduct NaCl that is generated from the deprotonation of **2.1a** with NaH. An additional step of filtering over Celite quickly removed the NaCl byproduct due to its poor solubility in toluene. In addition to the NaCl byproduct, purification of the pinacolboronic ester **2.18** proved challenging; the oxyboration product exhibited a similar R_f value to the excess PPh_3 from the quenching step of the active catalyst. To minimize this issue, less PPh_3 was used in the scale up procedure (5 mol % vs. 10 mol %, see Table 2.1). Not only did this improve atom economy, it made the purification of **2.18** via column chromatography more facile.

Figure 2.4. Optimization of the oxyboration reaction for *Organic Syntheses*.



2.1a **2.18**
80–82% yield

The last parameter examined was the possibility of performing the key catalytic oxyboration reaction outside the glovebox for operational ease. To compare, both oxyboration reactions were run on the 0.86 mmol scale, with the only variable being in or out of the glovebox. On this scale, a lower yield was obtained for the out-of-the-glovebox

reaction. Although lower in isolated yield (50% vs. 70%), we have successfully run the oxyboration reaction outside of the glovebox using standard air-free techniques. The lower yield for the out of the glovebox reaction is likely due to hydrolysis of the boric ester intermediate (**2.2a**).

Conclusions

This oxyboration reaction proceeds through an unprecedented activation of the strong B–O *σ* bond. This fundamentally new activation is showcased in a mild, scalable technique for the preparation of *O*-heterocyclic boronic acid derivatives and downstream-functionalized benzofurans. The reaction provides a simple new bond disconnection for constructing these motifs with different regioselectivity and broader functional group compatibility than existing methods. This compatibility yields highly functionalized bench-stable building blocks for divergent synthesis that are not directly accessible using alternative methods. The carbophilic Lewis-acid activation mechanism for B–X addition suggests its broader application to other B–X addition reactions and to the ability to synthesize previously inaccessible organoboron building blocks via this new strategy for turning over gold and other carbophilic metal catalysts.

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Experimental

General Considerations

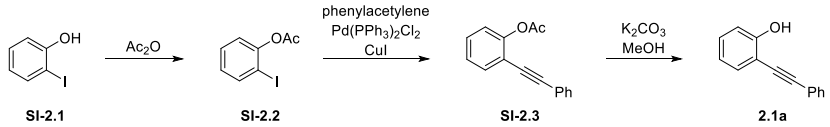
All chemicals were used as received from commercial sources unless otherwise noted. Sodium trifluoroacetate was dried at 130 °C at 10 mTorr for 18 h before use. Toluene and dichloromethane were purified by passage through an alumina column under argon pressure on a push-still solvent system. Anhydrous dimethylsulfoxide was obtained by stirring over activity I alumina 18 h under N_2 atmosphere, decanting the liquid, and distilling the liquid at 10 Torr over CaH_2. Acetone was dried by distillation over anhydrous $CaSO_4$ under N_2 atmosphere. d_8-Toluene 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 = 2.50 ppm for d_6-DMSO, or δ = 1.94 ppm for CD_3CN in ^{1}H NMR spectroscopy experiments; δ = 77.16 ppm for $CDCl_3$, δ = 39.52 ppm for d_6-DMSO, 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. Low- and high-resolution mass spectrometry data were obtained at the University of California, Irvine.

Sections with an asterisk (*) denote work done by graduate student Joshua J. Hirner.

Synthetic Procedures

Preparation of 2-alkynyl phenol substrates **2.1a–2.1j**



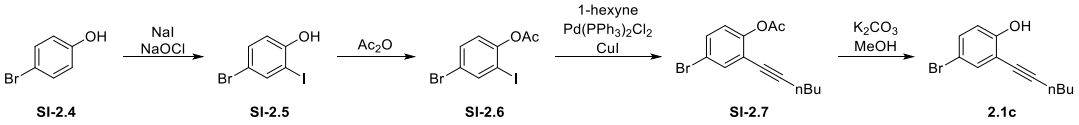
2-Iodophenyl acetate (SI-2.2). A solution of **SI-2.1** (6.72 g, 30.5 mmol, 1.00 equiv) and 4-dimethylaminopyridine (DMAP, 190 mg, 1.5 mmol, 5.0 mol %) was prepared in Et_3N (6.4 mL, 46 mmol, 1.5 equiv) and DCM (60 mL). Acetic anhydride (3.46 mL, 36.6 mmol, 1.20 equiv) was added dropwise. [Note: slight exotherm.] The reaction mixture stirred at 25 °C vented to air with a needle for 3 h. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full conversion to a single new product. To the reaction mixture was added 50 mL water, and the resulting biphasic mixture was separated. The aqueous

layer was extracted with DCM (3 × 25 mL), and then the combined organic layers were washed with brine (1 × 50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo to a colorless oil, which solidified to a white solid upon standing. The resulting solid was crushed to a powder, and volatiles were removed at ca. 10 mTorr for 2.5 h to afford **SI-2.2** as a white powder (7.27 g, 91% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.84 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.38 (td, *J* = 7.2, 1.3 Hz, 1H), 7.11 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.99 (td, *J* = 7.6, 1.3 Hz, 1H), 2.38 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]

2-(Phenylethynyl)phenyl acetate (SI-2.3). A 100-mL Schlenk tube was charged with Et_3N (20 mL) and sparged with N_2 for 20 min. Compound **SI-2.2** (2.62 g, 10.0 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (120 mg, 0.20 mmol, 2.0 mol %), and CuI (95 mg, 0.50 mmol, 5.0 mol %) were added under positive N_2 pressure, then neat phenylacetylene (1.20 mL, 11.0 mmol, 1.10 equiv) was added. The reaction mixture was heated at 45 °C for 19 h, at which time analysis by TLC (5% EtOAc/hexanes) indicated complete consumption of the aryl iodide. The reaction mixture was cooled to 25 °C and diluted with 75 mL Et_2O. The resulting mixture was washed with saturated aqueous NH_4Cl (4 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to a dark brown oil. The oily residue was purified by column chromatography using an elution gradient from 5% EtOAc/hexanes to 10% EtOAc/hexanes. Volatiles were removed at ca. 10 mTorr and 25 °C for 18 h to afford **SI-2.3** as a brown oil (2.50 g, quant.). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.52–7.50 (m, 2H), 7.39–7.35 (m, 4),

7.25 (td, *J* = 7.6, 1.3 Hz, 1H), 7.14 (dd, *J* = 8.0, 1.4 Hz, 1H), 2.38 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]

2-(Phenylethynyl)phenol (2.1a). A suspension of K_2CO_3 (2.00 g, 14.5 mmol, 2.05 equiv) in MeOH (100 mL) and THF (90 mL) was cooled to 0 °C in an ice bath. A solution of **SI-2.3** (1.69 g, 7.16 mmol, 1.00 equiv) in THF (10 mL) was added dropwise over 2 min. The resulting heterogeneous mixture was stirred vigorously at 0 °C vented to air with a needle for 1.5 h, at which time analysis by TLC (20% EtOAc/hexanes) revealed complete consumption of **SI-2.3**. The cold reaction mixture was decanted into 200 mL DCM and washed with saturated aqueous NH_4Cl (1 × 100 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown solid residue, which was purified by silica gel chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Removal of volatiles at ca. 10 mTorr and 50 °C for 18 h to afforded **2.1a** as a golden solid (970 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.57–7.55 (m, 2H), 7.44 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.40–7.39 (m, 3H), 7.30–7.27 (m, 1H), 7.00 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.93 (td, *J* = 7.5, 1.0 Hz, 1H), 5.83 (s, 1H). This spectrum is in agreement with previously reported spectral data.[2]



SI-2.4 SI-2.5 SI-2.6 SI-2.7 2.1c

***4-Bromo-2-iodophenol (SI-2.5)** was prepared according to a literature procedure[3] in 66% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (d, *J* = 2.3 Hz, 1H), 7.35 (dd, *J* = 8.6, 2.3

Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 5.25 (br. s, 1H). This spectrum is in agreement with previously reported spectral data.[3]

***4-Bromo-2-iodophenyl acetate (SI-2.6)**. A solution of **SI-2.5** (1.79 g, 6.00 mmol, 1.00 equiv) and 4-dimethylaminopyridine (DMAP, 40. mg, 0.30 mmol, 5.0 mol %) in Et_3N (1.0 mL, 7.2 mmol, 1.2 equiv) and DCM (12 mL) was cooled to 0 °C in an ice bath. Acetic anhydride (680 µL, 7.2 mmol, 1.2 equiv) was added dropwise over ca. 1 min, and then the cooling bath was removed. The reaction mixture was stirred at 25 °C while vented to air with a needle for 1 h. At this time, analysis by TLC (10% EtOAc/hexanes) indicated full conversion to a single new product. The reaction mixture was washed with water (3 × 3 mL) and brine (3 × 3 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a colorless oil, which solidified to a white solid upon standing. The resulting solid was crushed to a powder, and volatiles were removed at ca. 10 mTorr for 2.5 h to afford **SI-2.6** as a white powder (1.90 g, 93% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (d, *J* = 2.3 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 168.5, 150.6, 141.5, 132.6, 124.5, 119.9, 91.6, 21.3.

HRMS (GC/ESI): Calculated for $C_8H_{10}BrINO_2$ ($[M+NH_4]^+$), 357.8940; found 357.8942.

***4-Bromo-2-(hex-1-yn-1-yl)phenyl acetate (SI-2.7)**. A 100-mL Schlenk tube was charged with 25 mL THF, Et_3N (3.9 mL, 28 mmol, 4.1 equiv), and a stir bar. The combined solvents were sparged with N_2 for 25 min. Compound **SI-2.6** (2.34 g, 6.86 mmol, 1.00

equiv), $Pd(PPh_3)_2Cl_2$ (96 mg, 0.14 mmol, 2.0 mol %), and CuI (65 mg, 0.34 mmol, 5.0 mol %) were added under positive N_2 flow, followed by 1-hexyne (2.4 mL, 21 mmol, 3.0 equiv). The resulting dark brown solution was stirred at 25 °C for 15 h, at which time analysis by TLC (10% EtOAc/hexanes) suggested full consumption of the starting aryl iodide. [Note: The aryl iodide starting material overlaps the desired Sonogashira product in this solvent system, but the reaction progress can be judged through differential staining by $KMnO_4$ solution.] The reaction mixture was diluted with 75 mL EtOAc and washed with saturated aqueous NH_4Cl (3 × 20 mL), water (1 × 20 mL), and brine (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown oil. Purification by column chromatography using an elution gradient (100% hexanes to 20% EtOAc/hexanes) followed by removal of volatiles at ca. 10 Torr for 1 h afforded the desired product as a yellow-brown oil (1.91 g, 95% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.6 Hz, 2.3 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 2.43 (t, *J* = 7.0 Hz, 2H), 2.32 (s, 3H), 1.58 (m, 2H), 1.47 (app sextet, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.8, 150.7, 135.8, 131.7, 123.8, 120.3, 118.8, 97.2, 74.5, 30.7, 22.0, 20.9, 19.3, 13.7.

HRMS (GC/EI): Calculated for $C_{14}H_{19}BrO_2N$ ($[M+NH_4]^+$), 312.0599; found 312.0600.

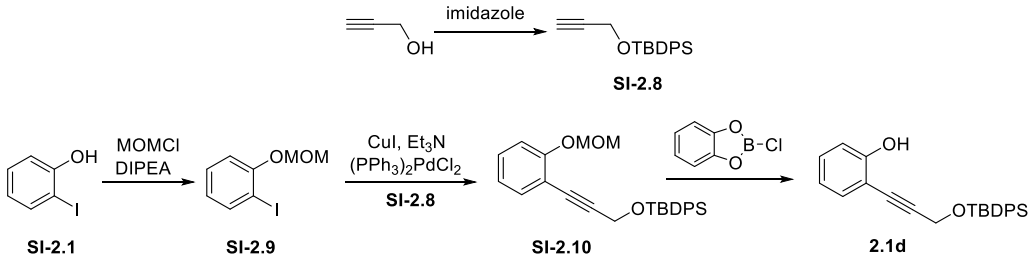
***4-Bromo-2-(hex-1-yn-1-yl)phenol (2.1c)**. A stirring suspension of K_2CO_3 (1.78 g, 12.9 mmol, 2.00 equiv) in 45 mL MeOH and 35 mL THF was cooled to 0 °C in an ice bath. To the vigorously stirring cold suspension was added solution of acetate **SI-2.7** (1.90 g, 6.44

mmol, 1.00 equiv) in 10 mL THF dropwise over ca. 2 min. The reaction mixture was stirred at 0 °C for 30 min, at which time analysis by TLC (10% EtOAc/hexanes) revealed full consumption of the acetate starting material. The reaction mixture was diluted with 100 mL EtOAc, then washed with saturated aqueous NH_4Cl (1 × 30 mL) and brine (3 × 10 mL). The organic layer was 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. Volatiles were removed at ca. 10 mTorr overnight with stirring to afford **2.1c** as a clear yellow oil (1.5 g, 89% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.41 (d, *J* = 2.4 Hz, 1H), 7.29 (dd, *J* = 8.7 Hz, 2.5 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 5.76 (s, 1H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.65–1.50 (m, 2H), 1.45–1.52 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.8, 133.8, 132.6, 116.2, 112.5, 111.9, 99.5, 73.5, 30.8, 22.2, 19.4, 13.7.

HRMS (GC/CI): Calculated for $C_{12}H_{13}BrO$ (M^+), 252.0150; found 252.0148.



***tert*-Butyldiphenyl(prop-2-yn-1-yloxy)silane (SI-2.8)** was prepared according to a literature procedure[4] in 77% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (d, *J* = 6.6 Hz, 4H),

7.33–7.49 (m, 6H), 4.32 (d, *J* = 2.3 Hz, 2H), 2.39 (t, *J* = 2.3 Hz, 1H), 1.07 (s, 9H). This spectrum is in agreement with previously reported spectral data.[4]

1-Iodo-2-(methoxymethoxy)benzene (SI-2.9) was prepared according to a literature procedure[5] in 97% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.78 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.26–7.30 (m, 1H), 7.07 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.76 (td, *J* = 7.6, 1.3 Hz, 1H), 5.24 (s, 2H), 3.52 (s, 3H). This spectrum is in agreement with previously reported spectral data.[5]

***tert*-Butyl((3-(2-(methoxymethoxy)phenyl)prop-2-yn-1-yl)oxy)diphenylsilane (SI-2.10)**. A flask was charged with compound **SI-2.9** (1.50 g, 5.67 mmol, 1.00 equiv), $(PPh_3)_2PdCl_2$ (0.20 g, 0.28 mmol, 0.050 equiv), and CuI (0.11 g, 0.57 mmol, 0.10 equiv). The flask was then evacuated and refilled with N_2 three times before Et_3N (6.3 mL, 45 mmol, 8.0 equiv) was added and stirred for 30 min. A separate flask was charged with compound **SI-2.8** (2.14 g, 7.28 mmol, 1.30 equiv), and then evacuated and refilled with N_2 three times before adding 11 mL MeCN. The resulting solution was then added dropwise over ca. 4 min to the stirring 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 50 mL EtOAc and washed with NH_4Cl (1 × 15 mL), water (1 × 10 mL), brine (1 × 10 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 ca. 10 mTorr for 18 h to afford **SI-2.10** as a light yellow oil. (2.18 g, 90% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76 (d, *J* = 6.7 Hz, 4H), 7.46–7.35 (m, 6H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.28–7.21 (m, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 5.21 (s, 2H), 4.59 (s, 2H), 3.49 (s, 3H), 1.09 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.9, 135.8, 133.8, 133.4, 129.9, 129.7, 127.8, 121.9, 115.4, 113.8, 95.1, 91.7, 81.5, 56.4, 53.6, 26.9, 19.4.

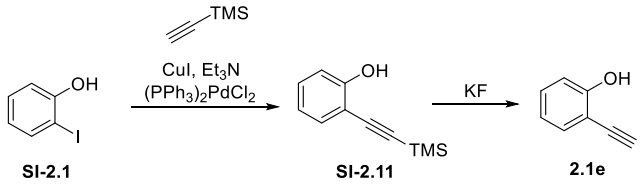
HRMS (ESI+): Calculated for $C_{27}H_{30}O_3SiNa$ ($[M+Na]^+$), 453.1862; found 453.1844.

2-(3-((*tert*-Butyldiphenylsilyl)oxy)prop-1-yn-1-yl)phenol (2.1d). To a stirring solution of *B*-chlorocatecholborane (0.34 g, 2.2 mmol, 1.2 equiv) in 15 mL DCM was added **SI-2.10** (0.80 g, 1.9 mmol, 1.0 equiv) in 4 mL DCM. The reaction mixture was stirred for 4.5 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 50 mL DCM, and the organic layer was washed with NH_4Cl (1 × 10 mL), brine (1 × 10 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 ca. 10 mTorr for 18 h to afford **2.1d** as a light yellow oil (320 mg, 45% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74 (d, *J* = 6.7 Hz, 4H), 7.47–7.44 (m, 2H), 7.42–7.40 (m, 4H), 7.24 (t, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 5.55 (s, 1H), 4.60 (s, 2H), 1.08 (s, 9H).

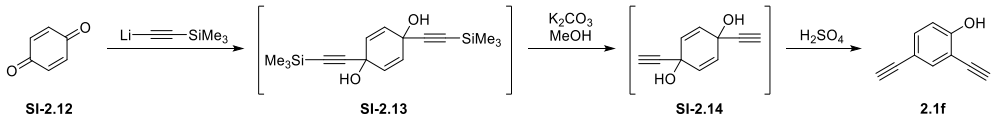
^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.9, 135.8, 133.1, 132.0, 130.6, 130.1, 128.0, 120.3, 114.8, 109.2, 95.0, 79.3, 53.3, 26.8, 19.3.

HRMS (ESI+): Calculated for $C_{25}H_{26}O_2SiNa$ ([M+Na]$^+$), 409.1600; found 409.1584.



2-((Trimethylsilyl)ethynyl)phenol (SI-2.11) was prepared according to a literature procedure[6] in 71% yield. ^{1}H NMR ($CDCl_3$, 600MHz) δ 7.34 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.26–7.22 (m, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.85 (t, *J* = 6.0 Hz, 1H), 5.82 (s, 1H), 0.28 (s, 9H). This spectrum is in agreement with previously reported spectral data.[6]

2-Ethynylphenol (2.1e) was prepared according to a literature procedure[6] in 82% yield. ^{1}H NMR ($CDCl_3$, 600MHz) δ 7.38 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.30–7.26 (dt, *J* = 7.8, 1.2 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.88 (dt, *J* = 7.5, 0.8 Hz, 1H), 5.77 (s, 1H), 3.47 (s, 1H). This spectrum is in agreement with previously reported spectral data.[6]



***1,4-Bis((trimethylsilyl)ethynyl)cyclohexa-2,5-diene-1,4-diol (SI-2.13)**. Anhydrous THF (60 mL) was cooled to -78 °C in a dry ice/isopropanol bath under a dynamic N_2 atmosphere. A solution of *n*-BuLi (1.0 M in hexanes, 50. mL, 50. mmol, 2.2 equiv) was cannulated slowly into the reaction vessel. To the resulting stirring solution was then added trimethylsilyl acetylene (7.1 mL, 50. mmol, 2.2 equiv) dropwise over 30 min. After stirring an additional 30 min to effect complete deprotonation of the terminal alkyne, a solution of 1,4-benzoquinone (2.45 g, 22.7 mmol, 1.00 equiv) in 20. mL anhydrous THF was added dropwise over 30 min. During this addition, the reaction mixture turned from a clear, pale yellow solution to a dark, teal solution. The reaction mixture was stirred for 18 h as the cooling bath warmed gradually to 25 °C. After this time, the resulting red-brown semisolid reaction mixture was cooled to 0 °C, and 100 mL EtOAc was added with vigorous agitation to break up the solid aggregate. Saturated aqueous NH_4Cl (50 mL) was added to quench the reaction mixture, and then the pH was further adjusted to pH = 5 with ca. 1 mL 2 N aqueous HCl. The resulting biphasic mixture was separated, and the organic layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a tan solid. Volatiles were removed at 25 °C and ca. 10 mTorr for 2 h to afford crude **SI-2.13** as a tan solid (6.08 g) in 70% purity. Crude **SI-2.13** was used without further purification or characterization.

***1,4-Diethynylcyclohexa-2,5-diene-1,4-diol (SI-2.14)**. A suspension of K_2CO_3 (5.5 g, 40. mmol, 4.0 equiv) in MeOH (50 mL) was cooled to 0 °C in an ice bath open to air. Solid

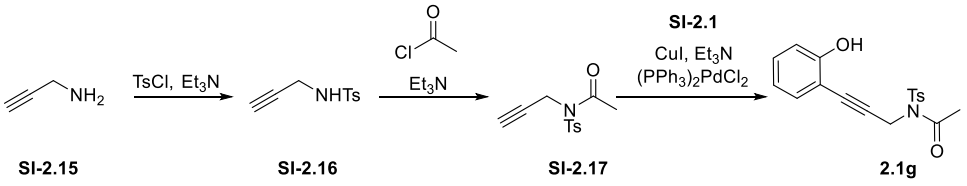
SI-2.13 (3.0 g, 9.9 mmol, 1.0 equiv) was added portion wise over ca. 1 min, and the resulting mixture was stirred vigorously at 0 °C for 1.5 h, at which time analysis by TLC (30% EtOAc/hexanes) indicated full consumption of **SI-2.13**. The reaction mixture was warmed to 25 °C and was decanted away from excess K_2CO_3. The resulting solution was diluted with 50 mL EtOAc and was then washed with saturated aqueous NH_4Cl (3 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to a tan solid containing crude **SI-2.14**, which was used directly in the next step without purification or characterization.

***2,4-Diethynylphenol (2.1f)** was prepared using a method adapted from Ried and Schmidt.[7] Crude **SI-2.14** was dissolved in 10 mL benzene, and to the resulting solution were added H_2O (10 mL) and 1 mL 1 N aqueous H_2SO_4 (1 mmol, 10 mol %). The resulting biphasic mixture was refluxed under air with vigorous stirring for 20 min. After cooling to 25 °C, the biphasic mixture was separated, and the aqueous layer was extracted with benzene (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown oil, which was purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. The purified product was dried at 25 °C and ca. 10 mTorr for 18 h to afford **2.1f** as a cream-colored solid (160 mg, 12% yield over 2 steps).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.33 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 1.1 Hz, 1H), 7.02 (dd, *J* = 8.0, 1.3 Hz, 1H), 5.79 (s, 1H), 3.55 (s, 1H), 3.16 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.1, 132.0, 124.7, 124.4, 118.5, 109.2, 86.0, 82.9, 79.2, 77.8.

HRMS (GC/ESI+): Calculated for $C_{10}H_{10}NO$ ($[M+NH_4]^+$), 160.0762; found 160.0764.



4-Ethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (SI-2.16) was prepared according to a literature procedure[8] in 91% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 4.66 (br. s, 1H), 3.83 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.43 (s, 3H), 2.10 (t, *J* = 2.4 Hz, 1H). This spectrum is in agreement with previously reported spectral data.[8]

***N*-(Prop-2-yn-1-yl)-*N*-tosylacetamide (SI-2.17)**. A flask was charged with **SI-2.16** (1.29 g, 6.16 mmol, 1.00 equiv), Et_3N (2.6 mL, 19 mmol, 3.0 equiv), and 13 mL DCM before it was cooled to 0 °C in an ice bath. At this time, acetyl chloride (0.88 mL, 12 mmol, 2.0 equiv) was syringed into the stirring reaction vessel over 3 min. The ice bath was removed, and the reaction mixture was stirred for 18 h before TLC (30% EtOAc/hexanes) revealed complete consumption of starting material. The reaction was quenched with 10 mL H_2O, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), and then 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 35% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles

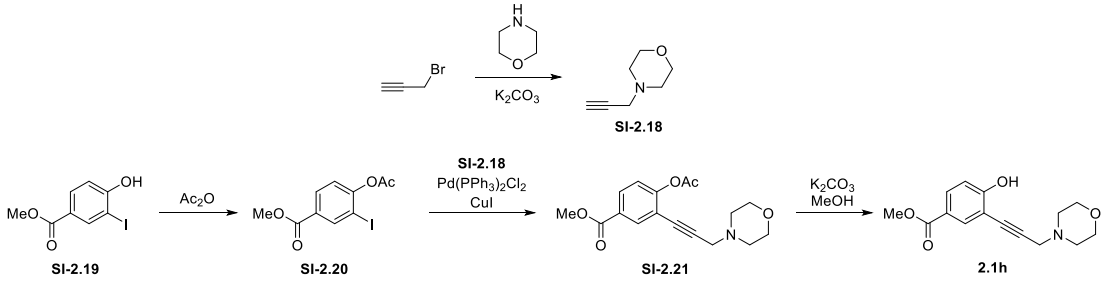
were removed at ca. 10 mTorr for 18 h to afford **SI-2.17** as a light yellow solid (1.1 g, 72% yield). ^{1}H NMR ($CDCl_3$, 600MHz) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.67 (d, *J* = 2.3 Hz, 2H), 2.45 (s, 3H), 2.33 (s, 3H), 2.28 (t, *J* = 2.4 Hz, 1H). This spectrum is in agreement with previously reported spectral data.[9]

***N*-(3-(2-Hydroxyphenyl)prop-2-yn-1-yl)-*N*-tosylacetamide (2.1g)**. A Schlenk tube was charged with **SI-2.1** (0.71 g, 3.2 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (23 mg, 0.032 mmol, 1.0 mol %), CuI (13 mg, 0.064 mmol, 2.0 mol %), and a stir bar. The tube was then evacuated and refilled with N_2 three times before the addition of Et_3N (1.8 mL, 13 mmol, 4.0 equiv) and 4 mL dioxane, and then stirred for 5 min. Compound **SI-2.17** (1.05 g, 4.18 mmol, 1.30 equiv) was added over positive N_2 pressure. The Schlenk tube was heated to 45 ^{o}C under dynamic N_2. After 4 h, analysis by TLC (30% EtOAc/hexanes) revealed complete consumption of starting material. To the flask was added 10 mL water, and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (1 × 10 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 30% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **2.1g** as a light yellow solid (0.15 g, 14% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.23 (td, *J* = 6.7, 1.5 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 5.92 (br. s, 1H), 4.88 (s, 2H), 2.42 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (d_8-toluene, 125 MHz): δ 169.2, 158.9, 144.8, 137.1, 131.7, 131.0, 129.9, 125.4, 120.1, 115.4, 109.0, 91.9, 79.2, 36.2, 24.4, 21.0.

HRMS (ESI+): Calculated for $C_{18}H_{17}NO_4SNa$ ([M+Na]$^+$), 366.0776; found 366.0768.



***4-(Prop-2-yn-1-yl)morpholine (SI-2.18)** was prepared by adding propargyl bromide (80 wt % in toluene, 15 g solution, 100 mmol, 1.0 equiv) dropwise over 20 min to a stirring suspension of morpholine (22 mL, 250 mmol, 2.5 equiv) and K_2CO_3 (35 g, 250 mmol, 2.5 equiv) in THF (100 mL) at 25 °C. The resulting mixture was stirred vigorously for 18 h, at which point the reaction mixture was diluted with 200 mL EtOAc. The mixture was washed with water (1 × 60 mL) and brine (3 × 20 mL), then the combined aqueous layers were back extracted with DCM (1 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to a yellow-orange oil. Purification by Kugelrohr distillation, (250 Torr, 150 °C) afforded **SI-2.18** as a clear, colorless oil (9.85 g, 79% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.74 (app t, *J* = 4.8 Hz, 4H), 3.29 (d, *J* = 2.5 Hz, 2H), 2.57 (app t, *J* = 4.7 Hz, 4H), 2.27 (t, *J* = 2.5 Hz, 1H). This spectrum is in agreement with previously reported spectral data.[10]

***Methyl 4-acetoxy-3-iodobenzoate (SI-2.20)**. A solution of iodophenol **SI-2.19** (5.00 g, 18.0 mmol, 1.00 equiv) and 4-dimethylaminopyridine (DMAP, 110 mg, 0.90 mmol, 5.0 mol %) in Et_3N (3.0 mL, 22 mmol, 1.2 equiv) and DCM (20 mL) was cooled to 0 °C in an

ice bath. Neat acetic anhydride (2.0 mL, 22 mmol, 1.2 equiv) was added dropwise over ca. 1 min, and then the cooling bath was removed. The reaction mixture was stirred at 25 °C while vented to air with a needle for 2 h. At this time, analysis by TLC (20% EtOAc/hexanes) indicated full conversion to a single new product. The reaction mixture was washed with water (1 × 40 mL), and then the aqueous layer was back extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (3 × 3 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a colorless oil, which was purified by silica gel chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Volatiles were removed from the purified product at ca. 10 mTorr for 2.5 h to afford **SI-2.20** as a white powder (5.41 g, 94% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.52 (d, *J* = 1.8 Hz, 1H), 8.05 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 2.40 (s, 3H). This spectrum is in agreement with previously reported spectral data.[11]

***Methyl 4-acetoxy-3-(3-morpholinoprop-1-yn-1-yl)benzoate (SI-2.21)**. A solution of **SI-2.20** (480. mg, 1.50 mmol, 1.00 equiv) in Et_3N (4 mL) was sparged with N_2 for 25 min. $PdCl_2(PPh_3)_2$ (18 mg, 0.026 mmol, 2.0 mol %) and CuI (12 mg, 0.065 mmol, 5.0 mol %) were added under positive N_2 flow, and to the resulting mixture was then added neat terminal alkyne **SI-2.18** (197 mg, 1.58 mmol, 1.05 equiv). The reaction mixture was then heated at 45 °C for 16 h. At this time, analysis by TLC (20% EtOAc/hexanes) indicated complete consumption of the starting aryl iodide. The reaction mixture was diluted with 10 mL DCM, then washed with water (1 × 15 mL) and brine (1 × 15 mL), and then the combined aqueous layers were back extracted with DCM (1 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting

brown oil was purified by silica gel chromatography using an elution gradient from 100% hexanes to 100% EtOAc. Volatiles were removed from the purified product at ca. 10 mTorr for 18 h to afford **SI-2.21** as a viscous, yellow-brown oil (223 mg, 55% yield) containing trace residual EtOAc.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.17 (d, *J* = 2.5 Hz, 1H), 8.00 (dd, *J* = 10.2, 2.5 Hz, 1H), 7.18 (d, *J* = 10.1 Hz, 1H), 3.92 (s, 3H), 3.77 (app t, *J* = 5.5 Hz, 4H), 3.56 (s, 2H), 2.64 (app t, *J* = 5.5 Hz, 4H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5, 165.8, 155.0, 135.0, 130.8, 128.1, 122.6, 117.6, 90.1, 80.0, 67.0, 52.5, 52.3, 48.1, 21.1.

HRMS (ESI+): Calculated for $C_{17}H_{19}NO_5Na$ ($[M+Na]^+$), 340.1161; found 340.1167.

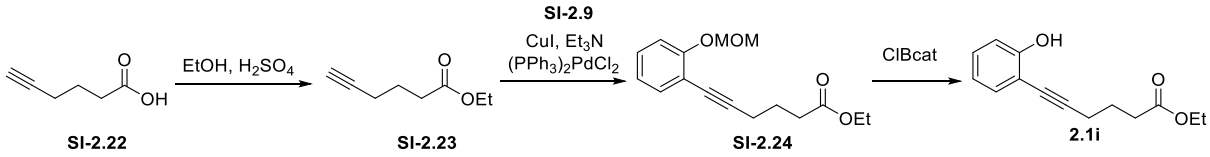
***Methyl 4-hydroxy-3-(3-morpholinoprop-1-yn-1-yl)benzoate (2.1h)**. A solution of **SI-2.21** (1.27 g, 4.00 mmol, 1.00 equiv) in THF (30 mL) was cooled to 0 °C in an ice bath. Solid K_2CO_3 (1.1 g, 8.0 mmol, 2.0 equiv) was added followed by slow addition of MeOH (30 mL). After completion of the addition, the reaction mixture was warmed slowly to 25 °C and was stirred vigorously for 2 h. At this time, analysis by TLC (5% MeOH/$CHCl_3$) indicated complete consumption of the starting acetate. The reaction mixture was diluted with 150 mL DCM and washed with water (1 × 30 mL) and brine (1 × 30 mL). The combined aqueous layers were back-extracted with DCM (1 × 30 mL), and then the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to a pale yellow oil. The oil was purified by silica gel chromatography using an elution gradient from 100% $CHCl_3$ to 5 % MeOH/$CHCl_3$. Volatiles were removed from the purified

product at ca. 10 mTorr for 18 h to afford **2.1h** as a cream-colored solid (175 mg, 16% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.07 (d, *J* = 2.1 Hz, 1H), 7.94 (d, *J* = 8.6, 2.1 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.27 (br. s, 1H), 3.90 (s, 3H), 3.78 (app t, *J* = 4.6 Hz, 4H), 3.60 (s, 2H), 2.65 (app t, *J* = 4.5 Hz, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.3, 160.5, 134.2, 132.2, 122.8, 114.9, 109.6, 92.2, 79.0, 66.9, 52.6, 52.2, 48.3.

HRMS (ESI+): Calculated for $C_{15}H_{17}NO_4Na$ ([M+Na]$^+$), 298.1055; found 298.1055.



Ethyl hex-5-ynoate (SI-2.23) was prepared according to a literature procedure[12] in 87% yield. ^{1}H NMR ($CDCl_3$, 600MHz): 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.[12]

Ethyl 6-(2-(methoxymethoxy)phenyl)hex-5-ynoate (SI-2.24). A flask was charged with **SI-2.9** (1.05 g, 3.98 mmol, 1.00 equiv), $(PPh_3)_2PdCl_2$ (0.14 g, 0.20 mmol, 0.050 equiv), and CuI (76 mg, 0.40 mmol, 0.10 equiv). The flask was then evacuated and refilled with N_2 three times before Et_3N (4.4 mL, 32 mmol, 8.0 equiv) and 5 mL MeCN were added, and this mixture was stirred for 30 min. Compound **SI-2.23** (0.98 g, 5.2 mmol, 1.30 equiv)

was added dropwise by syringe over 2 min. The reaction mixture was stirred for 18 h under dynamic N_2. At this time, analysis by TLC (30% EtOAc/hexanes) indicated full consumption of starting material. The reaction mixture was diluted with 50 mL DCM, and the organic layer was washed with saturated aqueous NH_4Cl (1 × 15 mL), water (1 × 10 mL), brine (1 × 10 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 40% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **SI-2.24** as a light yellow oil. (0.97 g, 88% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.37 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.22 (td, *J* = 7.8, 1.2 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 5.24 (s, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.52 (s, 3H), 2.59–2.48 (m, 2H), 1.95 (quin, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 157.8, 133.6, 129.1, 121.9, 115.3, 114.4, 95.1, 93.2, 77.7, 60.5, 56.4, 32.2, 24.1, 19.3, 14.4.

HRMS (ESI+): Calculated for $C_{16}H_{20}O_4Na$ ($[M+Na]^+$), 299.1259; found 299.1255.

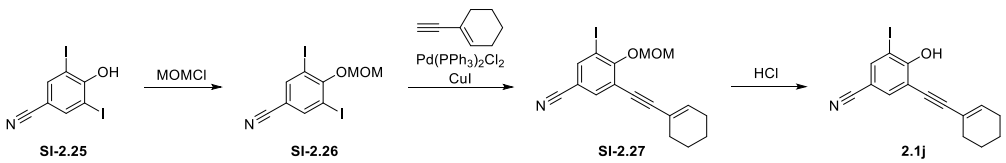
Ethyl 6-(2-hydroxyphenyl)hex-5-ynoate (2.1i). A flask was charged with **SI-2.24** (1.6 g, 5.8 mmol, 1.0 equiv), 58 mL DCM, and a stir bar. *B*-Chlorocatecholborane (1.2 g, 7.5 mmol, 1.3 equiv) was then added, and the mixture was sparged with N_2 for 10 min. The reaction mixture stirred for 18 h under dynamic N_2. At this time, analysis by TLC (20% EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL DCM and washed with water (3 × 30 mL) and brine (1 ×

30 mL). The organic layer was 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 ca. 10 mTorr for 18 h to afford **2.1i** as a light yellow oil. (1.2 g, 87% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.28 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 5.99 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.97 (quin, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.5, 156.9, 131.7, 129.9, 120.3, 114.7, 110.0, 96.2, 75.9, 60.8, 33.4, 23.8, 19.2, 14.4.

HRMS (CI): Calculated for $C_{14}H_{17}O_3$ ($[M+H]^+$), 233.1178; found 233.1182.



***3,5-Diiodo-4-(methoxymethoxy)benzonitrile (SI-2.26)**. A solution of **SI-2.25** (742 mg, 2.00 mmol, 1.00 equiv) and *N*,*N*-diisopropylethylamine (700. µL, 4.00 mmol, 2.00 equiv) in DCM (40 mL) was cooled to 0 °C under dynamic N_2 atmosphere. Chloromethyl methyl ether (210 µL, 2.8 mmol, 1.4 equiv) was then added dropwise. The reaction mixture was stirred at 0 °C for 40 min. It was then warmed gradually to 25 °C and stirred for 15 h, at which time analysis by TLC (20% EtOAc/hexanes) indicated full consumption of the

phenol starting material. The reaction mixture was diluted with 20 mL EtOAc and 10 mL H_2O. The resulting biphasic mixture was stirred vigorously for 20 min to quench unreacted MOMCl, and then the phases were separated. The organic layer was washed with H_2O (2 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to a pale yellow solid (780 mg, 94% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.08 (s, 2H), 5.22 (s, 2H), 3.75 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.1, 143.4, 115.4, 111.8, 100.9, 91.7, 59.2.

HRMS (GC/CI): Calculated for $C_9H_{11}I_2N_2O_2$ ($[M+NH_4]^+$), 432.8910; found 432.8896.

***3-(Cyclohex-1-en-1-ylethynyl)-5-iodo-4-(methoxymethoxy)benzonitrile (SI-2.27)**. A mixture of THF (24 mL) and Et_3N (2.6 mL, 19 mmol, 5.0 equiv) was sparged with N_2 for 20 min. Solid **SI-2.26** (1.56 g, 3.76 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (66 mg, 0.094 mmol, 2.5 mol %), and CuI (36 mg, 0.19 mmol, 5.0 mol %) were added under positive N_2 pressure. To the resulting solution was added 1-ethynylcyclohexene (463 µL, 3.95 mmol, 1.05 equiv). The reaction mixture was stirred at 25 °C for 20 h, at which time analysis by TLC (10% EtOAc/hexanes) indicated complete consumption of **SI-2.26**. The reaction mixture was diluted with 100 mL EtOAc, then washed with saturated aqueous NH_4Cl (3 × 20 mL) and brine (2 × 20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to an orange semisolid, which was purified using three successive silica gel chromatography columns using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Volatiles were removed at 25 °C and ca. 10 mTorr for 18 h to afford **SI-2.27** as a yellow oil in 90% purity (249 mg).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 6.27 (m, 1H), 5.44 (s, 2H), 3.68 (s, 3H), 2.23–2.15 (m, 4H), 1.72–1.61 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.0, 141.9, 137.7, 137.6, 120.1, 118.4, 116.6, 109.3, 99.6, 98.9, 92.5, 81.0, 58.9, 28.8, 26.0, 22.2, 21.4.

HRMS (ESI+): Calculated for $C_{17}H_{16}INO_2Na$ ($[M+Na]^+$), 416.0108; found 416.0124.

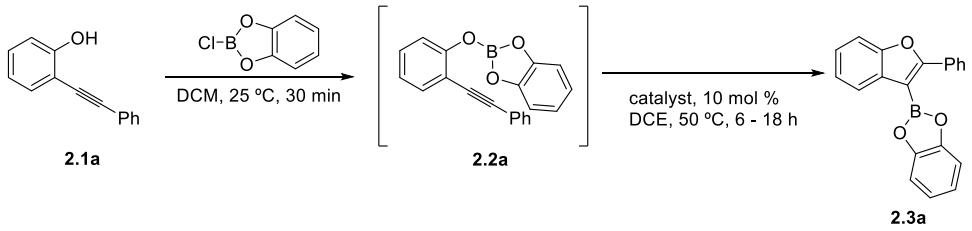
***3-(Cyclohex-1-en-1-ylethynyl)-4-hydroxy-5-iodobenzonitrile (2.1j)**. To a solution of **SI-2.27** (91 mg, 0.23 mmol, 1.0 equiv) in 2 mL DCM at 25 °C was added $HCl{\cdot}Et_2O$ (280 µL, 1.2 equiv). The reaction mixture was stirred for 3 h, at which time analysis by TLC (10% EtOAc/hexanes) revealed complete consumption of the MOM ether starting material. The reaction mixture was diluted with 10 mL EtOAc and washed with water (3 × 2 mL) and brine (3 × 2 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to a pale yellow oil. The product was purified by silica gel chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Volatiles were removed at 25 °C and ca. 10 mTorr for 18 h to afford **2.1j** as a white solid (45 mg, 55% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 2.3 Hz, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 6.67 (br. s, 1H), 6.35–6.32 (m, 1H), 2.24–2.16 (m, 4H), 1.74–1.62 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.0, 142.3, 138.8, 135.3, 119.5, 117.0, 106.1, 101.1, 81.9, 78.1, 29.0, 26.0, 22.2, 21.3.

HRMS (GC/CI): Calculated for $C_{15}H_{12}INO$ (M^+), 348.9964; found 348.9967.

*****Screen of potential oxyboration catalysts



Boric ester 2.2a. A flame-dried 25-mL Schlenk tube was charged with a solution of **2.1a** (97.0 mg, 0.500 mmol, 1.00 equiv) in dry DCM (3 mL). To this solution was then added a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in dry DCM (3 mL) at 25 °C. The reaction mixture was stirred for 30 min, and then the mixture was concentrated in vacuo to afford a moisture-sensitive, clear brown oil (159 mg, quant.) containing **2.2a**, which was used directly in the catalyst screen without further purification

^{1}H NMR (d_8-toluene, 600 MHz): δ 7.38 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.23–7.21 (m, 2H), 6.98 (dd, *J* = 10.2, 1.4 Hz, 1H), 6.92 (td, *J* = 8.7, 2.9 Hz, 1H), 6.86–6.84 (m, 3H), 6.82 (dd, *J* = 5.8, 3.4 Hz, 2H), 6.76 (td, *J* = 15.1, 9.5 Hz, 1H), 6.74 (*J* = 5.8, 3.4 Hz, 2H).

^{11}B NMR (d_8-toluene, 193 MHz): δ 23.2 (br. s).

Catalyst screening reactions were set up in an N_2-filled glovebox. Catalyst (0.0040 mmol, 10. mol %) was dissolved in anhydrous 1,2-dichloroethane (400 µL) and added to a dram vial containing **2.2a** (13 mg, 0.040 mmol, 1.0 equiv). After mixing thoroughly, the reaction mixture was transferred to a J. Young NMR tube, removed from the glovebox, and heated in a preheated 50 °C oil bath. After heating for the indicated time, the progress of the reaction was monitored by ^{1}H and ^{11}B NMR spectroscopy.

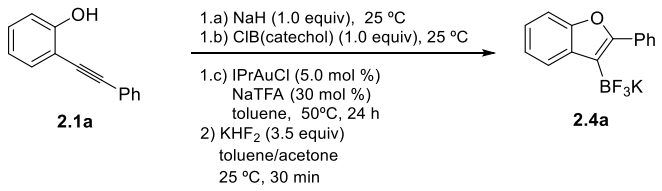
Table SI-2.1. Screen of potential oxyboration catalysts.

Entry	Catalyst	Product : Starting Material Ratio (**2.3a**:**2.2a**, ^{1}H NMR)
1	None	Only **2.2a**
2	$Pd(PPh_3)_2Cl_2$ + 20 mol % AgOTf	Only **2.2a**
3	PEPPSI-IPr + 20 mol % AgOTf	Only **2.2a**
4	IPrAuCl + 10 mol % AgOTf	> 95:5
5	IPrAuCl	Only **2.2a**
6	AgOTf	Only **2.2a**
7	IPrAuCl + 10 mol % AgTFA	> 95:5
8	IPrCuCl + 10 mol % AgTFA	Only **2.2a**
9	Trifluoroacetic acid	Only **2.2a**
10	$InBr_3$	Only **2.2a**

Synthesis and isolation of benzofuran oxyboration products **2.4a–2.4j**

Note: All oxyboration reactions were conducted in a N_2-filled glovebox due to the high moisture sensitivity of the boric ester intermediate **2.2**. All glassware and reagents must be rigorously dry for optimal yield. The reaction progress was monitored by removing a small aliquot of the reaction mixture from the glovebox and diluting it in 1:1 EtOAc:water. This results in rapid hydrolysis of boric ester intermediate **2.2** back to the phenol starting material **2.1**. Thus, co-spotting the reaction mixture versus phenol **2.1** provides a

convenient method for determining whether or not intermediate **2.2** has been fully consumed. The addition of PPh_3 to quench the Au catalyst[13] between the oxyboration step and the formation of the organotrifluoroborate or MIDA boronate was essential.



***Benzofuran trifluoroborate 2.4a**. A solution of phenol **2.1a** (97.0 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (69 wt % purity, 17.4 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30. mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to effect full deprotonation. To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2a**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1a**.

After 24 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2a**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 22 h at 25 °C in order to quench IPrAuTFA before proceeding.

The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with toluene (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (4.5 mL) and added to a stirring solution of KHF_2 (140 mg, 1.8 mmol, 3.5 equiv) in water (1.5 mL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. To this residue was added 2 mL Et_2O and subsequently concentrated at ca. 10 mTorr for 30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et_2O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional washing/extraction cycle to yield **2.4a** as a white powder (113 mg, 75% yield) after removing volatiles at 25 °C and ca. 10 mTorr for 18 h.

^{1}H NMR (d_6-DMSO, 600 MHz): δ 8.10 (d, J = 7.4 Hz, 2H), 7.88 (d, J = 7.7 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.13 (td, J = 6.5 Hz, 1.2 Hz, 1H), 7.08 (td, J = 7.4, 0.9 Hz, 1H).

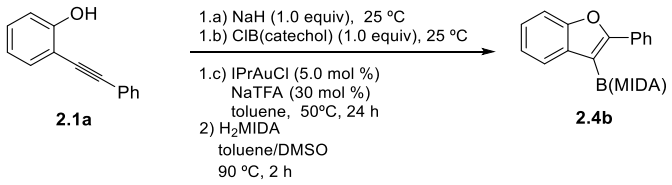
^{13}C NMR (d_6-DMSO, 125 MHz): δ 154.7 (q, $J_{C–F}$ = 4.6 Hz), 153.8, 135.4, 133.3, 127.9, 126.8, 126.7 (q, $J_{C–F}$ = 2.3 Hz), 124.1 (q, $J_{C–F}$ = 2.8 Hz), 122.7, 109.6. [Note: As with many organotrifluoroborates, the *ipso* carbon was not detected, presumably due to

broadening through coupling to the ^{11}B nucleus. The quaternary carbon at the benzofuran 2 position was also not detected.]

^{11}B NMR (d_6-DMSO, 193 MHz): δ 3.2 (br. s).

^{19}F NMR (d_6-DMSO, 376 MHz): δ -131.9 (br. s).

HRMS (ESI-): Calculated for $C_{14}H_9BF_3O$ ([M-K]$^-$), 261.0701; found 261.0706.



***MIDA boronate 2.4b**. A solution of phenol **2.1a** (97.0 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2a**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full

transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1a**.

After 24 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2a**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

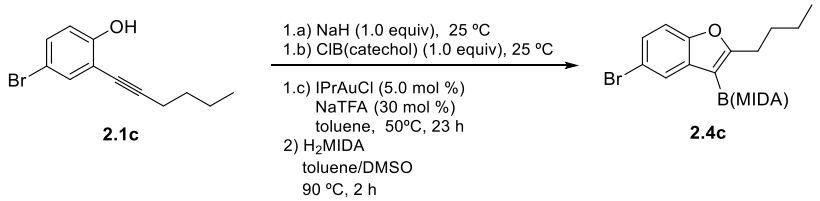
Anhydrous DMSO (2.0 mL) and H_2MIDA (81 mg, 0.55 mmol, 1.1 equiv) were added to the quenched oxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2 h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **2.4b** as a white powder (101 mg, 58% yield). Crystals suitable for X-ray diffraction analysis were prepared by slow diffusion of Et_2O into a saturated solution of **2.4b** in Et_2O/acetone at 25 °C over 3 days

^{1}H NMR (CD_3CN, 600 MHz): δ 7.72 (dd, *J* = 7.8 Hz, 0.8 Hz, 1H), 7.67–7.65 (m, 2H), 7.55 (d, *J* = 9.7 Hz, 1H), 7.47–7.44 (m, 3H), 7.35– 7.31 (m, 1H), 7.29– 7.26 (m, 1H), 3.97 (d, *J* = 17.1 Hz, 2H), 3.65 (d, *J* = 17.1 Hz, 2H), 2.56 (s, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.0, 156.0, 133.6, 133.0, 130.6, 130.2, 129.3, 125.2, 123.9, 123.5, 111.8, 63.0, 48.2. [Note: no signals were observed for the quaternary C–B *ipso* carbon or the quaternary carbon at the benzofuran 2 position.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.3 (br. s).

HRMS (ESI+): Calculated for $C_{17}H_{19}BBrNO_5$ ([M+Na]$^+$), 372.1023; found 372.1016.



***MIDA boronate 2.4c**. A solution of phenol **2.1c** (127 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2c**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1c**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2c**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

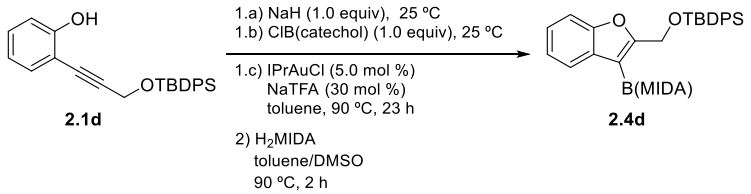
Anhydrous DMSO (2.0 mL) and H_2MIDA (160 mg, 1.1 mmol, 2.2 equiv) were added to the quenched oxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **2.4b** as a white powder (161 mg, 79% yield).

^{1}H NMR (CD_3CN, 600 MHz): δ 7.59 (dd, *J* = 1.9 Hz, 0.4 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H), 4.12 (d, *J* = 17.2 Hz, 2H), 3.92 (d, *J* = 17.2 Hz, 2H), 2.77 (app t, *J* = 7.7 Hz, 2H), 2.66 (s, 3H), 1.70 (app quintet, *J* = 7.7 Hz, 2H), 1.38 (sextet, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.4, 167.4, 154.6, 135.6, 126.8, 124.9, 116.1, 113.1, 63.0, 48.1, 31.6, 29.0, 23.2, 14.0. [Note: no signal was observed for the quaternary C–B *ipso* carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.3 (br. s).

HRMS (ESI+): Calculated for $C_{16}H_{17}BBrNO_5Na$ ($[M+Na]^+$), 430.0441; found 430.0425.



MIDA boronate 2.4d. A solution of phenol **2.1d** (85 mg, 0.22 mmol, 1.0 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 6.0 mg, 0.20 mmol, 1.0 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (9.0 mg, 0.070 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 45 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (34 mg, 0.22 mmol, 1.0 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2d**.

Next, a suspension of IPrAuCl (7.0 mg, 0.010 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1d**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2d**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3

(6.0 mg, 0.020 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

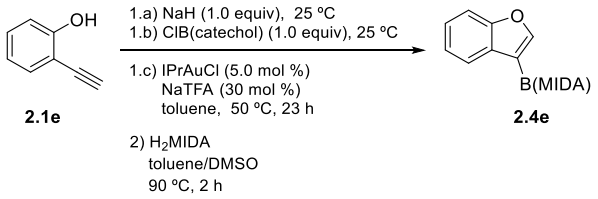
Anhydrous DMSO (2.0 mL) and H_2MIDA (35 mg, 0.24 mmol, 1.1 equiv) were added to the quenched oxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2 h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **2.4d** as a white powder (32 mg, 48% yield).

^{1}H NMR (CD_3CN, 600 MHz): δ 7.74 (dd, *J* = 7.8, 1.2 Hz, 4H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.51–7.46 (m, 3H), 7.46–7.40 (m, 4H), 7.32 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 4.87 (s, 2 H), 4.24 (d, *J* = 17.2 Hz, 2H), 3.92 (d, *J* = 17.2 Hz, 2H), 2.63 (s, 3 H), 1.02 (s, 9 H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.3, 161.7, 156.0, 136.5, 133.9, 132.7, 131.0, 128.8, 125.4, 123.8, 123.1, 111.9, 62.7, 59.6, 48.3, 27.1, 19.8. [Note: no signal was observed for the quaternary C–B *ipso* carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.2.

HRMS (ESI+): Calculated for $C_{30}H_{32}O_6BNSiNa$ ($[M+Na]^+$), 564.1995; found 564.1995.



2.1e **2.4e**

MIDA boronate 2.4e. A solution of phenol **2.1e** (90. mg, 0.76 mmol, 1.0 equiv) in 1.5 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 20. mg, 0.76 mmol, 1.00 equiv) in 1.0 mL toluene over 2 min. A suspension of NaTFA (31 mg, 0.23 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (120 mg, 0.76 mmol, 1.0 equiv) in toluene (1.5 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2e**.

Next, a suspension of IPrAuCl (25 mg, 0.040 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (3 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1e**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2e**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3

(20. mg, 0.080 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

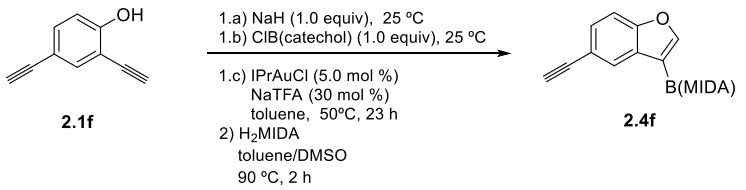
Anhydrous DMSO (2.0 mL) and H_2MIDA (124 mg, 0.84 mmol, 1.1 equiv) were added to the quenched oxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **2.4e** as an off-white powder (82 mg, 40% yield).

^{1}H NMR (CD_3CN, 600 MHz): δ 7.75 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 9.0 Hz, 1H), 4.12 (d, *J* = 17.2 Hz, 2H), 3.95 (d, *J* = 17.2 Hz, 2H), 2.67 (s, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.3, 157.0, 151.7, 131.1, 125.2, 123.9, 122.9, 112.2, 62.6, 48.1. [Note: no signal was observed for the quaternary C–B *ipso* carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.2 (br. s).

HRMS (ESI+): Calculated for $C_{12}H_{12}BNO_5Na$ ($[M+Na]^+$), 296.0709; found 296.0714.



***MIDA boronate 2.4f**. A solution of phenol **2.1f** (71.0 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30 mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (1.0 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2f**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1f**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2f**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

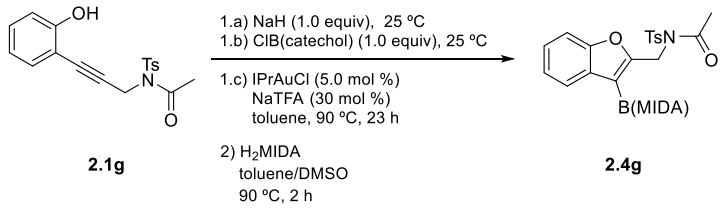
Anhydrous DMSO (2.0 mL) and H_2MIDA (160 mg, 1.1 mmol, 2.2 equiv) were added to the quenched oxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **2.4f** as a white powder (52 mg, 35% yield).

^{1}H NMR (CD_3CN, 600 MHz): δ 7.82 (s, 1H), 7.69 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.38 (dd, *J* = 7.1, 1.3 Hz, 1H), 4.12 (d, *J* = 17.2 Hz, 2H), 3.94 (d, *J* = 17.2 Hz, 2H), 3.40 (s, 1H), 2.66 (s, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 169.2, 156.4, 153.3, 132.1, 127.9, 123.1, 115.8, 84.4, 78.5, 62.6, 48.2. [Note: no signals were observed for the quaternary C–B *ipso* carbon and a second quaternary carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.0 (br. s).

HRMS (ESI+): Calculated for $C_{15}H_{12}BNO_5Na$ ($[M+Na]^+$), 320.0709; found 320.0713.



MIDA boronate 2.4g. A solution of phenol **2.1g** (99 mg, 0.29 mmol, 1.0 equiv) in 0.5 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 8.0 mg, 0.50 mmol, 1.0 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (9.0 mg, 0.090 mmol, 30. mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (45 mg, 0.29 mmol, 1.0 equiv) in toluene (0.5 mL), using additional toluene as a rinse to ensure full transfer (1 × 0.3 mL portion). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2g**.

Next, a suspension of IPrAuCl (9.0 mg, 0.010 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.2 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 90 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1g**.

After 23 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2g**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3

(8.0 mg, 0.030 mmol, 10. mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

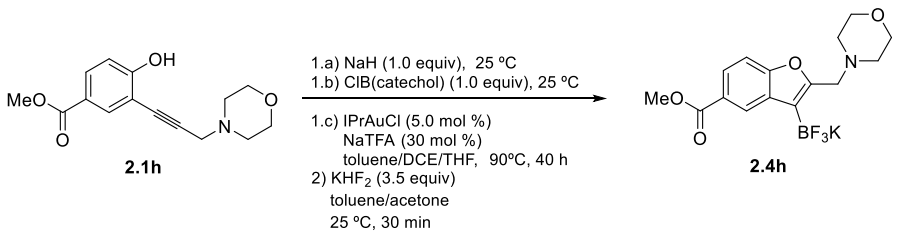
Anhydrous DMSO (2.0 mL) and H_2MIDA (52 mg, 0.35 mmol, 1.1 equiv) were added to the quenched oxyboration reaction mixture, and the resulting suspension was stirred at 90 °C for 2h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified by silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **2.4g** as a white powder (59 mg, 41% yield).

^{1}H NMR (CD_3CN, 600 MHz): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.34–7.29 (m, 3H), 7.26 (t, *J* = 7.2 Hz, 1H), 5.28 (s, 2H), 4.19 (d, *J* = 21.0 Hz, 2H), 4.12 (d, *J* = 21.0 Hz, 2H), 2.76 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 171.7, 169.6, 158.2, 155.6, 146.4, 137.2, 132.3, 130.6, 129.0, 125.4, 124.1, 122.9, 111.9, 64.0, 49.0, 44.5, 25.0, 21.6. [Note: no signal was observed for the quaternary C–B *ipso* carbon.]

^{11}B NMR (CD_3CN, 193 MHz): δ 11.3.

HRMS (ESI+): Calculated for $C_{23}H_{23}BN_2O_8SNa$ ($[M+Na]^+$), 521.1170; found 521.1153.



***Benzofuran trifluoroborate 2.4h**. A solution of phenol **2.1h** (138 mg, 0.500 mmol, 1.00 equiv) in 1.0 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 13.0 mg, 0.500 mmol, 1.00 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (20. mg, 0.15 mmol, 30 mol %) in 0.5 mL toluene was added next. Due to the low solubility of **2.1h** in toluene, dry dichloroethane (0.5 mL) and dry THF (1.0 mL) were added. The resulting suspension was stirred for 15 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (77.0 mg, 0.500 mmol, 1.00 equiv) in toluene (0.5 mL), using additional toluene as a rinse to ensure full transfer (1 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2h**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 90 °C copper shot heating bath. The final concentration of the reaction mixture was 0.08 M in **2.1h**.

After 40 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2h**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3

(13 mg, 0.050 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 26 h at 25 °C in order to quench IPrAuTFA before proceeding.

The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with chloroform (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (4.5 mL) and added to a stirring solution of KHF_2 (160 mg, 2.0 mmol 4.0 equiv) in water (1.5 mL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. To this residue was added 2 mL Et_2O and subsequently concentrated at ca. 10 mTorr for 30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et_2O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional washing/extraction cycle to yield **2.4h** as a light green powder (79 mg, 42% yield) with trace residual acetone after removing volatiles at 25 °C and ca. 10 mTorr for 18 h.

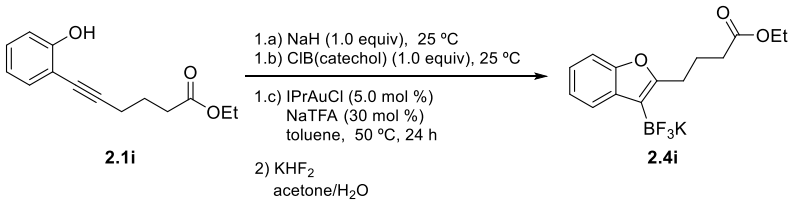
^{1}H NMR (d_6-DMSO, 600 MHz): δ 8.30 (s, 1H), 7.75 (dd, *J* = 9.4 Hz, 1.7 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 3.85, (s, 3H), 3.67 (br. s, 2H), 3.54 (app t, *J* = 4.1 Hz, 4H), 2.44 (s, 4H).

^{13}C NMR (d_6- DMSO, 125 MHz): δ 167.0, 157.3, 155.5, 134.1, 125.2, 123.9, 122.7, 109.8, 66.2, 54.2, 53.0, 51.8. [Note: As with many organotrifluoroborates, the *ipso* carbon was not detected, presumably due to broadening through coupling to the ^{11}B nucleus.]

^{11}B NMR (d_6- DMSO, 193 MHz): δ 2.8 (br. s).

^{19}F NMR (d_6-DMSO, 376 MHz): δ -133.1 (br. s).

HRMS (ESI-): Calculated for $C_{15}H_{16}BF_3NO_4$ ([M-K]$^-$), 342.1127; found 342.1125.



***Benzofuran trifluoroborate 2.4i**. A solution of phenol **2.1i** (101 mg, 0.440 mmol, 1.00 equiv) in 0.75 mL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 11 mg, 0.44 mmol, 1.0 equiv) in 0.5 mL toluene over 2 min. A suspension of NaTFA (18 mg, 0.13 mmol, 30. mol %) in 0.5 mL toluene was added next, and the resulting suspension was stirred for 15 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (67 mg, 0.44 mmol, 1.0 equiv) in toluene (0.75 mL), using additional toluene as a rinse to ensure full transfer (2 × 0.5 mL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2i**.

Next, a suspension of IPrAuCl (14 mg, 0.022 mmol, 5.0 mol %) in toluene (0.5 mL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 0.5 mL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1i**.

After 24 h, analysis by TLC (20% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2i**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (8.0 mg, 0.030 mmol, 10. mol %) in toluene (0.5 mL) was added. The resulting suspension stirred for 22 h at 25 °C in order to quench IPrAuTFA before proceeding.

The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with toluene (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (4.5 mL) and added to a stirring solution of KHF_2 (136 mg, 1.70 mmol, 3.50 equiv) in water (1.5 mL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. To this residue was added 2 mL Et_2O and subsequently concentrated at ca. 10 mTorr for 30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et_2O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional washing/extraction cycle to yield **2.4i** as a white powder (102 mg, 69% yield) after removing volatiles at 25 °C and ca. 10 mTorr for 18 h.

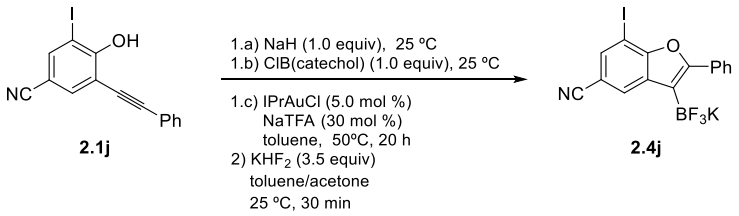
^{1}H NMR (d_6- DMSO, 600 MHz): δ 7.55 (t, J = 6.7 Hz, 1H), 7.27 (dd, J = 6.7, 1.8 Hz, 1H), 7.05–6.93 (m, 2H), 4.03 (q, J = 7.0 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H), 2.28 (t, J = 7.7 Hz, 2H), 1.85 (quin, J = 7.5 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (d_6- DMSO, 125 MHz): δ 172.9, 157.3, 154.0, 134.6, 122.5, 121.3, 120.7, 109.2, 59.6, 33.1, 27.0, 24.0, 14.1.

^{11}B NMR (d_6- DMSO, 193 MHz): δ 2.9 (br. s).

^{19}F NMR (d_6- DMSO, 377 MHz) δ −133.6 (m).

HRMS (ESI-): Calculated for $C_{14}H_{15}BF_3O_3$ ([M-K]$^-$), 299.1069; found 299.1063.



***Benzofuran trifluoroborate 2.4j**. A solution of phenol **2.1j** (41.4 mg, 0.119 mmol, 1.00 equiv) in 150 µL toluene was added to a flame-dried 10-mL Schlenk tube. To this stirring solution was added dropwise at 25 °C a suspension of NaH (92 wt % purity, 3.1 mg, 0.12 mmol, 1.0 equiv) in 150 µL toluene. A suspension of NaTFA (4.9. mg, 0.036 mmol, 30 mol %) in 150 µL toluene was added next. The resulting suspension was stirred for 15 min to effect full deprotonation.

To the resulting stirring sodium phenoxide suspension was added at 25 °C a solution of *B*-chlorocatecholborane (18.3 mg, 0.119 mmol, 1.00 equiv) in toluene (150 µL), using additional toluene as a rinse to ensure full transfer (1 × 150 µL portions). The resulting suspension was stirred vigorously for 30 min to allow for full conversion to boric ester intermediate **2.2j**.

Next, a suspension of IPrAuCl (16 mg, 0.025 mmol, 5.0 mol %) in toluene (150 µL) was added to the reaction mixture at 25 °C, using additional toluene as a rinse to aid in full transfer (1 × 150 µL portion). The reaction mixture was then sealed with a ground glass stopper and a PTFE sealing ring and placed in a preheated 90 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1j**.

After 20 h, analysis by TLC (10% EtOAc/hexanes) indicated full consumption of boric ester intermediate **2.2j**. The reaction mixture was cooled to 25 °C, and a solution of PPh_3 (3.1 mg, 0.012 mmol, 10 mol %) in toluene (0.5 mL) was added. The resulting suspension was stirred for 18 h at 25 °C in order to quench IPrAuTFA before proceeding.

The quenched reaction mixture was removed from the glovebox and filtered through a fiberglass filter to remove the suspended solids. The filter was then rinsed with chloroform (3 × 3 mL), and the combined filtrates were concentrated in vacuo to a pale yellow powder, which was suspended in acetone (1.0 mL) and added to a stirring solution of KHF_2 (37 mg, 0.48 mmol, 4.0 equiv) in water (300 µL). The resulting mixture was stirred at 25 °C for 30 min, and then concentrated in vacuo to remove the solvents. Residual water was removed azeotropically by adding 2 mL acetone and concentrating in vacuo again. To this residue was added 2 mL Et_2O and subsequently concentrated at ca. 10 mTorr for 30 min in order to remove residual acetone. The resulting pale yellow solid residue was washed with Et_2O (4 × 2 mL) and extracted with acetone (4 × 2 mL). The combined acetone extracts were concentrated in vacuo, and the resulting residue was subjected to an additional washing/extraction cycle to yield **2.4j** as a light green powder (12 mg, 23% yield) with trace residual acetone after removing volatiles at 25 °C and ca. 10 mTorr for 18 h.

^{1}H NMR (d_6-DMSO, 600 MHz): δ 8.07 (d, J = 1.4 Hz, 1H), 7.87 (d, J = 1.5 Hz, 1H), 7.59–7.57 (m, 1H), 2.56–2.53 (m, 2H), 2.23–2.20 (m, 2H), 1.69–1.65 (m, 2H), 1.62–1.58 (m, 2H).

^{13}C NMR (d_6-DMSO, 125 MHz): δ. 155.9, 135.4, 133.2, 129.4, 128.1, 127.7, 118.8, 105.6, 75.1, 25.3, 25.0, 22.2, 21.7. [Note: As with many organotrifluoroborates, the *ipso*

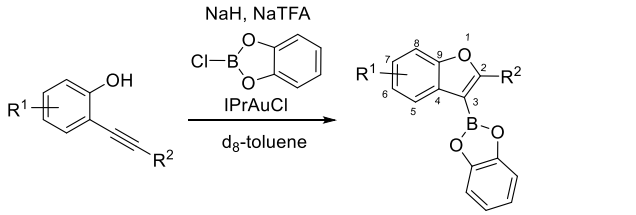
carbon was not detected, presumably due to broadening through coupling to the ^{11}B nucleus. A second quaternary carbon was also not detected.]

^{11}B NMR (d_6- DMSO, 193 MHz): δ 2.8 (br. s).

^{19}F NMR (d_6-DMSO, 376 MHz): δ -130.7 (br. s).

HRMS (ESI-): Calculated for $C_{15}H_{11}BF_3INO$ ([M-K]$^-$), 415.9933; found 415.9916.

General procedure NMR conversions using ERETIC

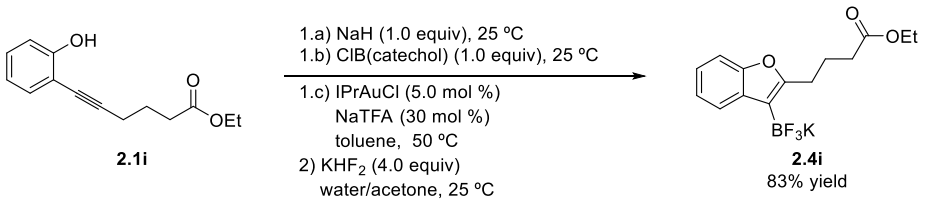


2.1a/2.1b, 2.1c, 2.1f, 2.1i **2.2a/2.2b, 2.2c, 2.2f, 2.2i**

A 4-mL vial was charged with a 2-substituted alkynylphenol (0.05 mmol, 1 equiv), and 0.5 mL d_8-toluene. A second 4-mL vial was charged with NaH (1.3 mg, 0.050 mmol, 1.0 equiv) and NaTFA (2.7 mg, 0.020 mmol, 0.30 equiv). The solution containing the phenol was then added dropwise to the vial containing NaH and NaTFA, and swirled intermittently for 15 min. This cloudy mixture was then added dropwise to another 4-mL vial containing *B*-chlorocatecholborane (7.7 mg, 0.050 mmol, 1.0 equiv). This mixture was then swirled intermittently for 30 min before transferring into a new vial containing IPrAuCl (1.6 mg, 0.0030 mmol, 0.050 equiv). This mixture was then transferred into a J. Young NMR tube, which was sealed and removed from the glove box. This tube was then heated to 50 ^oC for 18-24 h. An ^1H NMR was taken (600 MHz, d_8-toluene), and the signals correlating to the corresponding cyclized benzofuran boronic ester were compared to an external

standard of mesitylene (419 mmol/L in d_8-toluene) using the ERETIC method, ensuring the acquisition parameters were identical. This general procedure was used for R^1= H, R^2=Ph (**2.3a**, **2.3b**, 95%); R^1= 6-Br, R^2= Bu (**2.3c**, 88%); R^1= 6-CCH, R^2=H (**2.3f**, 42%), R^1= H, R^2= -$(CH_2)_3CO_2Et$ (**2.3i**, 71%).

*****<u>Gram-scale preparation of **2.4i**</u>



The gram-scale oxyboration reaction was conducted in an N_2-filled glovebox. A flame-dried 100-mL Schlenk tube with a stir bar was charged with NaH (92 wt % purity, 123 mg, 5.13 mmol, 1.00 equiv) and NaTFA (210 mg, 1.5 mmol, 30. mol %). Anhydrous toluene (12 mL) was added. To the resulting rapidly stirring suspension was added a solution of phenol **2.1i** (1.30 g, 5.13 mmol, 1.00 equiv) in toluene (2 mL) at 25 °C dropwise over 5 min. Additional toluene (3 × 2 mL) was used as a rinse to aid in complete transfer. The reaction mixture was stirred at 25 °C for 30 min to effect full deprotonation.

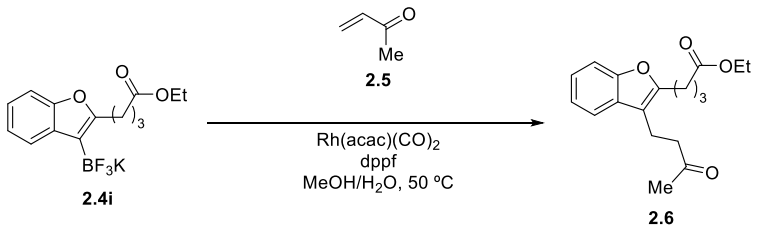
To the resulting pale yellow suspension was added a solution of *B*-chlorocatecholborane (790. mg, 5.13 mmol, 1.00 equiv) in toluene (5 mL) dropwise over 5 min. [Note: a slight exotherm occurs.] Additional toluene (3 × 5 mL) was used as a rinse to aid in complete transfer. The reaction mixture was stirred at 25 °C for 30 min to affect full formation of boric ester intermediate **2.2i**.

A suspension of IPrAuCl (80. mg, 0.13 mmol, 2.5 mol %) in toluene (2.5 mL) was added next, using additional toluene (3 × 2.5 mL) as a rinse to ensure full transfer. The reaction vessel was then sealed with a ground glass joint and a PTFE sealing ring and placed in a preheated 60 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.1i**.

After 22 h, analysis by TLC (10% EtOAc/hexanes) indicated complete consumption of boric ester intermediate **2.2i**. The reaction mixture was cooled to 25 °C, and then a solution of PPh_3 (67 mg, 0.26 mmol, 5.0 mol %) in 2.5 mL toluene was added to the reaction mixture. The resulting suspension was stirred for 23 h at 25 °C in order to quench IPrAuTFA before proceeding.

The suspension containing boronic ester **2.3i** was removed from the glovebox and concentrated in vacuo. The resulting solid residue was extracted with toluene (3 × 15 mL), and the combined extracts were filtered through a fiberglass filter to ensure removal of suspended solids. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in acetone (45 mL) and added to a vigorously stirring solution KHF_2 (1.6 g, 21 mmol, 4.0 equiv) in 15 mL H_2O. The reaction mixture was stirred open to air for 30 min at 25 ^oC before being concentrated in vacuo to remove the solvents. Residual water was removed azeotropically by adding 2 mL acetone and concentrating in vacuo again. The resulting solid residue was washed with Et_2O (15 × 30 mL) and extracted with acetone (3 × 15 mL), The combined acetone extracts were concentrated in vacuo to yield **2.4i** as a white powder (1.43 g, 83% yield) after removing volatiles at 25 ^oC and ca. 10 mTorr for 18 h. Spectral data were identical to those previously obtained for this compound.

Downstream functionalization reactions to produce **2.6**, **2.8**, and **2.10**



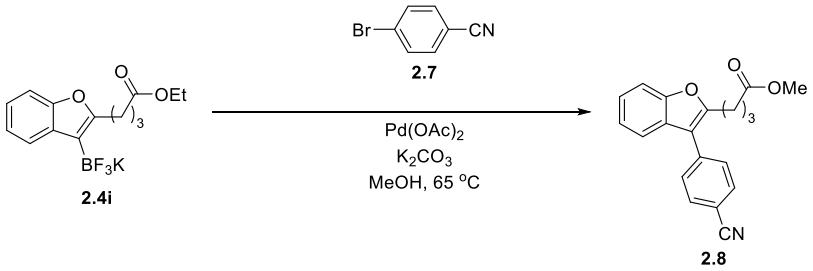
Ethyl 4-(3-(3-oxobutyl)benzofuran-2-yl)butanoate (2.6). The Rh-catalyzed conjugate addition of **2.4i** to methyl vinyl ketone was conducted using a procedure adapted from Batey.[14] A dram vial was charged with **2.4i** (85 mg, 0.25 mmol, 1.1 equiv) and a stir bar. The vial was pumped into an N_2-filled glovebox, where $Rh(acac)(CO)_2$ (1.9 mg, 7.1 μmol, 3.0 mol %) and dppf (40. mg, 72 μmol, 30. mol %) were added. The vial was sealed with a septum cap, removed from the glovebox, and placed under dynamic N_2 atmosphere. Methanol (2.2 mL) and water (0.40 mL) were added, and the resulting mixture was stirred at 25 °C for 15 min to dissolve the solids. Methyl vinyl ketone (19 μL, 0.23 mmol, 1.0 equiv) was added, and the reaction mixture was heated at 50 °C for 30 h. To the resulting heterogeneous brown mixture was added 10 mL DCM, and the resulting biphasic mixture was separated. The aqueous layer was back extracted with DCM (3 × 1 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to a brown solid residue. Purification by silica gel chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes and removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded **2.6** as a clear, colorless oil (33 mg, 44% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (d, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.23–7.18 (m, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.77

(t, *J* = 7.3 Hz, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 2.13 (s, 3H), 2.05 (quin, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.9, 173.3, 154.2, 153.8, 129.1, 123.5, 122.3, 118.9, 113.8, 111.0, 60.5, 43.4, 33.6, 30.3, 25.6, 23.6, 17.6, 14.4.

HRMS (ESI+): Calculated for $C_{18}H_{22}O_4Na$ ([M+Na]$^+$), 325.1416; found 325.1420.



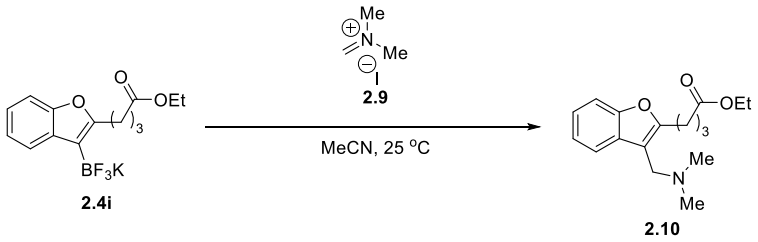
Methyl 4-(3-(4-cyanophenyl)benzofuran-2-yl)butanoate (2.8). A 20-mL vial was charged with **2.4i** (99 mg, 0.29 mmol, 1.1 equiv), K_2CO_3 (116 mg, 0.837 mmol, 3.00 equiv), and $Pd(OAc)_2$ (0.2 mg, 0.001 mmol, 0.3 mol %). The vial was then evacuated and refilled with N_2 three times. To this vial was then added 0.4 mL of MeOH that had been sparged for 10 min with N_2. In a separate flask was added 4-benzonitrile **2.7** (51 mg, 0.28 mmol, 1.0 equiv), which was then evacuated and refilled with N_2 three times before adding 0.4 mL MeOH that had been sparged 10 min with N_2. This solution was then syringed into the stirring reaction vial over 1 min. The vial was then equipped with an argon balloon and heated to 65 °C. The mixture stirred for 18 h before TLC (10% EtOAc/hexanes) showed the complete consumption of starting material. The reaction mixture was diluted with 20 mL toluene, and then the organic layer was washed with H_2O (1 × 5 mL), brine (1 × 5 mL), filtered, and 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 ca. 10 mTorr for 18 h to afford **2.8** as a white solid. (41 mg, 44% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.50 (dd, *J* = 16.3, 7.9 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 3.61 (s, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 2.13 (quin, *J* = 7.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 155.0, 154.3, 137.8, 132.8, 129.7, 127.8, 124.5, 123.3, 119.3, 119.0, 116.4, 111.4, 110.9, 51.8, 33.2, 26.2, 23.5.

HRMS (ESI+): Calculated for $C_{20}H_{17}NO_3Na$ ([M+Na]$^+$), 342.1106; found 342.1094.



***Ethyl 4-(3-((dimethylamino)methyl)benzofuran-2-yl)butanoate (2.10)**. A 10-mL Schlenk tube was charged with Eschenmoser's salt (**2.9**, 74.0 mg, 0.300 mmol, 1.00 equiv) and 1.0 mL anhydrous MeCN. To the resulting suspension was added a solution of organotrifluoroborate **2.4i** (101 mg, 0.300 mmol, 1.00 equiv) in 1.3 mL dry MeCN. The reaction mixture was stirred vigorously for 30 min at 25 °C, at which time a saturated aqueous solution of $NaHCO_3$ (1 mL) was added to quench the reaction. The resulting biphasic mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers

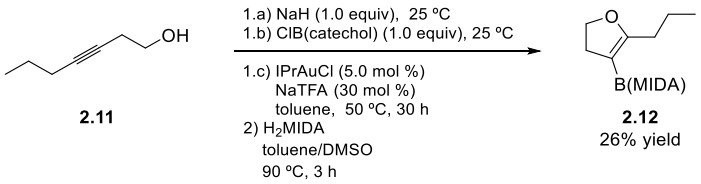
were washed with brine (3 × 3 mL), dried over Na_2SO_4, and concentrated in vacuo to an oily residue. Purification by column chromatography using an elution gradient from 1.5% Et_3N in hexanes to 40% EtOAc and 0.9% Et_3N in hexanes afforded **2.10** as a clear, pale yellow oil (63 mg, 72% yield).

^1H NMR ($CDCl_3$, 600 MHz): δ 7.63-7.61 (m, 1H), 7.41-7.30 (m, 1H), 7.24-7.19 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.26 (s, 6H), 2.09 (app. quin, *J* = 7.3 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 155.4, 154.1, 129.7, 123.5, 122.5, 119.9, 112.6, 110.7, 60.5, 53.2, 45.6, 33.6, 25.8, 23.5, 14.4.

HRMS (ESI+): Calculated for $C_{17}H_{23}NO_3Na$ ($[M+Na]^+$), 312.1576; found 312.1570.

*****<u>Synthesis of dihydrofuran product **2.12**</u>



Prior to use, **2.11** was dried by distilling over anhydrous K_2CO_3 (15 Torr, 80 °C) and was stored over activated 3Å molecular sieves. The oxyboration reaction was set up and conducted in an N_2-filled glovebox. A flame-dried 100 mL Schlenk tube with a stir bar was charged with NaH (92 wt % purity, 26.0 mg, 1.00 mmol, 1.00 equiv) and NaTFA (41 mg, 0.30 mmol, 30 mol %). Anhydrous toluene (4 mL) was added. Compound **2.11** (103 µL, 1.00 mmol, 1.00 equiv) was added dropwise over 1 min, and then the reaction mixture was stirred at 25 °C for 40 min to affect full deprotonation.

To the resulting suspension was added a solution of *B*-chlorocatecholborane (154 mg, 1.00 mmol, 1.00 equiv) in toluene (2 mL) dropwise over 5 min. Additional toluene (2 × 1 mL) was used as a rinse to aid in complete transfer. The reaction mixture was stirred at 25 °C for 30 min to affect full formation of the boric ester intermediate.

A suspension of IPrAuCl (31 mg, 0.050 mmol, 5.0 mol %) in toluene (1 mL) was added next, using additional toluene (2 × 0.5 mL) as a rinse to ensure full transfer. The reaction vessel was then sealed with a ground glass joint and a PTFE sealing ring and placed in a preheated 50 °C copper shot heating bath. The final concentration of the reaction mixture was 0.1 M in **2.11**.

Analysis by TLC (20% EtOAc/hexanes) at 23 h and 30 h indicated stalled, nearly complete consumption of the boric ester intermediate. The reaction mixture was cooled to 25 °C, and then a solution of PPh_3 (26 mg, 0.10 mmol, 10 mol %) in 1 mL toluene. The resulting suspension was stirred for 16 h at 25 °C in order to quench IPrAuTFA before proceeding.

To the quenched reaction mixture were added H_2MIDA (160 mg, 1.1 mmol, 1.1 equiv) and dry DMSO (4 mL), and the resulting suspension was stirred at 90 °C for 3 h. The reaction mixture was then cooled to 25 °C and removed from the glovebox. Toluene was removed in vacuo at 25 °C and ca. 10 Torr, then DMSO was removed by Kugelrohr distillation at ca. 10 mTorr. The resulting semisolid residue was adsorbed onto Celite from a MeCN suspension and purified twice by successive silica gel chromatography using an elution gradient from 100% Et_2O to 100% MeCN. Removal of volatiles at 25 °C and ca. 10 mTorr for 18 h afforded MIDA boronate **2.12** as a white powder (83 mg, 26% yield).

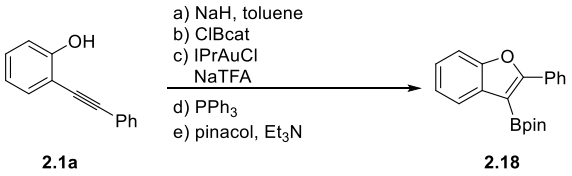
^{1}H NMR (CD_3CN, 600 MHz): δ 3.94 (d, *J* = 17.2 Hz, 2H), 3.84 (d, *J* = 17.2 Hz, 2H), 3.68 (t, *J* = 6.8 Hz, 2H), 2.86 (s, 3H), 2.38 (tt, *J* = 6.9, 2.3 Hz, 2H), 2.11 (tt, *J* = 6.9, 2.3 Hz, 2H), 1.46 (sextet, *J* = 7.3 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (CD_3CN, 125 MHz): δ 168.3, 82.0, 78.3, 63.3, 63.1, 46.1, 23.2, 22.7, 21.1, 13.7.

^{11}B NMR (CD_3CN, 193 MHz): δ 8.8 (br. s).

HRMS (ESI+): Calculated for $C_{12}H_{18}BNO_5Na$ ([M+Na]$^+$), 290.1178; found 290.1180.

Multigram Scale Synthesis of **2.18** for *Organic Syntheses*



2.1a **2.18**

4,4,5,5-tetramethyl-2-(2-phenylbenzofuran-3-yl)-1,3,2-dioxaborolane (2.18). This procedure was done in a nitrogen-filled glove box. A 500-mL round-bottomed flask was charged with a stir bar, sodium hydride (0.81 g, 31 mmol, 1.0 equiv, 92% wt.), and 192 mL toluene. In a separate 20-mL vial, **2.1a** (6.1 g, 31 mmol, 1.0 equiv) was dissolved in 15 mL of toluene. This solution was then drawn into a 24-mL syringe with a long-stem needle. The vial was then rinsed with an additional 3 mL of toluene, which was also drawn into the same syringe. This solution was then added to the reaction flask via syringe pump over 30 min. The reaction was then stirred for an additional 15 min.

In a separate 20-mL vial, *B*-chlorocatecholborane (4.8 g, 31 mmol, 1.0 equiv) was dissolved in 15 mL toluene. This was then drawn up into another 24-mL syringe equipped with a long stem needle. The vial was then rinsed with 3 mL of toluene, which was then

drawn up into the same syringe. This combined solution was then added to the reaction mixture in the round-bottomed flask over 1 min and then the flask was capped with a glass stopper equipped with a Teflon ring. The reaction mixture was then stirred for 30 min. In another 20-mL vial, 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride, also known as IPrAuCl (0.58 g, 0.94 mmol, 3.0 mol%) was dissolved in 18 mL toluene. This solution was then transferred via pipette to the reaction mixture over 1 min. The vial was then rinsed with 10 mL toluene and this rinse was added via pipette to the reaction mixture. Sodium trifluoroacetate (1.3 g, 9.4 mmol, 0.30 equiv) was added to a 20-mL vial, and then added in one portion to the reaction mixture. This vial was then rinsed with 6 mL toluene, and this rinse was then added to the reaction mixture via pipette. The round-bottomed flask was then capped with a glass stopper equipped with a Teflon ring, and a Keck plastic joint clip. The flask was then placed in a pre-heated copper shot bath (60 ^{o}C) and allowed to stir in the glovebox for 21 h.

At this time, TLC indicated that the reaction was complete. The mixture was then cooled to room temperature before triphenylphosphine (0.41 g, 1.6 mmol, 5.0 mol%) was added in one portion. The reaction flask was then allowed to stir for 3 h. In a separate 100-mL round-bottomed flask, pinacol (11 g, 94 mmol, 3.0 equiv) was dissolved in triethylamine (65 mL, 470 mmol, 15 equiv). This solution was then added to the reaction mixture via pipette over 4 min. The flask was capped with a glass stopper, and the reaction mixture was stirred for 1 h. The flask was then taken out of the glovebox and the resulting suspension was filtered through celite, using 200 mL of toluene as a rinse. The recovered liquid was transferred to a new 1-L round-bottomed flask and concentrated by rotary evaporation (40 ^{o}C, 10 Torr). The dark brown oil was then dissolved in 20 mL of

dichloromethane and transferred to a 100-mL round-bottomed flask and then concentrated by rotary evaporation (30 °C, 10 Torr). The mixture was then placed under high vacuum (200 mTorr) for 16 h. Column chromatography using 20% dichloromethane in hexanes yielded 8.0–8.2 g of a light yellow solid (80–82%) after drying under high vacuum for 18 h (25 °C, 200 mTorr).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.17 (d, *J* = 7.5 Hz, 2H), 8.01–8.00 (m, 1H), 7.51–7.50 (m, 1H), 7.46–7.43 (m, 2H), 7.41–7.38 (m, 1H), 7.30-7.24 (m, 2H), 1.41 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 163.1, 154.7, 133.4, 131.4, 129.2, 128.3 (overlapping, two separate signals), 124.4, 123.2, 123.1, 110.7, 83.7, 25.0.

^{11}B NMR ($CDCl_3$, 192 MHz) δ 30.4.

IR (film): 3048, 2950, 1606, 1561, 1389, 1011, 760, 685 cm^{-1}.

Melting Point: 85.7–86.6 °C.

HRMS calc. for $C_{20}H_{21}BO_3Na$ $[M+Na]^+$: 343.1485. Found 343.1494.

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Chapter 3

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

Abstract: The catalyst-free oxyboration reaction of alkynes is developed. The resulting borylated isocoumarins and 2-pyrones are isolated as boronic acids, pinacolboronate esters, or potassium organotrifluoroborate salts, thus providing a variety of bench stable organoboron building blocks for downstream functionalization. This method has functional group compatibility, is scalable, and proceeds with readily available materials: *B*-chlorocatecholborane and methyl esters. Mechanistic studies indicate that the *B*-chlorocatecholborane acts as a carbophilic Lewis acid toward the alkyne, providing a mechanistically distinct pathway for oxyboration that avoids B–O σ bond formation and that enables this catalyst-free route. I initiated this project and worked with graduate student Adena Issaian and undergraduate student Ashlee J. Davis on its publication.[1] For scientific clarity, the full story is shared here; my contribution is noted in the experimental section.

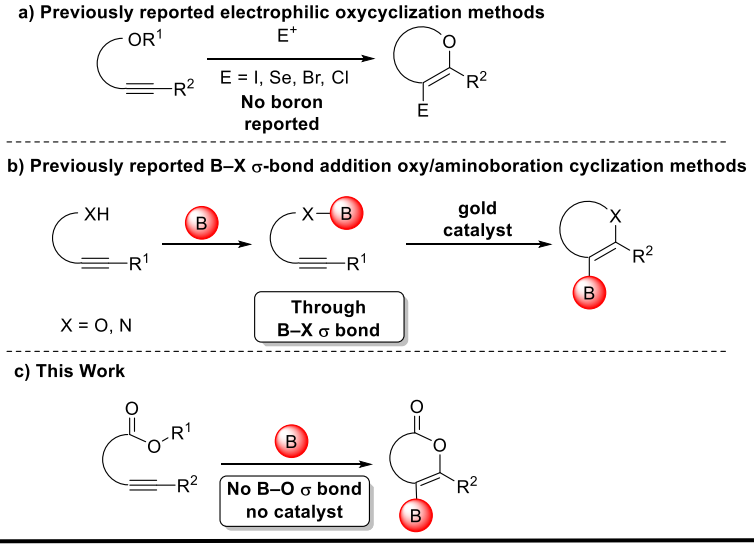
Introduction

Addition reactions of boron reagents to carbon–carbon π systems have provided powerful routes to organoboron compounds for over 65 years.[2–7] The first oxyboration reaction of carbon–carbon π systems, however, was only recently reported in 2014 through our laboratory's contribution (as described in Chapter 2),[8,9] possibly due to the high strength of B–O σ bonds (~136 kcal/mol).[10] This reaction proceeded through a B–O σ bond intermediate and required a gold catalyst. We herein report a boron reagent that promotes oxyboration of alkynes in the absence of a catalyst. This reaction does not proceed via a B–O σ bond intermediate, instead accessing an electrophilic oxycyclization/dealkylation pathway. The fact that boron is able to access an oxycyclization pathway—previously known only for other elements[11–17]—provides an

example of an important class of mechanistically distinct oxyboration reactions, which yield borylated heterocycles without the use of strongly basic reagents[18] or transition metal catalysts (Scheme 3.1).[19,20] The absence of previously reported oxyclization/dealkylation reactions with electrophilic boron may be due to competitive formation of boron–oxygen bonds, formation of which is here shown surprisingly to inhibit oxyboration rather than promote it. We herein apply this method to the synthesis of borylated isocoumarins and 2-pyrones, classes of compounds with important biological activity[21,22] but with few prior reports of their borylated analogs.[23–25] We envision that demonstration of this mechanistically distinct pathway for oxyboration will open up new pathways for the practical synthesis of borylated heterocyclic building blocks.

Primary competing strategies to synthesize borylated heterocycles include lithiation/electrophilic trapping[17] and transition metal-catalyzed borylation.[19,20,26] The few prior reports of borylated lactones employed Pd-catalyzed cross coupling[27] and lithiation/borylation.[28] The oxyboration strategy demonstrated here provides complementary functional group tolerance to these alternative borylation strategies.

Scheme 3.1. Previous work in contrast to mechanistically distinct oxyboration (this work).

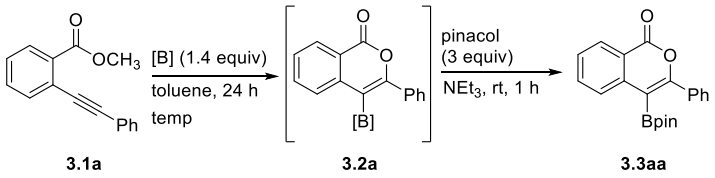


Results and Discussion

Given that boron halides are known to dealkylate esters to generate B–O σ bonds,[29,30] we anticipated that boron trihalides should promote oxyboration of **3.1a** due to previously reported carboboration and haloboration reactivity with alkynes.[31] To our surprise, both trihalogenated boron sources BBr_3 and BCl_3 (Table 3.1, entries 1 and 2, respectively) failed to yield any desired borylated isocoumarin **3.3aa**. *B*-Chlorocatecholborane (ClBcat), on the other hand, which to our knowledge has not been previously used for alkyne activation, provided the borylated isocoumarin in yields of 25% and 75% at 45 °C and 100 °C, respectively (entries 3 and 4). The use of *B*-bromocatecholborane, which is known to demethylate methyl esters more quickly than ClBcat (and thus would be expected to yield **3.2** more quickly or at the same rate),[32] provided a lower isolated yield of the desired oxyboration product (entry 5). These results provided an early indication that the operative oxyboration pathway proceeded without initial dealkylation/B–O σ-bond formation and thus may be mechanistically distinct from prior reports that proceeded through the B–O σ bond.

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

Table 3.1. Boron reagent variation.



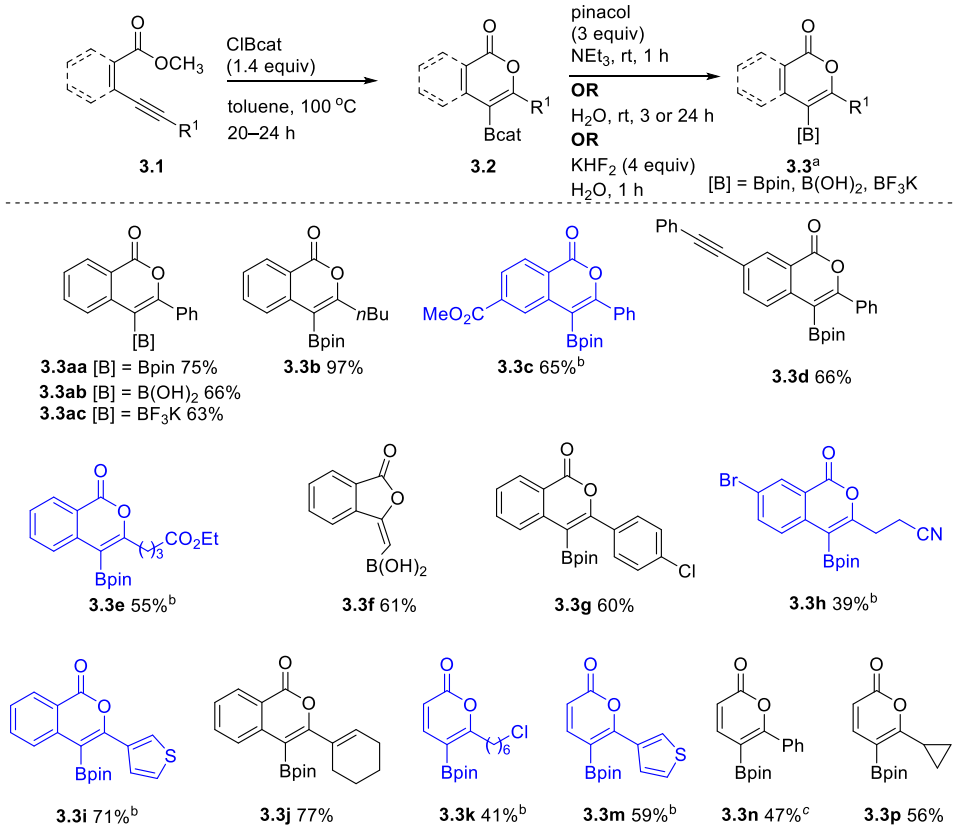
3.1a 3.2a 3.3aa

Entry	*Boron Electrophile [B]*	*Temp*	*Yield (%)[a] 3.3aa*
1	BBr_3[b]	45 °C	0
2	BCl_3[b]	45 °C	0
3	*B*-chlorocatecholborane	45 °C	25
4	*B*-chlorocatecholborane	100 °C	75
5	*B*-bromocatecholborane	100 °C	48

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

The product isolation scope and substrate scope were next investigated (Table 3.2). For synthetic variety, the products can be isolated three different ways: as the pinacolboronic ester (**3.3aa**), the boronic acid (**3.3ab**), or the potassium organotrifluoroborate salt (**3.3ac**). Each method provides complementary advantages. Pinacolboronic esters are stable toward silica gel chromatography, provided the best isolated yield for the test compound, and can be easily cross-coupled under basic conditions; it was therefore chosen as the preferred isolation method.[33] Boronic acids, although not as bench stable as the other options, are a preferred transition metal-catalyzed cross coupling partner and provide the best atom economy.[34] Potassium organotrifluoroborates, although slightly lower yielding, provide a column-free workup procedure after oxyboration, making them a practical target for large-scale synthesis.[35,36] The use of *B*-chloropinacolborane rather than ClBcat, which would provide a direct route to analogous isolable products, was avoided due to this reagent's lack of commercial availability and poor thermal stability (decomposition above –70 °C),[37] which would preclude oxyboration reactions above this temperature.

Table 3.2. Synthesis of borylated isocoumarins and 2-pyrones via the oxyboration reaction.[a,b]



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

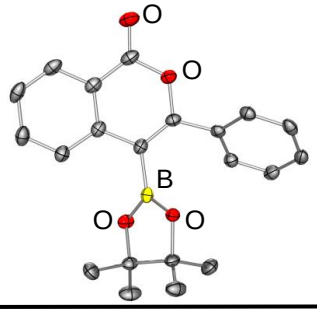
We attempted an alternative oxyboration through the corresponding carboxylic acid rather than methyl ester. An intractable product mixture was produced. The route from the methyl ester is fortunately much cleaner. The methyl esters are also bench stable and therefore a more practical synthetic precursor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

Functional groups that can be tolerated with this oxyboration strategy include esters, cyanides, aryl bromides and chlorides, and thiophenes, which are incompatible with competing lithiation/borylation routes and/or palladium catalyzed oxidative addition routes. The tolerance towards esters (**3.3c**) was particularly noteworthy given that these boron reagents are known to dealkylate esters; this tolerance was examined further in

mechanistic studies (vide infra). Similarly, the tolerance of alkynes distal to esters (**3.3d**) implies that independent reactivity of the alkyne (e.g., haloboration[6,7]) is not part of the operative pathway. An aromatic backbone was not a requirement for the oxyboration reaction. Alkenyl esters also underwent the oxyboration reaction to produce 2-pyrones **3.3k**–**3.3p**, albeit in lower yields. Because of the reactivity of *B*-chlorocatecholborane, ethers, an *O*-TBDPS protecting group, furans, and a ketone with α protons were not tolerated by the oxyboration reaction.

The oxyboration reaction could theoretically produce either the regioisomer from *5-exo-dig* or *6-endo-dig* cyclization.[38] X-ray crystallographic analysis of **3.3aa** confirmed that it was the product of *6-endo-dig* cyclization (Figure 3.1). No other regioisomer was observed in the crude ^{1}H NMR spectrum. Compound **3.3f** is the only product formed from *5-exo-dig* cyclization. Consistent with the mechanistic proposal, formation of the unobserved *6-endo-dig* product would have required disfavored build up of primary cationic character on the terminal carbon of the unsubstituted alkyne (vide infra).

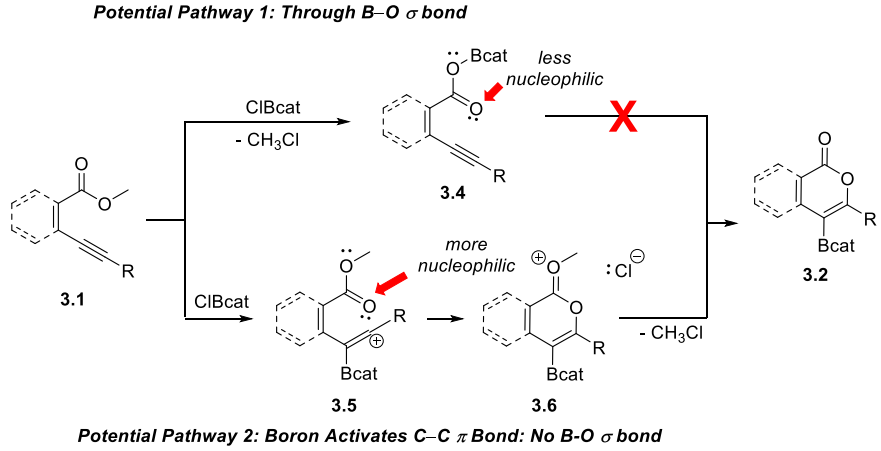
Figure 3.1. X-Ray crystallographic structure of **3.3aa** confirming 6-membered ring formation, with the thermal ellipsoids shown at 50% probability (B, yellow; C, gray; O, red). Non-carbon elements also labelled.



Mechanistic studies. Two mechanistic pathways were considered for this oxyboration reaction (Scheme 3.2). In the top pathway, dealkylation occurs first to produce intermediate **3.4**, followed by the oxyboration/cyclization with the alkyne. In the bottom pathway, however, boron-induced electrophilic cyclization, possibly through a

formal vinylic cation, **3.5**, or alternatively directly from **3.1** to **3.6**, as has been proposed for alkyne activation by BCl_3,[39,40] precedes dealkylation (bottom). Cyclized oxocarbenium ion **3.6** is then primed for rapid dealkylation due to the increased positive charge on the oxygen. The oxygen in **3.4** would be less nucleophilic toward cyclization than the oxygen in **3.5** due to donation of the electron density of the carboxy group into the empty *p* orbital on boron. This decrease in nucleophilicity may rationalize why direct dealkylation of **3.1** via the top pathway inhibits the oxyboration reaction rather than promotes it.

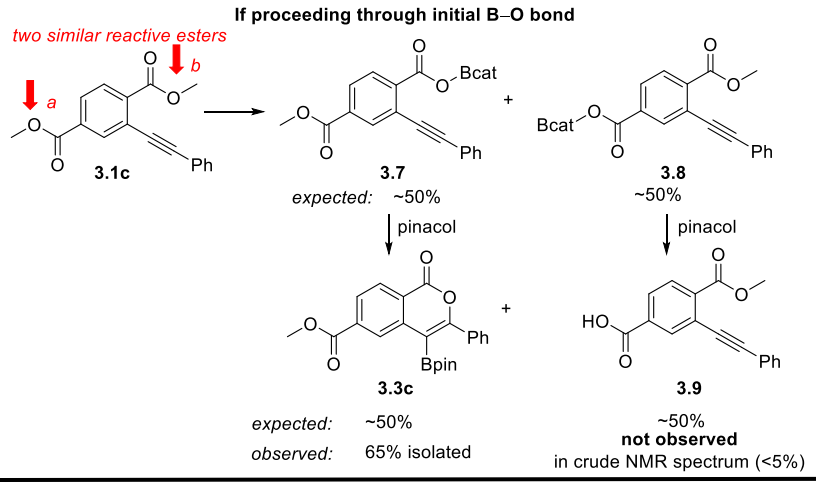
Scheme 3.2. Two proposed pathways: demethylation-cyclization through B–O bond (top) and cyclization-demethylation without B–O bond formation (bottom).



If demethylation occurred before cyclization, in the operable pathway to the oxyboration product, then the similar esters (*a* and *b*) in **3.1c** should demethylate at similar rates (Scheme 3.3). This demethylation would produce intermediates **3.7** and **3.8** in approximately equal quantities, resulting in formation of **3.3c** and **3.9**. Product **3.9** is not observed, however, in the crude reaction mixture by ^{1}H NMR spectroscopy. Product **3.3c** was isolated in 65% yield, with the majority of the mass balance being unreacted **3.1c**. Therefore, ester *b* demethylates significantly faster than ester *a*, consistent with cyclization preceding demethylation. The position of ester *a* does not permit cyclization, thus it does not have access to that pathway for demethylation. This data is inconsistent

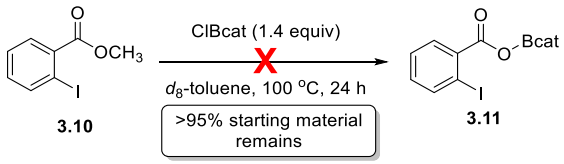
with operation of the top pathway (dealkylation-cyclization) and is consistent with the bottom pathway (cyclization-dealkylation) in the overall oxyboration reaction.

Scheme 3.3. Intramolecular competition experiment.



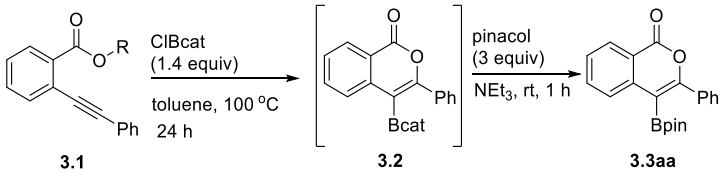
To further probe the operative mechanism, demethylation of test compound **3.10** was examined. Compound **3.10** has no alkyne; therefore, if demethylation occurs, it must proceed directly, rather than through a precyclization pathway. Under identical conditions that produced compound **3.3aa** from **3.1a** in 75% isolated yield, compound **3.10** led to no detectible decrease in starting methyl ester as determined by ^{1}H NMR spectroscopy relative to 1,3,5-triisopropylbenzene internal standard (<5%, Figure 3.2). No borenium species were detected via ^{11}B NMR spectroscopy, in contrast to the arene borylation conditions reported by Ingleson.[41] Thus, the rate of reactivity of methyl esters with ClBcat in the absence of tethered alkynes is insufficiently rapid to account for the observed oxyboration reactivity. This data further supports that cyclization precedes demethylation in the operative oxyboration reaction mechanism (Scheme 3.2, bottom).

Figure 3.2. No-alkyne control for the oxyboration reaction.



Various *O*-alkyl esters were examined with the oxyboration method (Table 3.3). The oxyboration reaction tolerated methyl, ethyl, and isopropyl groups with iterative reductions in ^{1}H NMR yields. The *t*-butyl ester, in contrast, failed to furnish any of the desired borylated isocoumarin, despite successful dealkylation, as characterized by isobutylene formation and the quantification of the benzoic acid derivative of **3.1a** in 68% ^{1}H NMR spectroscopy yield. This detection is consistent with the reported ability of ClBcat to dealkylate *t*-butyl esters at ambient temperature while ethyl esters remain unreacted.[32] This result provides further evidence that cyclization precedes dealkylation in the pathway that generates the oxyboration product, because when dealkylation occurs rapidly at ambient temperature, presumably generating B–O σ bonds, oxyboration does not occur even at elevated temperatures.

Table 3.3. Mechanistic insight from *O*-alkyl group variance of the oxyboration reaction.



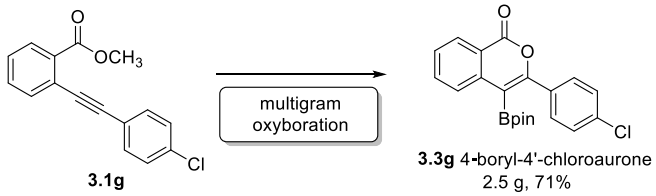
Entry	*R*	*^{1}H NMR Yield (%)[a] 3.3aa*
1	Me	81
2	Et	68
3	*i*Pr	60
4	*t*Bu	0

[a]Yield determined relative to mesitylene internal standard.

Synthetic applications. The oxyboration reaction provides scalable access to borylated building blocks of bioactive cores (Figure 3.3). Subjecting 2.5 g of methyl

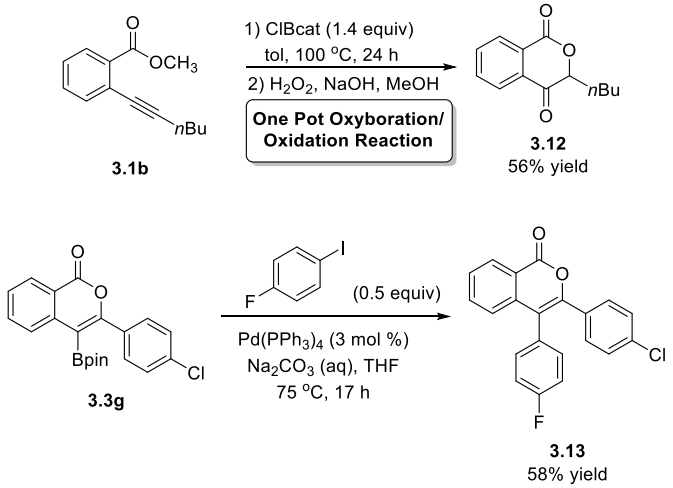
benzoate ester **3.1g** to the standard oxyboration reaction conditions yielded 2.5 g (71%) of the desired borylated isocoumarin **3.3g**. Compound **3.3g** is the 4-borylated analogue of the marine natural product chloroaurone, isolated from *Spatoglossum variabile*.[42]

Figure 3.3. Scale-up of the oxyboration reaction.



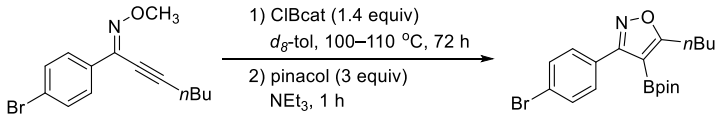
Moreover, the boron functional group provides a handle for downstream functionalization of the newly formed lactone core. One example of this utility is demonstrated in the synthesis of isochroman-1,4-diones, which are biologically relevant compounds.[43,44] The previously reported synthesis of **3.12** employed chromium trioxide and sulfuric acid.[45] Subjecting butyl alkynyl ester **3.1b** to the standard oxyboration conditions, followed by oxidative workup, furnished **3.12** in 56% yield over two steps in one pot (Scheme 3.4). The utility of these borylated isocoumarins in the construction of new C–C bonds was highlighted in a Suzuki crosss-coupling reaction of borylated lactone **3.3g** with *p*-fluoroiodobenzene to generate isocoumarin **3.13**.

Scheme 3.4. Downstream functionalization reactions of oxyboration products.



Extension of the mechanistic concept to other systems. Having established the feasibility of using an external boron electrophile to generate borylated isocoumarin products, we explored the applicability of the oxyboration strategy to synthesize borylated isoxazoles, an important pharmaceutical heterocyclic motif (Figure 3.4).[46,47] Treatment of *O*-methyl oxime **3.14** with ClBcat at 100–110 °C for 72 h furnished the desired borylated isoxazole **3.15** in 35% yield. This illustrates the potential for the mechanistic concept to be applied to other systems to generate value-added borylated heterocycles from simple alkylated heteroatoms.

Figure 3.4. Extension of the oxyboration reaction to generate borylated isoxazoles.



3.14 **3.15**
35% yield

Conclusions

In summary, a transition metal-free oxyboration reaction that adds boron and oxygen to carbon–carbon π systems is reported. It is the first formal carboxyboration—addition of the CO_2 group and boron—across alkynes. This new reactivity is enabled by dioxaborole activation of an alkyne to promote oxycyclization/dealkylation.[48] The reactivity lessons learned converge on employing electrophilic boron reagents with the right balance of carbophilicity vs. oxyphilicity, and with substrates exhibiting slow competitive dealkylation prior to cyclization. These balances enable the desired reactivity by avoiding competitive formation of the strong B–O σ bond, which prevents oxyboration reactivity under these catalyst-free conditions. These balances are conveniently achieved with commercially available ClBcat and readily available methyl ester substrates. This scalable method can tolerate a variety of functional groups that are incompatible with the

alternative strongly basic or oxidative-addition pathways that comprise other leading borylation strategies. Additional mechanistic studies and substrate class expansions are currently ongoing in our research group. We envision that this mechanistically distinct oxyborylation strategy will serve as a springboard toward broader application of catalyst-free boron–element addition reactions to generate valuable borylated heterocyclic products.

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Experimental

General Considerations

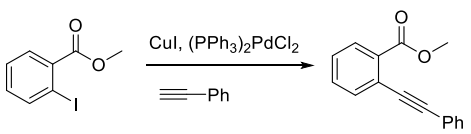
All chemicals were used as received from commercial sources unless otherwise noted. Triethylamine, acetonitrile, toluene, tetrahydrofuran, and dichloromethane were purified by passage through an alumina column under argon pressure on a push-still solvent system. d_8-Toluene was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. All manipulations were conducted 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 = 2.08 ppm for d_8-toluene, 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 for d_6-acetone, δ = 20.4 ppm for d_8-toluene, 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.

An asterisk (*) denotes work I completed towards the progress of my thesis. Sections without asterisks denote work done by graduate student Adena Issaian or undergraduate student Ashlee J. Davis.

Synthetic Procedures

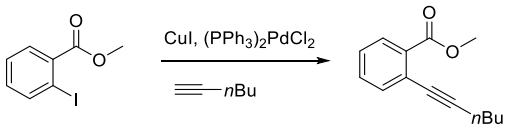
Preparation of Esters **3.1a–3.1p**



3.10 **3.1a**

***Methyl 2-(phenylethynyl)benzoate (3.1a)**. A flask was charged with compound **3.10** (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

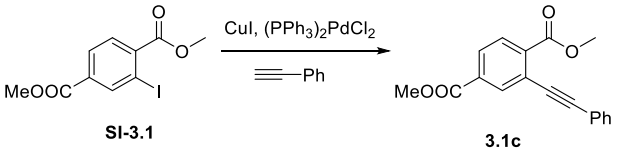
concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **3.1a** as a light yellow oil (4.2 g, 88% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.98 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.59–7.57 (m, 2H), 7.59–7.57 (m, 1H), 7.40–7.35 (m, 4H), 3.97 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]



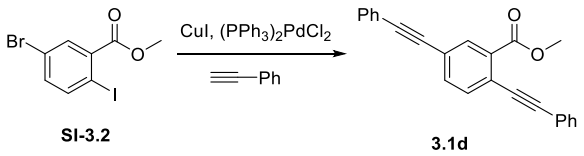
3.10 **3.1b**

***Methyl 2-(hex-1-yn-1-yl)benzoate (3.1b)**. A flask was charged with compound **3.10** (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 then 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 ca. 10 mTorr for 18 h to afford **3.1b** as a light yellow oil (0.80 g, 74% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.88 (d J = 7.9 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.41 (td, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 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* = 7.3 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[2]

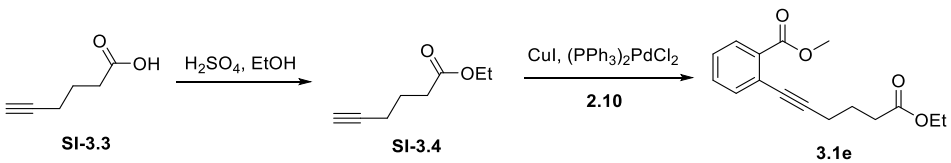


Methyl 4-acetoxy-2-(phenylethynyl)benzoate (3.1c). A flask was charged with $(PPh_3)_2PdCl_2$ (0.022 g, 0.030 mmol, 0.020 equiv), and CuI (0.011 g, 0.060 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 4 mL of Et_3N were added. The reaction mixture was then sparged for 5 minutes before compound **SI-3.1** (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 ^oC 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 ca. 10 mTorr for 18 h to afford **3.1c** as a yellow solid (0.44 g, 95% yield). ^1H 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-3.2 3.1d

Methyl 2,5-bis(phenylethynyl)benzoate (3.1d) 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 Et_3N were added. The reaction mixture was then sparged for 5 min before **SI-3.2** (2.00 g, 5.87 mmol, 1.00 equiv) was added. Phenylacetylene (0.70 mL, 6.5 mmol, 1.1 equiv) was then added via syringe, and the reaction mixture was heated to 55 ^oC 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 ca. 10 mTorr for 18 h to afford the minor product **3.1d** as a white solid (0.17 g, 11% yield). ^1H NMR ($CDCl_3$, 600 MHz): δ 8.15 (s, 1H), 7.60–7.54 (m, 6H), 7.38–7.36 (m, 6H), 4.0 (s, 3H). This spectrum is in agreement with previously reported spectral data.[3]



SI-3.3 SI-3.4 3.1e

***Ethyl hex-5-ynoate (SI-3.4)** was prepared according to a literature procedure[4] in 87% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 4.14 (q, J = 7.1 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 2.27

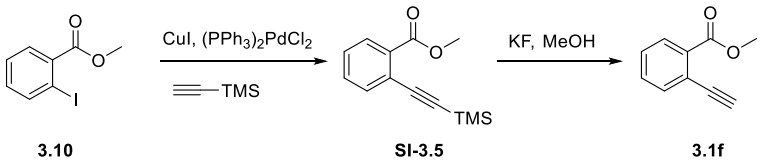
(dt, *J* = 7.0, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.85 (quin, *J* = 7.2 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[4]

***Methyl 2-(6-ethoxy-6-oxohex-1-yn-1-yl)benzoate (3.1e)**. A flask was charged with compound **3.10** (0.50 g, 1.8 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (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) were added. Compound **SI-3.4** (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 ca. 10 mTorr for 18 h to afford **3.1e** as a light yellow oil (0.42 g, 80% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 2.56–2.52 (m, 4H), 1.95 (quin, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.1 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, 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.

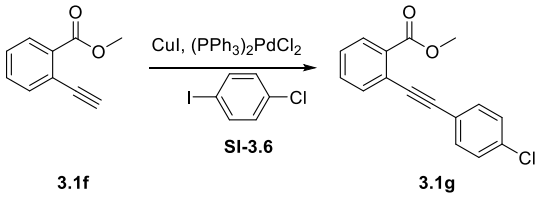


3.10 **SI-3.5** **3.1f**

Methyl 2-((trimethylsilyl)ethynyl)benzoate (SI-3.5). A flask was charged with compound **3.10** (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. Trimethylsilyl 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 ca. 10 mTorr for 18 h to afford **SI-3.5** 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]

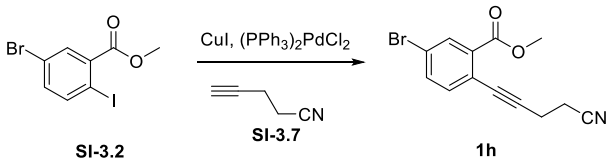
Methyl 2-ethynylbenzoate (3.1f). A flask was charged with compound **SI-3.5** (2.9 g, 13 mmol, 1.0 equiv), 63 mL methanol, and potassium fluoride (2.6 g, 44 mmol, 3.5 equiv). The flask was then sealed with a ground glass stopper and heated to 40 ^{o}C while stirring

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 ^oC [warning: product is volatile], yielding **3.1f** as a dark yellow/red liquid (1.7 g, 84% yield). ^1H NMR ($CDCl_3$, 600 MHz): δ 7.94 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 3.93 (s, 3H), 3.40 (s, 1H). This spectrum is in agreement with previously reported spectral data.[6]



***Methyl 2-((4-chlorophenyl)ethynyl)benzoate (3.1g)**. A flask was charged with compound **SI-3.6** (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) were added. Compound **3.1f** (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 ca. 10 mTorr for 18 h to afford **3.1g** as a light yellow liquid that solidified upon standing at room temperature (0.34 g, 84% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): 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.[7]



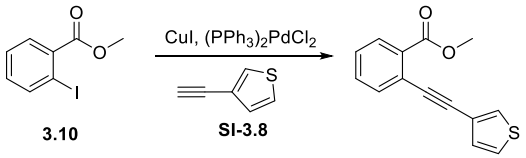
SI-3.2 **SI-3.7** **1h**

***Methyl 5-bromo-2-(4-cyanobut-1-yn-1-yl)benzoate (3.1h)**. A flask was charged with compound **SI-3.2** (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. Compound **SI-3.7** (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 ca. 10 mTorr for 18 h to afford **3.1h** 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, 133.41, 133.38, 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.



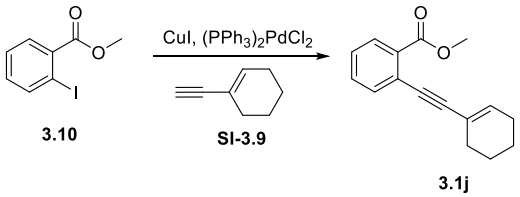
3.10 **SI-3.8** **3.1i**

Methyl 2-(thiophen-3-ylethynyl)benzoate (3.1i). A flask was charged with compound **3.10** (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) were added. Compound **SI-3.8** (0.17 mL, 1.7 mmol, 1.1 equiv) was then syringed into the reaction mixture, which was then 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 ca. 10 mTorr for 18 h to afford **3.1i** as a light yellow solid (0.37 g, 78% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.58–7.56 (m, 1H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.23 (app. d, *J* = 5.0 Hz, 1H), 3.93 (s, 3H).

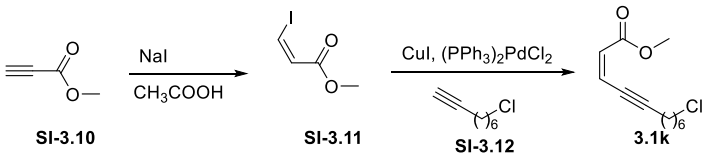
^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.7, 134.0, 131.8, 131.7, 130.5, 130.0, 129.2, 127.9, 125.5, 123.8, 122.5, 89.7, 87.9, 52.2.

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



Methyl 2-(cyclohex-1-en-1-ylethynyl)benzoate (3.1j). A flask was charged with compound **3.10** (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) were added. Compound **SI-3.9** (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 ca. 10 mTorr for 18 h to afford **3.1j** as a 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]



Methyl (Z)-3-iodoacrylate (SI-3.11) was prepared according to a literature procedure[9] in 75% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47 (d, *J* = 8.9 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H). This spectrum is in agreement with previously reported spectral data.[9]

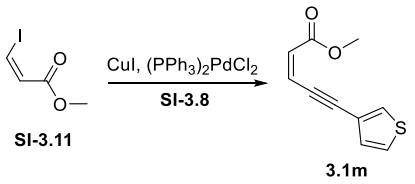
Methyl (Z)-11-chloroundec-2-en-4-ynoate (3.1k). This procedure was performed in a N_2-filled glove box. A 20 mL vial was charged with compound **SI-3.11** (0.42 g, 2.0 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.105 mg, 0.150 mmol, 0.0750 equiv), CuI (0.014 g, 0.074 mmol, 0.037 equiv), and a stir bar. 5 mL of Et_3N were added. Compound **SI-3.12** (0.37 mL, 2.4 mmol, 1.2 equiv) was then syringed into the reaction mixture, which was then heated to 50 ^{o}C and stirred for 18 h. At this time, analysis by TLC (10% 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 10%

EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **3.1k** as a viscous yellow oil (0.19 g, 41% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.15 (dt, *J* = 11.3, 2.3, 2.3 Hz, 1H), 6.05 (d, *J* = 11.4 Hz, 1H), 3.75 (s, 3H), 3.55 (t, *J* = 6.7, 2H), 2.47 (td, *J* = 7.0, 7.0, 2.1 Hz, 2H), 1.80 (t, *J* = 6.8 Hz, 2H), 1.61 (m, 2H), 1.47 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.4, 127.2, 124.4, 104.2, 77.9, 51.5, 45.2, 32.6, 28.3, 28.2, 26.5, 20.1.

HRMS (CI+): Calculated for $C_{12}H_{18}ClO_2$ ($[M+H]^+$), 229.0995; found 229.0990.



SI-3.11 3.1m

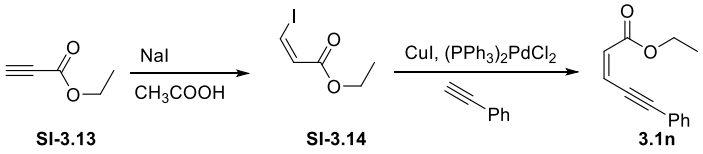
***Methyl (Z)-5-(thiophen-3-yl)pent-2-en-4-ynoate (3.1m)**. A flask was charged with compound **SI-3.11** (0.500 g, 2.35 mmol, 1.00 equiv), $(PPh_3)_2PdCl_2$ (0.124 mg, 0.176 mmol, 0.0750 equiv), CuI (0.017 g, 0.087 mmol, 0.037 equiv), and a stir bar. The flask was then evacuated and refilled with N_2 three times before 5.3 mL of Et_3N was added. Compound **SI-3.8** (0.28 mL, 2.8 mmol, 1.2 equiv) was then syringed into the reaction mixture, which was then heated to 50 ^{o}C and stirred for 18 h. 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 ca. 10 mTorr for 18 h to afford **3.1m** as a viscous light yellow oil (0.22 g, 48% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.59 (d, J = 2.9 Hz, 1H), 7.28 (dd, J = 4.9, 3.1 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 6.34 (d, J = 11.5 Hz, 1H), 6.12 (d, J = 11.5 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.3, 130.7, 130.0, 127.5, 125.7, 123.3, 121.8, 96.8, 86.3, 51.6.

HRMS (CI+): Calculated for $C_{10}H_8SO_2$ ($[M]^+$), 192.0245; found 192.0240.

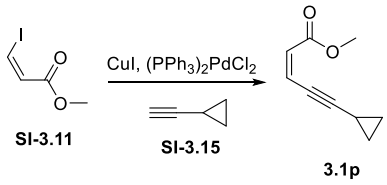


SI-3.13 SI-3.14 3.1n

***Ethyl (Z)-3-iodoacrylate (SI-3.14)** was prepared according to a literature procedure[10] 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.[10]

Ethyl (Z)-5-phenylpent-2-en-4-ynoate (3.1n). A flask was charged with compound **SI-3.14** (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 ca. 10 mTorr for 18 h to afford **3.1n** 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-3.11 SI-3.15 3.1p

***Methyl (Z)-5-cyclopropylpent-2-en-4-ynoate (3.1p)**. This procedure was performed in a N_2-filled glove box. A 20 mL vial was charged with compound **SI-3.11** (0.424 g, 2.00 mmol, 1.00 equiv), $(PPh_3)_2PdCl_2$ (0.112 g, 0.160 mmol, 0.0750 equiv), CuI (0.015 g, 0.080 mmol, 0.037 equiv), and a stir bar. 5 mL of Et_3N was added. Compound **SI-3.15** (0.20 mL, 2.4 mmol, 1.2 equiv) was then syringed into the reaction mixture, which was then heated

to 50 °C and stirred for 18 h. 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 [NOTE: product may be volatile] to afford 115 mg of **3.1p** as a yellow liquid in ~91% purity.

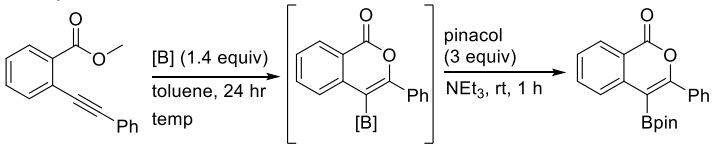
^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.11 (dd, J = 11.4, 2.4 Hz, 1H), 6.01 (d, J = 11.3 Hz, 1H), 3.74 (s, 3H), 1.49 (ddt, 7.9, 5.3, 2.8, 2.8 Hz, 1H), 0.93–0.91 (m, 2H), 0.87–0.85 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.5, 126.7, 124.5, 108.3, 73.6, 51.5, 9.7, 1.1.

HRMS (CI+): Calculated for $C_9H_{10}O_2$ ($[M]^+$), 150.0681; found 150.0677.

*****<u>Boron Electrophile Screen</u>

Table SI-3.1. Boron electrophile screen.



3.1a **3.2a** **3.3aa**

Entry	*Boron Electrophile [B]*	*Temp*	*Yield (%) 3.3aa*
1	BBr_3	45 °C	0
2	BCl_3	45 °C	0
3	*B*-Chlorocatecholborane	45 °C	25
4	*B*-Chlorocatecholborane	100 °C	75
5	*B*-Bromocatecholborane	100°C	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 **3.1a** (0.118 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. 0.6 mL (1.2 equiv) of a 1 M solution of either BBr_3 or BCl_3 was then added to the vial, and the vial was sealed and heated to 45 ^oC 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, 3.0 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 then stirred for 1 h at room temperature. The solution was then concentrated in vacuo. Analysis of the resulting residue via ^1H NMR spectroscopy ($CDCl_3$, 600 MHz) and ^{11}B NMR Spectroscopy ($CDCl_3$, 126 MHz) confirmed that the desired product **3.3aa** was not produced.

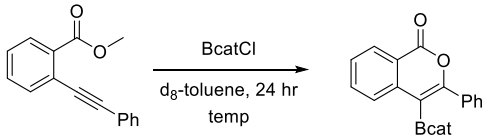
General Procedure: Entries 3–5

This screen was carried out in a nitrogen-filled glove box. A 4 mL vial was charged with **3.1a** (0.118 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. In a separate vial, *B*-chlorocatecholborane (0.70 mmol, 1.4 equiv) or *B*-bromocatecholborane (0.70 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, 3.0 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 then stirred for 1 h at room temperature. The solution was then 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 ca. 10 mTorr for 18 h to afford **3.3aa** as a light yellow oil, which solidified upon standing. The ^{1}H NMR spectrum for each entry was then compared to the authentic sample to establish identity.

*****Reaction Condition Optimization

Table SI-3.2. Optimization of the oxyboration reaction.



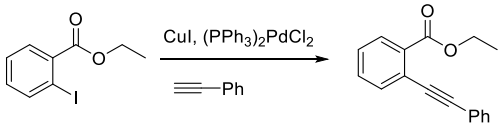
3.1a **3.2a**

Entry	*Equivalents of BcatCl*	*Temp*	*3.2a:3.1a*
1	1.0 equiv	100 °C	76:24
2	1.2 equiv	100 °C	81:19
3	1.3 equiv	100 °C	87:13
4	1.4 equiv	100 °C	95:5
5	1.4 equiv	75 °C	86:14
6	1.4 equiv	45 °C	40:60

Reaction condition screening reactions were set up in a N_2-filled glovebox. Compound **3.1a** (118 mg, 0.500 mmol, 1.00 equiv) was dissolved in d_8-toluene (0.50 mL) and added to a dram vial containing *B*-chlorocatecholborane in the below amounts (1.00–1.40 equiv). After mixing thoroughly, the reaction mixture was transferred to a J. Young NMR tube, removed from the glovebox, and heated in a preheated oil bath for 24 h. The progress of the reaction was then monitored by ^{1}H and ^{11}B NMR spectroscopy, with characteristic product (**3.2a**) peaks at δ = 8.26 ppm in the ^{1}H NMR spectrum, and δ ~ 32.1 ppm in the ^{11}B NMR spectrum in d_8-toluene.

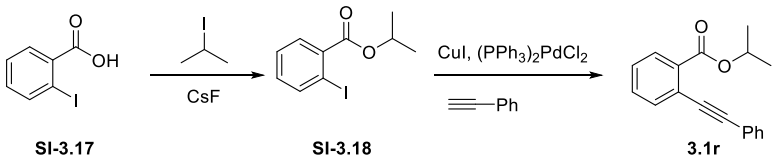
Note: the optimized concentration was found to be 1.0 M; when higher concentrations were tested, solubility issues were encountered.

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



SI-3.16 **3.1q**

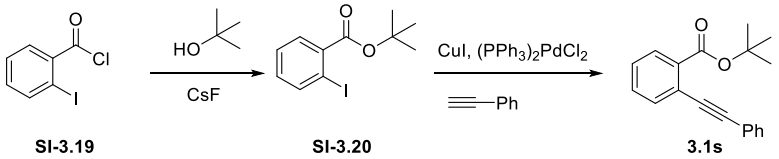
Ethyl 2-(phenylethynyl)benzoate (3.1q). A flask was charged with compound **SI-3.16** (0.96 g, 3.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (0.049 g, 0.070 mmol, 0.020 equiv), and CuI (0.027 g, 0.14 mmol, 0.040 equiv). The flask was then evacuated and refilled with N_2 three times before 7 mL of acetonitrile and Et_3N (3.8 mL, 28 mmol, 8.0 equiv) were 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 ca. 10 mTorr for 18 h to afford **3.1q** 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.[12]



Isopropyl 2-iodobenzoate (SI-3.18) was prepared according to a literature procedure[13] 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.[13]

Isopropyl 2-(phenylethynyl)benzoate (3.1r). A flask was charged with compound **SI-3.18** (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) were 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 ca. 10 mTorr for 18 h to afford **1r** 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.[14]



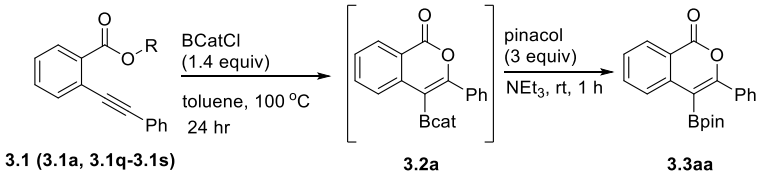
SI-3.19 **SI-3.20** **3.1s**

***tert*-Butyl 2-iodobenzoate (SI-3.20)** was prepared according to a literature procedure[13] 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, 9H). This spectrum is in agreement with previously reported spectral data.[13]

***tert*-Butyl 2-(phenylethynyl)benzoate (3.1s)**. A flask was charged with compound **SI-3.20** (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) were 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 ca. 10 mTorr for 18 h to afford **3.1s** 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]

Table SI-3.3. Mechanistic insight from *O*-alkyl group variance of the oxyboration reaction.



3.1 (3.1a, 3.1q-3.1s) **3.2a** **3.3aa**

Entry	***R***	***^{1}H NMR Yield (%) 3.3aa***
1	Me	81
2	Et	68
3	iPr	60
4	tBu	0

General Procedure for Investigating Effect of R Group on Dealkylation

This procedure was carried out in a nitrogen-filled glove box. A 4 mL vial was charged with the desired *O*-alkyl ester (**3.1a**, **3.1q**–**3.1s**) (0.50 mmol, 1.0 equiv) and 0.5 mL toluene. In a separate vial, *B*-chlorocatecholborane (0.70 mmol, 1.4 equiv) was added. The solution in the initial reaction vial was then transferred to the boron-containing vial via pipette, and this vial was sealed and heated to 100 °C for 24 h. At this time, the reaction mixture was cooled to room temperature. In a separate vial, pinacol (0.18 g, 1.5 mmol, 3.0 equiv) was dissolved in Et_3N (1.0 mL, 7.5 mmol, 15 equiv). This solution was then added to the reaction mixture via pipette. The resulting solution was then stirred for

1 h at room temperature and then concentrated in vacuo. An ^{1}H NMR spectrum was then taken of each crude mixture in $CDCl_3$; mesitylene (50. μL, 0.36 mmol, 0.72 equiv) was added to the sample via gas tight syringe to determine the yield of the desired borylated isocoumarin **3.3aa**. In entry 4 (R = *t*Bu), the mesitylene was compared to characteristic peaks of the benzoic acid derivative of **3.1a** from an authentic sample synthesized using a known procedure.[15]

*****Procedure to Monitor the Formation of Isobutylene from Entry 4

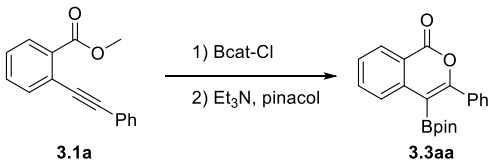
A 4 mL vial was charged with compound **3.1s** (0.10 g, 0.37 mmol, 1.0 equiv), 1,3,5-triisopropylbenzene (30 μL, 0.12 mmol, 0.24 equiv), and 0.4 mL d_8-toluene. In a separate vial, *B*-chlorocatecholborane (0.080 g, 0.52 mmol, 1.4 equiv) was added. The solution in the initial reaction vial was then transferred to the boron-containing vial via pipette, and then this mixture was transferred to a J. Young tube via pipette. The tube was heated to 100 ^{o}C. ^{1}H NMR spectra were taken at *t* = 3 h and 24 h to monitor isobutylene formation, as well as to confirm that catecholboronic ester **3.2s** did not form.

Synthesis and Isolation of Carboxyboration Products **3.3aa–3.3p**

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. The ipso C–B bond is not detected by ^{13}C NMR spectroscopy.



3.1a **3.3aa**

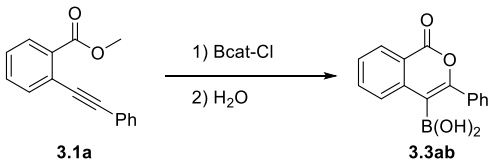
***3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3.3aa).** A vial was charged with **3.1a** (0.118 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 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 dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **3.3aa** as a yellow oil (0.13 g, 75% yield).

^{1}H NMR (d_8-toluene, 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 (d_8-toluene, 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 (d_8-toluene, 193 MHz): δ 31.5.

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



3.1a **3.3ab**

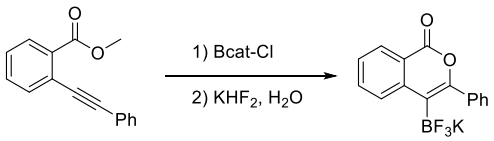
(1-oxo-3-phenyl-1*H*-isochromen-4-yl)Boronic acid (3.3ab). A vial was charged with **3.1a** (0.118 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 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 was 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 ca. 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, 129.1, 128.7, 128.2, 127.5, 127.0, 121.0.

^{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.



3.1a **3.3ac**

***3-Phenyl-4-(trifluoro-λ^4-boranyl)-1*H*-isochromen-1-one, potassium salt (3.3ac).** A vial was charged with **3.1a** (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 dropwise over ca. 2 min to the boron-containing vial, which stirred for 24 h at 100 ^{o}C. At this time, the reaction mixture was cooled to room temperature and then concentrated in vacuo. The residue was then dissolved in 1 mL of acetone and then transferred via pipette to another flask containing a solution of KHF_2 (0.137g, 1.80 mmol, 3.50 equiv) in 1.5 mL of H_2O. The resulting mixture was stirred for 1 h then concentrated in vacuo at ca. 10 mTorr for 1 h. The product was then filtered through a medium porosity fritted funnel. The solid was then rinsed with cold (~0 ^{o}C) water (3 × 3 mL) and ether (3 x 3 mL). The solid was dried in vacuo ca. 10 mTorr for 18 h to afford **3.3ac** as a white solid (0.103 g, 63% yield).

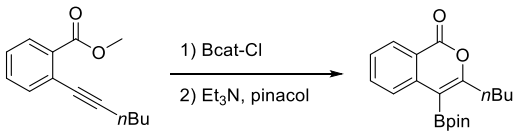
^{1}H NMR ((CD$_3$)$_2$CO, 600 MHz): δ 8.37 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 6.4 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.31–7.30 (m, 3H).

^{13}C NMR ((CD$_3$)$_2$CO, 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$_3$)$_2$CO, 193 MHz): δ 2.9.

^{19}F NMR ((CD$_3$)$_2$CO, 376 MHz): δ -131.6.

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



3.1b **3.3b**

3-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3.3b). A vial was charged with **3.1b** (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 dropwise over ca. 2 min to the boron-containing vial, which stirred for 24 h at 100 ^{o}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$_3$N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was

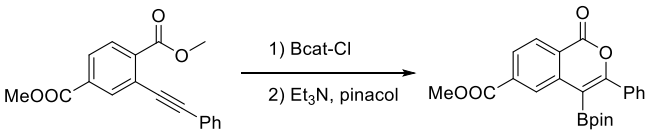
purified by column chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **3.3b** as a yellow oil (0.16 g, 97% yield).

^{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.



3.1c **3.3c**

***Methyl 1-oxo-3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromene-6-carboxylate (3.3c)**. A vial was charged with **3.1c** (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 dropwise over ca. 2 min to the boron-containing vial, which stirred for 24 h at 100 ^{o}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

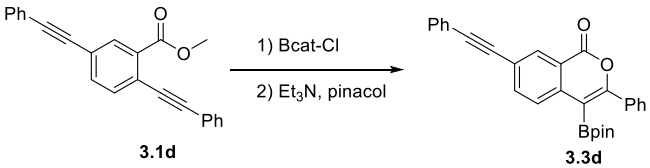
pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified by column 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 ca. 10 mTorr for 18 h to afford **3.3c** 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.



3.1d 3.3d

3-phenyl-7-(phenylethynyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3.3d). A vial was charged with **3.1d** (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 dropwise over ca. 2 min to the boron-containing

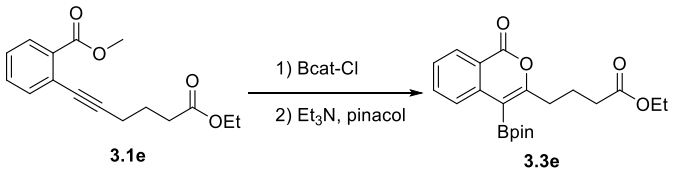
vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with pinacol (0.177 g, 1.50 mmol, 3.00 equiv) and Et_3N (1.0 mL, 7.5 mmol, 15 equiv). The reaction mixture was added dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **3.3d** 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.



3.1e 3.3e

Ethyl 4-(1-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-3-yl)butanoate (3.3e). A vial was charged with **3.1e** (0.064 g, 0.23 mmol, 1.0 equiv) and

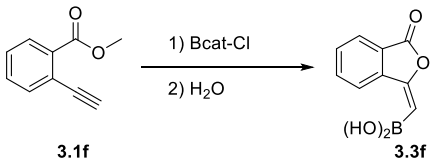
0.23 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.050 g, 0.33 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 2 min to the boron-containing vial, which stirred for 24 h at 100 °C. At this time, 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 (0.50 mL, 3.8 mmol, 15 equiv). The reaction mixture was added dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **3.3e** 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.



3.1f 3.3f

***(E)-((3-oxoisobenzofuran-1(3H)-ylidene)methyl)boronic acid (3.3f)**. A vial was charged with **3.1f** (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 dropwise over ca. 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 then dried in vacuo ca. 10 mTorr for 18 h to afford **3.3f** as a white 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).

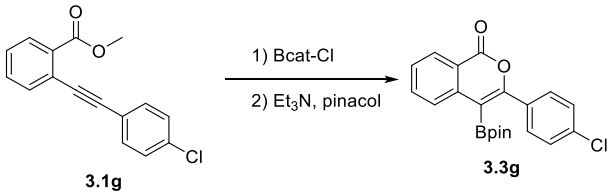
^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 157.2, 139.3, 135.6, 131.8, 127.5, 125.99, 125.4, 118.3.

^{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.

HMQC was used to confirm the formation of the 5-*exo-dig* product. Because ipso B–C resonances are not detected in ^{13}C NMR, the resonance at δ = 5.48 ppm in the HMQC

must be attached to an ipso B–C bond because no ^{13}C NMR signal correlates. 1D ^{1}H NOE confirmed the stereochemistry of **3.3f**.



3.1g **3.3g**

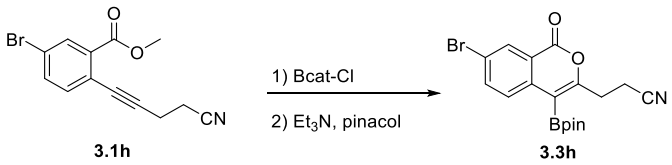
***3-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3.3g)**. A vial was charged with **3.1g** (0.135 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 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 dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **3.3g** 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.



3.1h **3.3h**

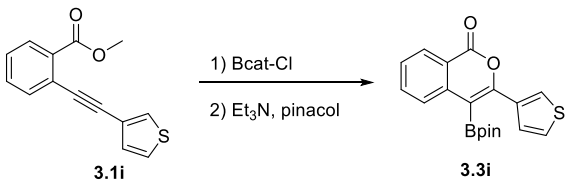
***3-(7-bromo-1-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-3-yl)propanenitrile (3.3h)**. A vial was charged with **3.1h** (0.146 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 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 dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was 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 ca. 10 mTorr for 18 h to afford **3.3h** 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.



3.1i **3.3i**

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(thiophen-3-yl)-1H-isochromen-1-one (3.3i). A vial was charged with **3.1i** (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 dropwise over ca. 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 dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and

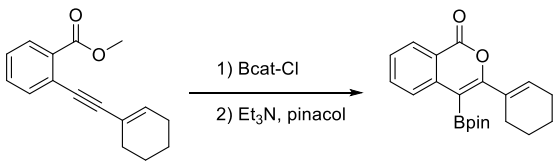
concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **3.3i** as a white solid (0.13 g, 71% yield).

^{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.



3.1j **3.3j**

3-(cyclohex-1-en-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-isochromen-1-one (3.3j). A vial was charged with **3.1j** (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 dropwise over ca. 2 min to the boron-containing vial, which stirred for 24 h at 100 ^{o}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 dropwise over ca. 2 min to this vial, and the resulting mixture

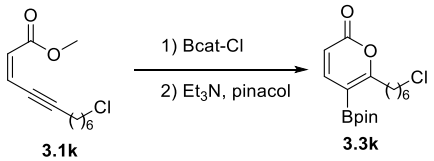
stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified by column chromatography using an elution gradient from 100% hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **3.3j** 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.



3.1k **3.3k**

6-(6-chlorohexyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-pyran-2-one (3.3k). A vial was charged with **3.1k** (0.179 g, 0.780 mmol, 1.00 equiv) and 0.8 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.170 g, 1.10 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 2 min to the boron-containing

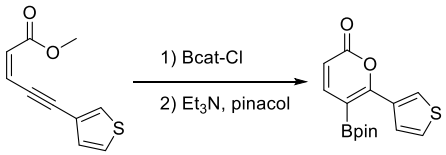
vial, which stirred for 24 h at 100 °C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.8 mL toluene. A separate vial was then charged with pinacol (0.272 g, 2.30 mmol, 3.00 equiv) and Et_3N (1.6 mL, 12 mmol, 15 equiv). This mixture was added to the reaction mixture dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **3.3k** as a yellow oil that solidified upon standing (0.11 g, 41% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.51 (d, *J* = 9.4 Hz, 1H), 6.07 (d, *J* = 9.4 Hz, 1H), 3.48 (t, *J* = 6.7 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 1.72 (m, 2H), 1.64 (quin, *J* = 7.6, 2H), 1.42 (t, *J* = 7.8 Hz, 2H), 1.32 (quin, *J* = 7.5 Hz, 2H), 1.26 (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 30.2.

HRMS (ESI+): Calculated for $C_{17}H_{26}ClBO_4$ ([M]$^+$), 340.1616; found 340.1609.



3.1m **3.3m**

5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(thiophen-3-yl)-2H-pyran-2-one (3.3m). A vial was charged with **3.1m** (0.096 g, 0.50 mmol, 1.0 equiv) and 0.5 mL toluene.

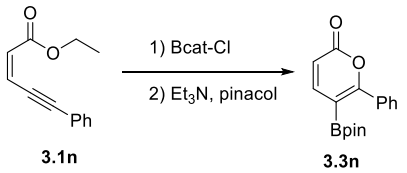
A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.500 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 2 min to the boron-containing vial, which stirred for 21 h at 100 ^{o}C. At this time, the reaction 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). This mixture was added to the reaction mixture dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **3.3m** as a yellow oil that solidified upon standing (0.090 g, 59% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.07 (d, *J* = 2.1 Hz, 1H), 7.66 (d, *J* = 9.4 Hz, 1H), 7.56 (d, *J* = 5.0 Hz, 1H), 7.28 (dd, *J* = 5.1, 3.0 Hz, 1H), 6.20 (d, *J* = 9.4 Hz, 1H), 1.29 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.1, 161.7, 149.6, 134.6, 129.6, 128.1, 125.1, 112.6, 84.6, 24.8.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 30.3.

HRMS (ESI+): Calculated for $C_{15}H_{17}BO_4SNa$ ($[M+Na]^+$), 327.0841; found 327.0834.



3.1n **3.3n**

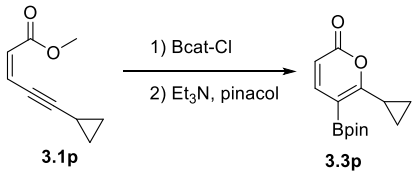
***6-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-pyran-2-one (3.3n)**. A vial was charged with **3.1n** (0.070 g, 0.35 mmol, 1.0 equiv) and 0.4 mL of toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.075 g, 0.49 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 2 min to the boron-containing vial, which stirred for 24 h at 100 ^{o}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 dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was 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 ca. 10 mTorr for 18 h to afford **3.3n** 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.



3.1p 3.3p

6-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-pyran-2-one (3.3p). A vial was charged with **3.1p** (0.100 g, 0.670 mmol, 1.00 equiv) and 0.7 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.144 g, 0.930 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 2 min to the boron-containing vial, which stirred for 24 h at 100 ^{o}C. At this time, the reaction mixture was cooled to room temperature and then diluted with 0.7 mL toluene. A separate vial was then charged with pinacol (0.237 g, 2.01 mmol, 3.00 equiv) and Et_3N (1.4 mL, 10. mmol, 15 equiv). This mixture was added to the reaction mixture dropwise over ca. 2 min to this vial, and the resulting mixture stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **3.3p** as a yellow solid (0.098 g, 56% yield).

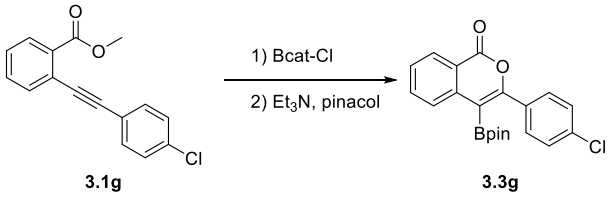
^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.52 (d, J = 9.2 Hz, 1H), 6.00 (d, J = 9.4 Hz, 1H), 2.74–2.71 (m, 1H), 1.28 (s, 12H), 1.22–1.20 (m, 2H), 1.00–0.99 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.3, 162.1, 149.3, 110.4, 84.1, 24.9, 13.9, 10.2.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 30.9.

HRMS (CI) Calculated for $C_{14}H_{19}BO_4$ ([M]$^+$), 262.1379; found 262.1368.

Multigram Scale Preparation of **3.3g*

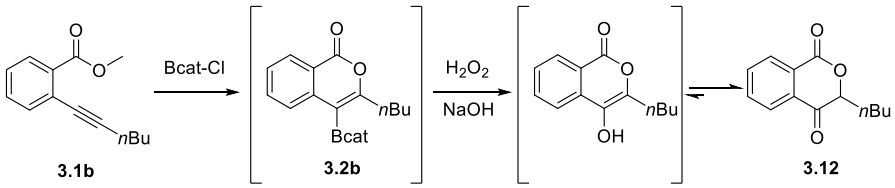


3.1g **3.3g**

In a nitrogen-filled glove box, a Schlenk bomb was charged with a solution of **3.1g** (2.50 g, 9.23 mmol, 1.00 equiv) in 4.6 mL toluene via pipette. A solution of *B*-chlorocatecholborane (1.99 g, 12.9 mmol, 1.40 equiv) in 4.6 mL toluene was then added via pipette. The Schlenk bomb was then sealed, brought outside of the glove box, and cooled to -78 ^{o}C using an isopropanol/dry ice bath. The headspace in the Schlenk bomb was then removed under reduced pressure (ca. 10 mTorr for 10 sec) before resealing. The solution was then stirred under static vacuum for 24 h at 100 ^{o}C in an oil bath. At this time, the reaction mixture was cooled to room temperature and returned to the glove box. A solution of pinacol (3.27 g, 27.7 mmol, 3.00 equiv) and Et_3N (19.2 mL, 139 mmol, 15.0 equiv) was then added to the reaction mixture over 5 min and the resulting solution was stirred for 1.5 h at room temperature. The contents of the Schlenk bomb were then filtered over a bed of celite and rinsed with toluene (3 × 20 mL), and the filtrate was concentrated in vacuo. The resulting 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 ca. 10 mTorr for 18 h to afford **3.3g** as an off-white solid (2.5 g, 71% yield). Spectral data were identical to those previously obtained for this compound.

Synthesis of **3.12*



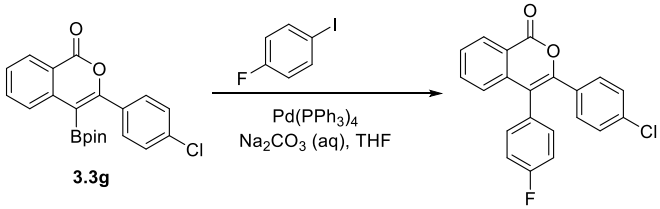
3-butylisochromane-1,4-dione (3.12). The initial oxyboration step was performed in a N_2-filled glove box. A vial was charged with **3.1b** (0.108 g, 0.500 mmol, 1.00 equiv) and 0.5 mL toluene. A separate vial equipped with a stir bar was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 2 min to the boron-containing vial, which stirred for 24 h at 100 ^oC. The reaction mixture was then cooled to room temperature and taken out of the glovebox before 1 mL of methanol, NaOH (0.30 mL of a 3.0 M solution, 0.80 mmol, 1.6 equiv) and H_2O_2 (82 μL of a 30 wt% solution, 0.80 mmol, 1.6 equiv) were added. The reaction mixture was stirred for 2 h, then diluted with 100 mL EtOAc and washed with NH_4Cl (1 × 20 mL), water (1 × 20 mL), brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography using an elution gradient from 100% hexanes to 30% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **3.12** as a yellow oil. (0.12 g, 56% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.27 (m, 1H), 8.06 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.87–7.81 (m, 2H), 5.09 (dd, *J* = 7.5. 4.7 Hz, 1H), 2.06–1.99 (m, 2H), 1.49–1.44 (m, 2H), 1.39–1.30 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.7, 162.0, 135.7, 134.7, 131.6, 130.7, 128.3, 126.0, 84.6, 33.8, 26.7, 22.4, 13.9.

HRMS (ESI+): Calculated for $C_{13}H_{18}NO_3$ ($[M+NH_4]^+$), 236.1287; found 236.1281.

*****<u>Suzuki Cross-Coupling of **3.3g** to Generate **3.13**</u>



3-(4-chlorophenyl)-4-(4-fluorophenyl)-1H-isochromen-1-one (3.13). This procedure was performed in a N_2-filled glove box. A 20 mL vial was charged with $Pd(PPh_3)_4$ (21 mg, 0.020 mmol, 0.030 equiv), THF (4.0 mL), 4-fluoroiodobenzene (69 μL, 0.60 mmol, 1.0 equiv), **3.3g** (0.229 g, 0.599 mmol, 2.00 equiv), sodium carbonate (1.2 mL of a 2.0 M aqueous solution, 2.3 mmol), and a stir bar. The vial was then quickly sealed and brought out of the glove box. The vial was then heated to 75 °C for 17 h. At this time, TLC (80:20 hex:EtOAc) indicated complete consumption of starting material. The reaction mixture was cooled to room temperature, then diluted with 100 mL EtOAc and washed with water (2 × 20 mL), brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography using an elution gradient from 100%

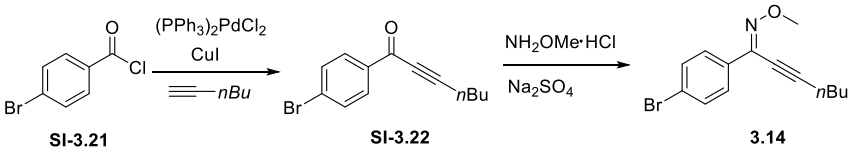
hexanes to 20% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **3.13** as a yellow solid (0.12 g, 58% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.43 (d, J = 7.8 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.29–7.16 (m, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.7, 162.0, 161.8, 150.2, 138.6, 135.3, 135.0, 133.0, 132.97, 130.6, 129.9, 128.6, 128.4, 125.3, 120.6, 116.7, 116.5.

HRMS (ESI+): Calculated for $C_{21}H_{12}ClFO_2Na$ ([M+Na]$^+$), 373.0407; found 373.0414.

*****<u>Synthesis of Borylated Isoxazole Product **3.15**</u>



1-(4-bromophenyl)hept-2-yn-1-one (SI-3.22) was prepared according to a literature procedure[16] in 86% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.99 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 2.50 (t, J = 7.1 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H), 1.50 (sxt, J = 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[17]

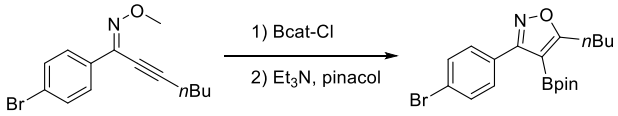
(Z)-1-(4-bromophenyl)hept-2-yn-1-one *O*-methyl oxime (3.14) was prepared according to a modified literature procedure.[18] A round-bottom flask was charged with

$H_2NOMe \cdot HCl$ (0.38 g, 4.5 mmol, 2.0 equiv), Na_2SO_4 (0.64 g, 4.5 mmol, 2.0 equiv), and a stir bar. The solids were suspended in 8 mL of MeOH. Pyridine (0.68 mL, 8.4 mmol, 3.7 equiv) and then ketone **SI-3.22** (0.60 g, 2.3 mmol, 1.0 equiv) were consecutively added. The reaction was stirred at 25 °C for 23 h without special precautions for oxygen or moisture. The reaction was then quenched with 30 mL DI water and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography using an elution gradient from 100% hexanes to 40% DCM/hexanes. Product-containing fractions were combined and concentrated in vacuo to afford **3.14** as light yellow oil (0.27 g, 41% isolated yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.70 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 4.07 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 1.65 (quin, J = 7.3 Hz, 2H), 1.51–1.47 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.4, 133.0, 131.6, 128.1, 123.9, 104.6, 71.2, 63.2, 30.5, 22.2, 19.6, 13.7.

HRMS (ESI+): Calculated for $C_{14}H_{17}NBrO$ ($[M+H]^+$), 294.0493; found 294.0493.



3.14 **3.15**

3-(4-bromophenyl)-5-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (3.15). A vial was charged with **3.14** (0.147 g, 0.500 mmol, 1.00 equiv) and 0.5 mL

d_8-toluene [Note: the deuterated toluene was used to monitor this unoptimized reaction by ^{1}H and ^{11}B NMR spectroscopy]. A separate vial 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 dropwise over ca. 2 min to the boron-containing vial, which was then transferred to a J-Young tube via pipette. The tube was then heated to 100 ^{o}C for 48 h, and subsequently to 110 ^{o}C for 48 h. 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 dropwise over ca. 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 40% DCM/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **3.15** as an off-white solid (72 mg, 35% yield).

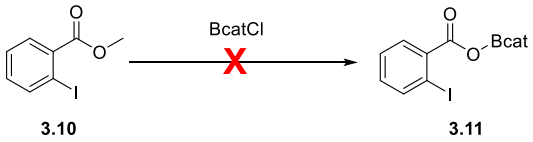
^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H), 1.71 (quin, *J* = 7.5 Hz, 2H), 1.41–1.37 (m, 2H), 1.29 (s, 12H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 183.3, 165.2, 131.3, 130.7, 129.2, 123.8, 83.8, 30.6, 27.0, 24.8, 22.3, 13.8.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.9.

HRMS (ESI+): Calculated for $C_{19}H_{25}NBBrO_3$ ($[M]^+$), 405.1115; found 405.1107.

*****Procedure for ^{1}H NMR observation of the rate of demethylation of methyl 2-iodobenzoate **3.10**



This procedure was performed in a N_2-filled glove box. A 4 mL vial was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv) and 0.5 mL of d_8-toluene. To this vial was sequentially added **3.10** (75 μL, 0.50 mmol, 1.0 equiv) and 1,3,5-triisopropylbenzene (40. μL, 0.17 mmol, 0.33 equiv) via syringe. The contents of this vial were then transferred to a J-young tube, which was sealed, and then removed from the glove box. Single scan ^{1}H and ^{11}B NMR spectra were taken at time points t = 0 h, 18 h, and 24 h. The resonances corresponding to **3.10** were compared to the internal standard to determine the percent of **3.10** remaining at t = 24 h (>95% **3.10** remaining at 24 h).

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Chapter 4

Catalyst-Free Formal Thioboration to Synthesize Borylated Benzothiophenes and Dihydrothiophenes

Abstract: The first ring-forming thioboration reaction of C–C π bonds is reported. This catalyst-free method proceeds in the presence of a commercially available external electrophilic boron source (*B*-chlorocatecholborane) in good to high yields. The method is scalable and tolerates a variety of functional groups that are intolerant of other major borylation methods. The resulting borylated benzothiophenes participate in a variety of in situ derivatization reactions, showcasing that these borylated intermediates do not need to be isolated prior to downstream functionalization. This methodology has been extended to the synthesis of borylated dihydrothiophenes. Mechanistic experiments suggest that the operative mechanistic pathway is through boron-induced activation of the alkyne followed by electrophilic cyclization, as opposed to S–B σ bond formation, providing a mechanistically distinct pathway to the thioboration of C–C π bonds. I initiated this project and worked with undergraduate student Ashlee J. Davis and visiting student Fiach B. Meany on its publication.[1] For scientific clarity, the full story is shared here; my contribution is noted in the experimental section.

Introduction

Thioboration, the addition of sulfur and boron across C–C π bonds, holds promise as an efficient route to synthesize functionalized thioethers.[2] This area of research has focused on reagents containing B–S σ bonds that can add in a direct fashion to π systems. In 2015, Bo, Fernández, and Westcott demonstrated the ability of B–S σ bonds from in-house synthesized reagents to add across Michael acceptors through boron activation of the carbonyl oxygen (Scheme 4.1a, top), but without generation of a B–C bond for downstream functionalization.[3] In 1993, Miyaura and Suzuki developed a thioboration reaction of B–S σ bonds across alkynes.[4,5] This method similarly employed in-house synthesized reagents containing B–S σ bonds, however it used a carbophilic palladium

catalyst to activate the C–C π bond. Protodeboration and in situ Suzuki cross-coupling reactions of these thioboration products were demonstrated, establishing the utility of such synthetic intermediates (Scheme 4.1a, bottom).

In contrast, *formal* thioboration, wherein the equivalents of boron and sulfur add across a C–C π bond, is underexplored, despite the potential advantages of employing commercially available boron reagents as opposed to the thioboration reagents requiring synthesis, and the plausibility of avoiding a palladium catalyst as previously required in the direct thioboration of alkynes.[4,5] Although little is known about the thiophilicity versus carbophilicity of boron reagents in synthesis, such knowledge would facilitate the development of thioboration reactions by indicating when B–S σ bonds are necessary and when such bonds can be avoided, aiming instead for previously unknown carbophilic activation of the C–C π bond by boron with simultaneous attack by sulfur via an Ad_E3 or Ad_E2 reaction mechanism (Scheme 4.1b).[6,7] Herein the first formal thioboration of C–C π bonds is reported, concurrently developing fundamental knowledge about guiding principles of relative carbophilicity and thiophilicity. The experiments were motivated by a broader study on gold-catalyzed and catalyst-free oxyboration and aminoboration (B–O and B–N addition) reactions in our research group.[8–11] This catalyst-free thioboration method generates borylated benzothiophene derivatives, a heterocyclic scaffold found in a variety of bioactive molecules and pharmaceuticals, such as raloxifene and sertaconazole (Figure 4.1).[12–14] These borylated benzothiophenes can then be further elaborated using the wide range of established boron functionalization chemistry.[15–17] This reaction employs a commercial boron reagent, *B*-chlorocatecholborane (ClBcat),

removing the need for B–S σ bond formation in starting materials or in intermediates and making the reaction mechanistically distinct for thioboration.

Scheme 4.1. a) Previously reported thioboration methods. b) This work demonstrating the first formal thioboration. ClBcat = *B*-chlorocatecholborane.

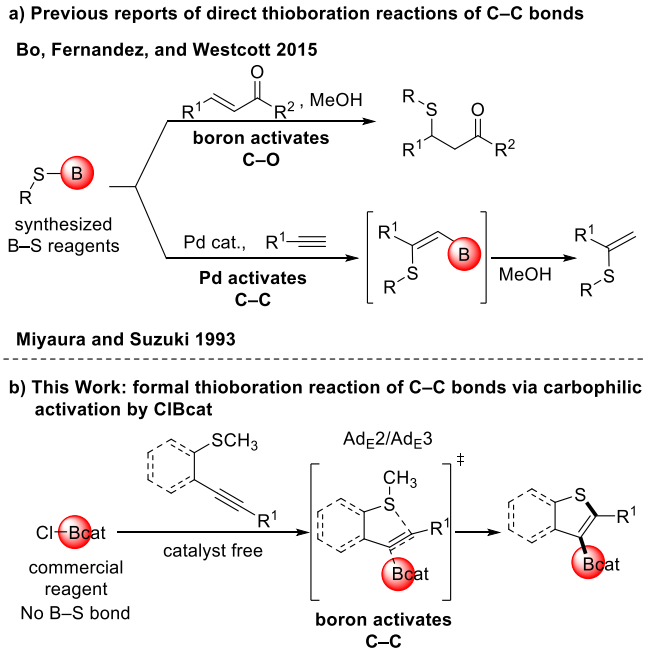
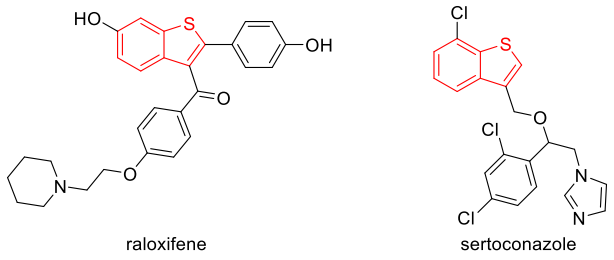


Figure 4.1. Two bioactive molecules that contain a benzothiophene core.



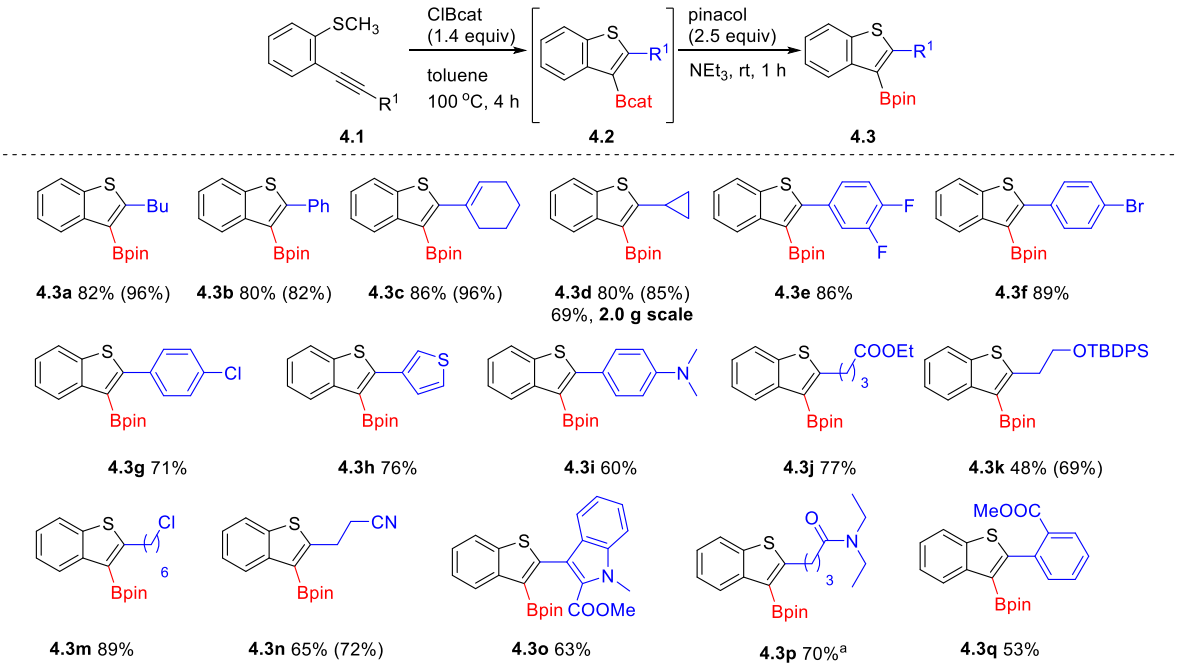
Primary competing strategies for the synthesis of borylated benzothiophenes include lithiation/electrophilic trapping[18,19] and transition metal-catalyzed borylation of the benzothiophene core.[20,21] The formal thioboration strategy described herein provides complementary functional group tolerance to these other borylation methods, and also furnishes the benzothiophene core in the same synthetic step. Alternative routes to

borylated benzothiophenes, in contrast, require separate steps for borylation and generation of the benzothiophene core.

Results and Discussion

We hypothesized that 2-alkynylthioanisoles (**4.1**) would react upon treatment with ClBcat to yield thioboration products **4.2** (Table 4.1). After initial identification of successful reactivity, reaction conditions were optimized. Examination of the equiv of ClBcat (1.0–1.4 equiv) identified 1.4 equiv as the optimal value at 1.3 M concentration in substrate **4.1** as determined by ^{1}H NMR spectroscopy relative to 1,3,5-triisopropylbenzene as an internal standard. Transesterification of **4.2** to the more air and moisture stable pinacolboronic ester (**4.3**) provided bench-stable organoboron building blocks. The use of ClBpin as an alternative electrophilic boron reagent, which would theoretically provide direct access to the desired pinacolboronic ester **4.3** from **4.1**, was not evaluated because of its instability above –35 ^{o}C and its difficulty of synthesis.[22]

Table 4.1. Synthesis of borylated benzothiophenes via the formal thioboration reaction.

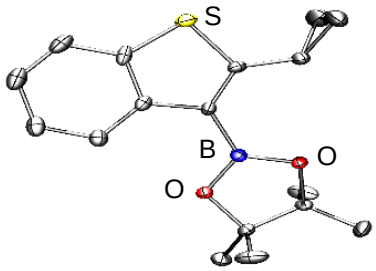


Yield is that of the isolated product. ^{1}H NMR yields were determined using mesitylene as an internal standard in d_8-toluene, and are listed in parantheses. [a]Required 24 h.

The functional group compatibility of the thioboration reaction was next examined (Table 4.1). Esters, aryl and alkyl halides, amines and cyano groups, an *O*-silyl protecting group, and several heterocycles tolerated the thioboration reaction conditions in good yields. Functional groups that were incompatible with the thioboration reaction included pyridinyl and alcohol (in both cases, only starting material was observed by ^{1}H NMR spectroscopy, consistent with reaction inhibition by the heteroatom lone pairs). Consistent with the need to favor carbophilicity and avoid competing heteroatomphilicity of boron in the formal thioboration reaction, amide-containing compound **4.3p** required 24 h rather than the standard 4 h to reach complete conversion (70% isolated yield at 24 h vs 25% isolated yield at 4 h). The slower reactivity was attributed to competitive coordination of the amide to boron. Notably, functional groups that cannot be tolerated by existing

methods of borylation of benzothiophenes (i.e., lithiation/electrophilic trapping or Pd-catalyzed Miyaura borylation)[18–21] were tolerated by these thioboration reaction conditions (e.g., substrates **4.3f**–**4.3h**, **4.3j**, **4.3m**, **4.3n**). Thus, this thioboration reaction provided access to borylated benzothiophenes that had limited accessibility through traditional methods. A crystal structure confirmed the regioselectivity of the thioboration method (Figure 4.2).

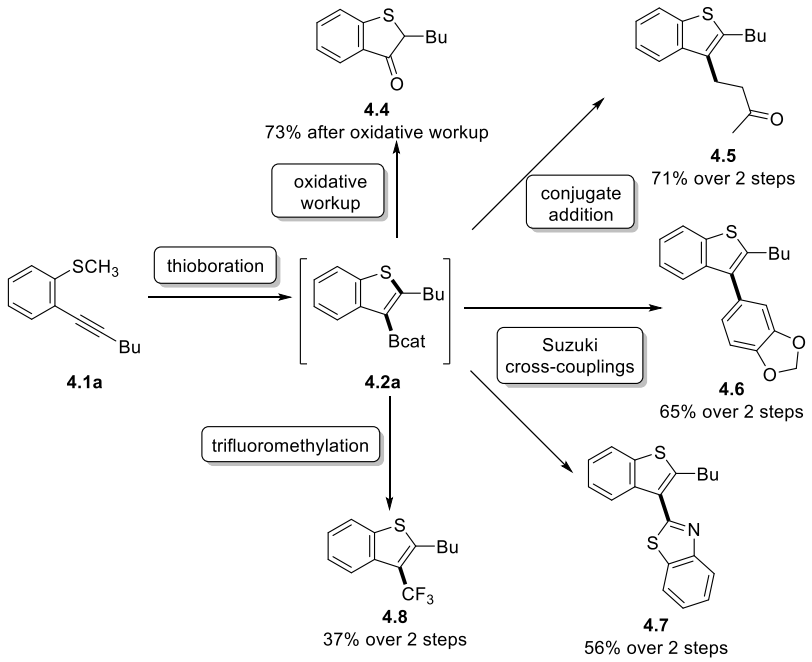
Figure 4.2. X-ray crystallographic structure of **4.3d**, with the thermal ellipsoids shown at 50% probability (B, blue; C, gray; S, yellow; O, red). Non-carbon elements also labelled.



Scale up. In addition to its good functional group tolerance, the thioboration reaction was scalable. Alkynylthioanisole **4.1d** underwent smooth thioboration at the 2.0 g scale to generate **4.3d** in 69% yield (Table 4.1).

In situ functionalizations. We hypothesized that the catalyst-free conditions of the formal thioboration reaction would provide minimal interference to downstream functionalization conditions due to the absence of residual metal salts. Indeed, synthetic intermediate **4.2a** participated in a wide range of C–B σ-bond functionalization reactions without the need for the additional synthetic manipulations of boron ligand exchange from catechol to pinacol or the requirement to isolate any boron-containing compound (Scheme 4.2).

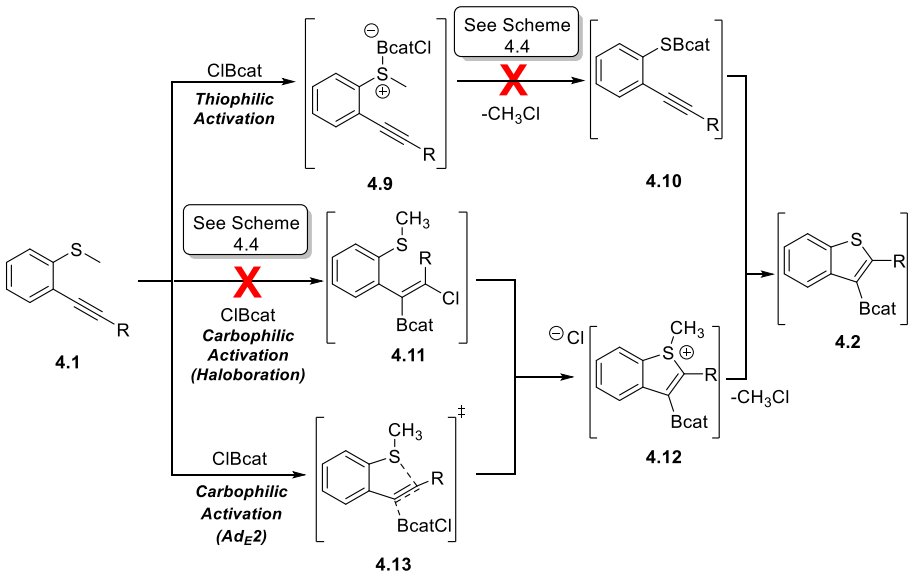
Scheme 4.2. In situ functionalization without isolation of organoboron intermediates: direct access to downstream products.



Oxidative workup of the C–B bond furnished 1-benzothiophene-3(2H)-one derivative **4.4**, a heterocyclic motif that has been examined as a donor-acceptor chromophore,[23] in 73% yield from **4.1a**. Rhodium-catalyzed conjugate addition to methyl vinyl ketone furnished product **4.5** in 71% yield over two steps.[24,25] Subjecting intermediate **2a** to two different Suzuki conditions[16,26] produced products **4.6** and **4.7** in 65% and 56% yield over two steps, respectively. Trifluoromethylation using a modification of a procedure developed by Sanford[27] furnished **4.8** in 37% yield over two steps. Albeit in low yield, this reaction provided access to 3-trifluoromethylated benzothiophenes, which have limited alternative synthetic routes.[28,29] These in situ reactions illustrate strategies for efficiently generating the heterocyclic core and functionalizing at the 3-position in one pot.

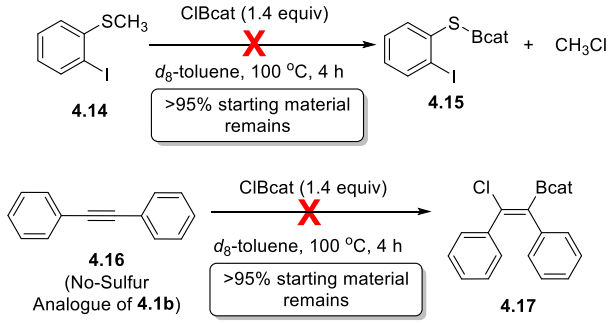
Mechanistic studies: boron as a thiophilic or carbophilic Lewis acid. Three main mechanistic pathways were considered for the thioboration reaction (Scheme 4.3). The first route was through thiophilic activation of **4.1** via coordination of ClBcat to the sulfur rather than the C–C π bond, forming activated intermediate **4.9** (Scheme 4.3, top). Demethylation furnishes thioboric ester **4.10**; subsequent B–S bond addition across the alkyne yields product **4.2**, which is a known pathway for several other B–X σ bond addition reactions.[30–33] In order to examine the thiophilicity of ClBcat toward **4.1a** at ambient temperature, the initial reaction mixture was evaluated by NMR spectroscopy in d_8-toluene. ^{1}H and ^{11}B NMR spectra obtained at t = 0 at ambient temperature showed no evidence of sulfur coordination to boron as judged by persistence resonances corresponding to starting material **4.1a** and ClBcat and the absence of other resonances. This result provided an early indication of the lack of thiophilicity of this reagent, but did not rule out sulfur–boron coordination or activation leading to possible reaction intermediates, which was next investigated.

Scheme 4.3. Three possible mechanistic pathways: B–S σ bond formation (top), haloboration (middle), and alkyne activation by ClBcat (bottom).



If demethylation were occurring first, through activated sulfonium intermediate **4.9** and B–S bond containing **4.10**, then a no-alkyne control would demethylate at the same rate (or faster, but not slower) than the thioboration reaction proceeds (4 h at 100 °C). Treatment of *o*-iodothioanisole **4.14**, however, under these conditions resulted in no reaction: >95% of the starting material remained after 4 h as determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard, with no demethylated product **4.15** observed (Scheme 4.6). Moreover, by ^{11}B NMR spectroscopy, only the ClBcat peak at δ = 28.6 ppm was detected, suggesting that the sulfur was not significantly coordinating to ClBcat, even after extended reaction times. This lack of chemical shift change in the ^{11}B NMR spectrum also ruled out formation of detectable amounts of sulfur-based borenium species.[34,35] This mechanistic control reaction demonstrated that demethylation of **4.1** is too slow relative to the timescale of the overall thioboration reaction (4 h) to be a step in the operative pathway and therefore ruled out the thiophilic activation pathway.

Scheme 4.4. Control reactions to determine the mechanism of the thioboration reaction.



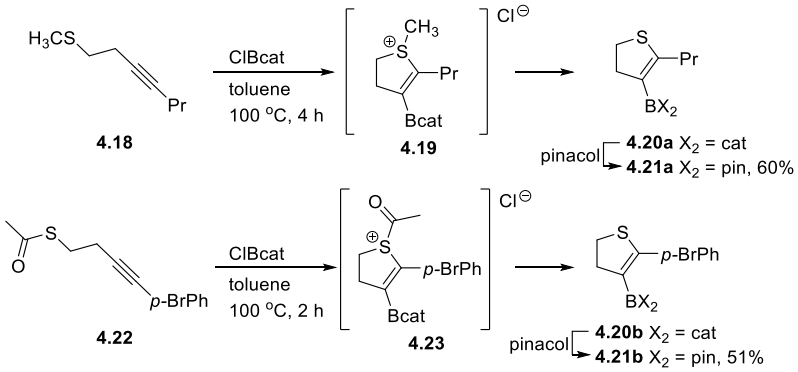
Next, two pathways were considered in which the ClBcat acts as a carbophilic Lewis acid by activating the C–C π system.[35] The first is through a haloboration/cyclization pathway proceeding through a chloroboration reaction analogous to that reported for alkynes,[31] generating intermediate **4.11** (Scheme 4.3, middle). This chloroboration product then undergoes cyclization to form sulfonium **4.12**. This mechanism was probed

by using a substrate without sulfur (Scheme 4.4). Chloroboration of alkynes with other reagents containing B–Cl bonds is thermodynamically downhill,[31,36] we therefore hypothesize that the chloroborated products in this system would be observable. Treatment of diphenylacetylene **4.16**, which is the no-sulfur analogue of substrate **4.1b**, under the otherwise standard thioboration conditions resulted in no reaction by ^{1}H (>95% **4.16** remaining using mesitylene as an internal standard) or ^{11}B NMR spectroscopy (only signal detected at δ = 28.6 ppm, corresponding to unreacted ClBcat) in 4 h. This demonstrated that chloroboration product **4.17** did not form, and thus is an unlikely operative pathway in this thioboration reaction.

On the basis of these mechanistic experiments, a role for boron as a carbophilic Lewis acid in this cyclization is proposed, plausibly through an Ad_E2/Ad_E3 mechanism[6,7] (Scheme 4.3, bottom). Subsequent attack by the sulfur via transition state **4.13** generates sulfonium intermediate **4.12**. Demethylation furnishes borylated benzothiophene **4.2**. Notably, this proposed pathway has no productive B–S coordination.

Extension of the mechanistic concept to other substrate classes. Having established the feasibility of this thioboration reaction, we hypothesized that this method could be extended towards the synthesis of dihydrothiophenes, a class of compounds that are useful toward anti-HIV therapeutics[37] and in agricultural products.[38] Subjecting alkynyl thioether **4.18** to the standard thioboration reaction conditions furnished the desired cyclic thioether **4.20a**, which was transesterified to the bench-stable pinacolboronic ester **4.21a** in 60% overall yield (Scheme 4.5). This additional substrate class established that the thioboration reaction did not require the entropic assistance of a rigid backbone or the enthalpic assistance of a gain of aromaticity to proceed.

Scheme 4.5. Extension of the thioboration reaction to synthesize borylated dihydrothiophenes.



The formal thioboration reaction also proceeded from thioacetate **4.22**, expanding the reactivity concept from dealkylation to deacylation of sulfur. Subjecting thioacetate **4.22** to ClBcat at 100 °C for 2 h furnished the desired cyclic thioether **4.20b**, plausibly via the analogous sulfonium intermediate **4.23** (Scheme 4.5). Compound **4.20b** was transesterified to the bench-stable pinacolboronic ester **4.21b** in 51% overall yield.

Conclusions

The first formal thioboration of C–C π bonds is reported. This scalable method efficiently generates both the benzothiophene core and a C–B functional group handle in one synthetic step. These borylated products are primed for downstream in situ functionalization reactions or for isolation as bench-stable building blocks. The mechanistic concept of this thioboration reaction was extended to the synthesis of borylated dihydrothiophenes via both demethylation and deacylation pathways. Mechanistic studies documented an unusual pathway for thioboration reactions in which an S–B σ bond is not formed. This thioboration reaction demonstrates a strategy for harnessing the carbophilic reactivity of boron without concurrent thiophilicity. We envision that this knowledge gained about the thiophilic versus carbophilic reactivity available to

boron reagents can be used as a guiding principle for the design of catalyst-free direct or formal boron–element addition reactions.

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Experimental

General Considerations

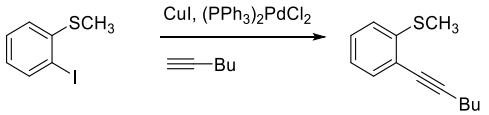
All chemicals were used as received from commercial sources unless otherwise noted. Triethylamine, acetonitrile, toluene, tetrahydrofuran, *N*,*N*-dimethylformamide, and dichloromethane were purified by passage through an alumina column under argon pressure on a push-still solvent system. d_8-Toluene was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. All manipulations were conducted 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-500 spectrometer

outfitted with a cryoprobe, or a Bruker AVANCE-600 spectrometer outfitted with a cryoprobe. All boron nuclear magnetic resonance (^{11}B NMR) spectra and fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker AVANCE-600 spectrometer. 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 = 2.08 ppm for d_8-toluene; δ = 77.2 ppm for $CDCl_3$ or δ = 20.4 ppm for d_8-toluene 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.

An asterisk (*) denotes work I completed towards the progress of my thesis.

Synthetic Procedures

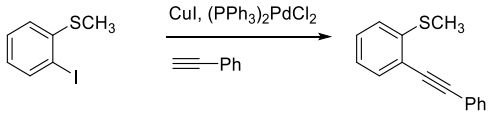
Preparation of Substrates **4.1a**–**4.1q**



4.14 **4.1a**

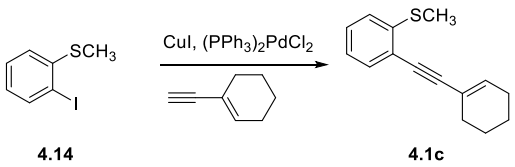
***(2-(Hex-1-yn-1-yl)phenyl)(methyl)sulfane (4.1a)**. In an N_2-filled glovebox, a 20 mL scintillation vial was charged with *o*-iodothioanisole **4.14** (0.28 mL, 2.0 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (42 mg, 0.10 mmol, 0.050 equiv), CuI (19 mg, 0.20 mmol, 0.10 equiv), Et_3N (6 mL), and a stir bar. 1-Hexyne (0.35 mL, 3.0 mmol, 1.5 equiv) was then added to the reaction mixture via syringe. The vial containing the resulting mixture was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC

indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1a** as a yellow oil (360 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.36 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.47 (s, 3H), 1.64 (quin, *J*=7.9 Hz, 2H), 1.60–1.50 (m, 2H), 1.25 (t, *J* = 7.4 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[1]



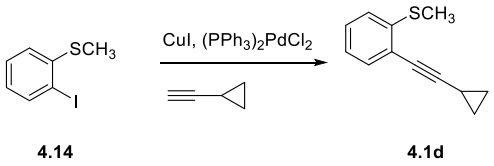
4.14 **4.1b**

***Methyl(2-(phenylethynyl)phenyl)sulfane (4.1b)** was synthesized using a literature procedure[2] in 79% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.59–7.57 (m, 2H), 7.48 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.37–7.32(m, 3H), 7.31–7.29 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.11 (td, *J* = 7.5, 1.1 Hz, 1H), 2.52 (s, 3H). This spectrum is in agreement with previously reported spectral data.[2]



4.14 4.1c

(2-(Cyclohex-1-en-1-ylethynyl)phenyl)(methyl)sulfane (4.1c) was synthesized using a literature procedure[2] in 89% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.37 (dd, J = 7.7, 1.1 Hz, 1H), 7.24 (dd, J = 7.5, 1.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.05 (td, J = 7.6, 1.1 Hz, 1H), 6.27–6.25 (m, 1H), 2.48 (s, 3H), 2.28–2.26 (m, 2H), 2.16–2.15 (m, 2H), 1.70–1.68 (m, 2H), 1.63–1.61 (m, 2H). This spectrum is in agreement with previously reported spectral data.[2]



4.14 4.1d

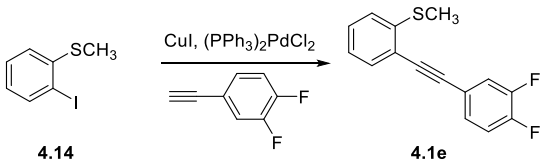
***(2-(Cyclopropylethynyl)phenyl)(methyl)sulfane (4.1d)**. A flask was charged with $(PPh_3)_2PdCl_2$ (421 mg, 0.600 mmol, 0.0500 equiv), CuI (57.3 mg, 0.300 mmol, 0.100 equiv), and a stir bar. The flask was then connected to a Schlenk line and evacuated and refilled with N_2 three times before *o*-iodothioanisole **4.14** (4.22 mL, 30.0 mmol, 1.00 equiv) and Et_3N (80 mL) were added via syringe. Cyclopropylacetylene (3.05 mL, 36.0 mmol, 1.20 equiv) was then syringed into the reaction mixture, which stirred for 18 h under dynamic N_2. At this time, analysis by TLC indicated full consumption of starting material. The reaction mixture was diluted with 200 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 30 mL), water (1 × 30 mL), and brine (1 × 30 mL). The organic layer was dried

over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1d** as a yellow liquid (5.5 g, 97% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.33 (dd, J = 7.6, 1.4 Hz, 1H), 7.23 (dt, J = 7.9, 1.1 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.03 (td, J = 7.5, 1.1 Hz, 1H), 2.46 (s, 3H), 1.55–1.50 (m, 1H), 0.92–0.86 (m, 4H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 141.4, 132.3, 128.0, 124.1, 123.8, 121.9, 100.5, 73.2, 15.0, 9.0, 0.5.

HRMS (ESI+): Calculated for $C_{12}H_{12}SNa$ ([M+Na]$^+$), 211.0557; found 211.0560.



4.14 4.1e

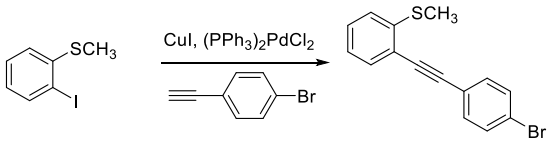
***(2-((3,4-Difluorophenyl)ethynyl)phenyl)(methyl)sulfane (4.1e)**. In an N_2-filled glovebox, a 20 mL scintillation vial was charged with *o*-iodothioanisole **4.14** (0.22 mL, 1.6 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (56 mg, 0.080 mmol, 0.050 equiv), CuI (31 mg, 0.16 mmol, 0.10 equiv), Et_3N (3 mL), and a stir bar. 3,4-Difluorophenylacetylene (0.22 mL, 1.8 mmol, 1.1 equiv) was then added to the reaction mixture via syringe. The vial containing the resulting mixture was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material.

The reaction mixture was diluted with 100 mL EtOAc and washed with saturated NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1e** as a solid (330 mg, 79% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.39–7.36 (m, 1H), 7.32–7.31 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.16–7.11 (m, 2H), 2.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.4 (dd, *J* = 77.7, 12.0 Hz), 149.4 (dd, *J* = 75.5, 12.6 Hz), 142.0, 132.4, 129.4–129.3 (m), 129.2–129.1 (m), 128.5–128.2 (m), 124.7–123.9 (m), 120.7, 120.6–120.1 (m), 118.0–117.8 (m), 117.3 (d, *J* = 19.9 Hz), 93.7, 87.5, 15.1.

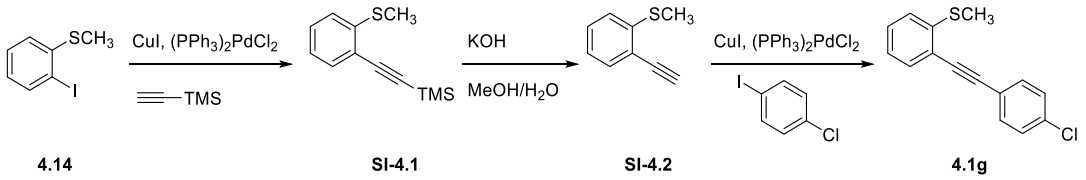
HRMS (CI+): Calculated for $C_{15}H_{10}SF_2$ ($[M]^+$), 260.0471; found 260.0471.



4.14 **4.1f**

***(2-((4-Bromophenyl)ethynyl)phenyl)(methyl)sulfane (4.1f)**. In an N_2-filled glovebox, a 20 mL scintillation vial was charged with *o*-iodothioanisole **4.14** (0.22 mL, 1.6 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (56 mg, 0.080 mmol, 0.050 equiv), CuI (31 mg, 0.16 mmol, 0.10 equiv), Et_3N (3 mL), and a stir bar. 4-Bromophenylacetylene (330 mg, 1.8 mmol, 1.1 equiv) was then added to the reaction mixture. The vial containing the resulting mixture was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL EtOAc and washed with saturated NH_4Cl (1 × 20 mL), water (1 × 20

mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1f** as a yellow solid (420 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.50–7.46 (m, 3H), 7.44–7.43 (m, 2H), 7.32 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 2.51 (s, 3H). This spectrum is in agreeance with previously reported spectral data.[3]



4.14 SI-4.1 SI-4.2 4.1g

Trimethyl((2-(methylthio)phenyl)ethynyl)silane (SI-4.1) was synthesized using a literature procedure[2] in 98% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.42 (dd, *J* = 7.6, 0.2 Hz, 1H), 7.27 (td, *J* = 8.0, 1.5 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.06 (td, *J* = 7.6, 1.1 Hz, 1H), 2.48 (s, 3H), 0.30 (s, 9H). This spectrum is in agreement with previously reported spectral data.[2]

(2-Ethynylphenyl)(methyl)sulfane (SI-4.2) was synthesized using a literature procedure[4] in 99% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 3.48 (s, 1H), 2.49 (s, 3H). This spectrum is in agreement with previously reported spectral data.[4]

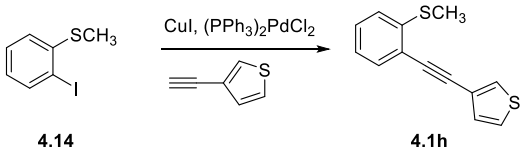
(2-((4-Chlorophenyl)ethynyl)phenyl)(methyl)sulfane (4.1g). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with 1-chloro-4-iodobenzene (270 mg, 1.1 mmol, 1.0

equiv), $(PPh_3)_2PdCl_2$ (39 mg, 0.056 mmol, 0.050 equiv), CuI (22 mg, 0.11 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-4.2** (250 mg, 1.7 mmol, 1.5 equiv) was dissolved in Et_3N (2.3 mL). This solution was then added to the reaction vial via pipette, and the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 10% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1g** as a yellow oil (250 mg, 86% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.50 (d, *J* = 10.2 Hz, 2H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.33–7.30 (m, 3H), 7.18 (d, *J* = 9.6Hz, 1H), 7.12 (t, *J* = 9.1 Hz, 1H), 2.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 141.8, 134.7, 132.8, 132.3, 129.0, 128.7, 124.3, 124.1, 121.7, 121.0, 94.7, 87.9, 15.1.

HRMS (CI+): Calculated for $C_{15}H_{10}SCl$ ($[M-H]^+$), 257.0192; found 257.0192.



4.14 **4.1h**

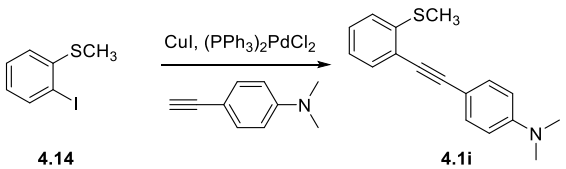
3-((2-(Methylthio)phenyl)ethynyl)thiophene (4.1h). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with **4.14** (0.35 mL, 2.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (88

mg, 0.13 mmol, 0.050 equiv), CuI (48 mg, 0.25 mmol, 0.10 equiv), Et_3N (5 mL), and a stir bar. 3-Ethynylthiophene (0.37 mL, 3.8 mmol, 1.5 equiv) was added to the reaction mixture via syringe. The vial containing the resulting mixture was then capped and removed from the glovebox, and the reaction mixture was stirred for 18 h. At this time, the reaction mixture was diluted with 100 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 10% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1h** as a yellow oil (520 mg, 92% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.48 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 9.2 Hz, 1H), 7.21–7.18 (m, 2 H), 7.16–7.14 (m, 1H), 7.06 (d, *J* = 9.7 Hz, 1H), 7.01 (t, *J* = 9.0 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 141.7, 132.3, 130.0, 129.0, 128.9, 125.6, 124.4, 124.2, 122.3, 121.3, 91.2, 86.6, 15.1.

HRMS (ESI+): Calculated for $C_{13}H_{10}S_2Na$ ([M+Na]$^+$), 253.0122; found 253.0117.



4.14 **4.1i**

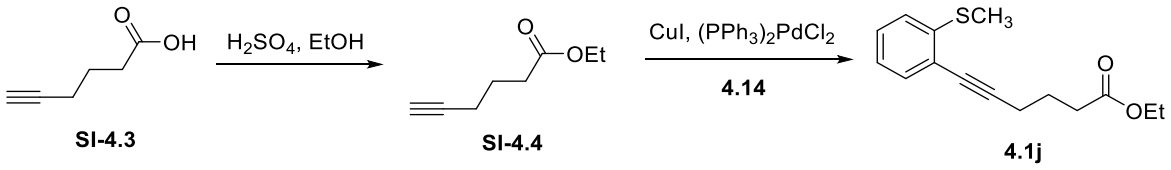
***N,N*-Dimethyl-4-((2-(methylthio)phenyl)ethynyl)aniline (4.1i)**. In an N_2-filled glovebox, a 20 mL scintillation vial was charged with *o*-iodothioanisole **4.14** (0.42 mL, 3.0 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (42 mg, 0.060 mmol, 0.020 equiv), CuI (6 mg, 0.03 mmol,

0.01 equiv), and a stir bar. In a separate dram vial, 4-ethynyl-*N,N*-dimethylaniline (500. mg, 3.45 mmol, 1.15 equiv) was dissolved in Et_3N (6 mL). This solution was then added to the vial containing the reaction mixture. The vial containing the resulting mixture was then capped, removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 150 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 20% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1i** as a yellow solid (780 mg, 97% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47 (d, *J* = 10.9 Hz, 3H), 7.26 (t, *J* = 9.5 Hz, 1H), 7.16 (d, *J* = 9.3 Hz, 1H), 7.10 (t, *J* = 9.0 Hz, 1H), 6.66 (d, *J* = 10.7 Hz, 2H), 2.99 (s, 6H), 6.51 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 150.3, 141.1, 132.8, 131.9, 128.0, 124.3, 124.1, 122.3, 111.9, 110.0, 97.4, 85.0, 40.3, 15.2.

HRMS (ESI+): Calculated for $C_{17}H_{17}NSNa$ ([M+Na]$^+$), 290.0979; found 290.0985.



SI-4.3 **SI-4.4** **4.1j**

Ethyl hex-5-ynoate (SI-4.4) was prepared according to a literature procedure[5] in 87% yield. ^{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

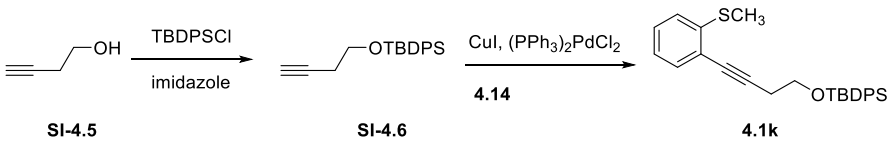
(dt, *J* = 7.0, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.85 (quin, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[5]

Ethyl 6-(2-(methylthio)phenyl)hex-5-ynoate (4.1j). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with *o*-iodothioanisole **4.14** (0.21 mL, 1.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (21 mg, 0.030 mmol, 0.020 equiv), CuI (2.9 mg, 0.015 mmol, 0.010 equiv), and a stir bar. In a separate dram vial, **SI-4.4** (250 mg, 1.8 mmol, 1.2 equiv) was dissolved in Et_3N (3 mL). This solution was then added to the reaction mixture. The vial containing the resulting mixture was capped, removed from the glovebox, and the solution was stirred for 18 h. The reaction mixture was then diluted with 150 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 15% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1j** as a yellow oil (260 mg, 65% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.35 (d, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.14 (q, *J* = 7.9 Hz, 2H), 2.57 (q, *J* = 7.0 Hz, 4H), 3.47 (s, 3H), 1.97 (quin, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 173.3, 141.3, 132.3, 128.3, 124.2, 123.8, 121.7, 95.9, 79.0, 60.4, 33.2, 24.0, 19.2, 15.0, 14.3.

HRMS (ESI+): Calculated for $C_{15}H_{18}O_2SNa$ ($[M+Na]^+$), 285.0925; found 285.0917.



SI-4.5 SI-4.6 4.1k

(But-3-yn-1-yloxy)(tert-butyl)diphenylsilane (SI-4.6) was prepared according to a literature procedure[6] in 82% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.68 (d, *J* = 6.7 Hz, 4H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 4H), 3.79 (t, *J* = 7.0 Hz, 2H), 2.45 (dt, *J* = 7.1 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.06 (s, 9H). This spectrum is in agreement with previously reported spectral data.[6]

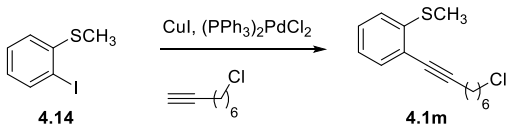
***tert*-Butyl((4-(2-(methylthio)phenyl)but-3-yn-1-yl)oxy)diphenylsilane** (**4.1k**). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with *o*-iodothioanisole **4.14** (0.35 mL, 2.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (88 mg, 0.13 mmol, 0.050 equiv), CuI (48 mg, 0.25 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-4.6** (1.2 g, 3.8 mmol, 1.5 equiv) was dissolved in Et_3N (5 mL). This solution was then added to the reaction mixture. The vial containing this resulting mixture was then capped and removed from the glovebox, and the solution was stirred for 18 h. The reaction mixture was then diluted with 200 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1k** as a viscous yellow oil (610 mg, 57% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.74–7.72 (m, 4H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.40–7.37 (m, 4H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.26–7.24 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* =

7.6 Hz, 1H), 3.94–3.91 (m, 2H), 2.79 (dt, *J* = 8.6, 1.6 Hz, 2H), 2.45 (s, 3H), 1.09 (s, 9H).

^{13}C NMR ($CDCl_3$. 151 MHz): δ 141.3, 135.7, 133.8, 132.5, 129.8, 128.3, 127.8, 124.2, 124.0, 121.9, 94.1, 79.2, 62.6, 26.9, 24.0, 19.4, 15.1.

HRMS (ESI+): Calculated for $C_{27}H_{30}OSSiNa$ ([M+Na]$^+$), 453.1684; found 453.1667.



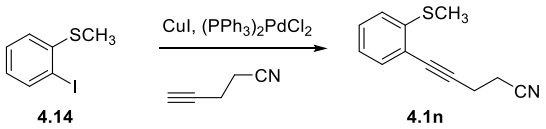
4.14 **4.1m**

***(2-(8-Chlorooct-1-yn-1-yl)phenyl)(methyl)sulfane (4.1m)**. In an N_2-filled glovebox, a 20 mL scintillation vial was charged with *o*-iodothioanisole **4.14** (0.31 mL, 2.2 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (77 mg, 0.11 mmol, 0.050 equiv), CuI (42 mg, 0.22 mmol, 0.10 equiv), Et_3N (6.7 mL), and a stir bar. 8-Chloro-1-octyne (0.51 mL, 3.3 mmol, 1.5 equiv) was then added via syringe. The vial containing the resulting mixture was then capped and removed from the glovebox, and the solution was stirred for 18 h. The reaction mixture was then diluted with 200 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 10% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1m** as a viscous yellow oil (520 mg, 89% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.36 (d, *J* = 7.6 Hz, 1H), 7.24 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H) 7.05 (t, *J* = 7.5 Hz, 1H), 3.55 (t, *J* = 6.7 Hz, 2H), 2.50 (t, *J* = 6.9 Hz, 2H), 2.46 (s, 3H), 1.80 (quin, *J* = 6.8 Hz, 2H), 1.66 (quin, *J* = 6.9 Hz, 2H), 1.57–1.47 (m, 4H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 141.3, 132.2, 128.2, 124.1, 123.7, 121.9, 97.1, 78.4, 45.1, 32.6, 28.5, 28.1, 26.5, 19.6, 15.0.

HRMS (CI+): Calculated for $C_{15}H_{19}ClSH$ ($[M+H]^+$), 267.0974; found 267.0972.



4.14 4.1n

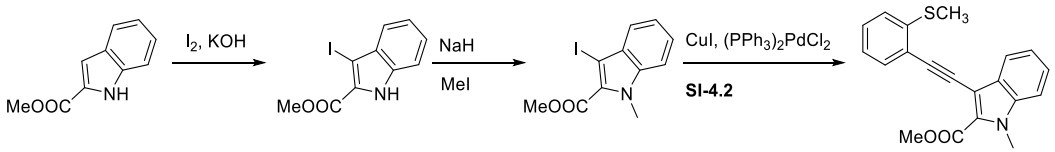
5-(2-(Methylthio)phenyl)pent-4-ynenitrile (4.1n). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with *o*-iodothioanisole **4.14** (0.35 mL, 2.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (88 mg, 0.13 mmol, 0.050 equiv), CuI (48 mg, 0.25 mmol, 0.10 equiv), Et_3N (5 mL), and a stir bar. 4-Pentynenitrile (0.33 mL, 3.8 mmol, 1.5 equiv) was then added via syringe. The vial containing this resulting mixture was then capped and removed from the glovebox, and the solution was stirred for 18 h. The reaction mixture was then diluted with 200 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 20% EtOAc in hexanes. Product-containing fractions

were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1n** as a yellow oil (260 mg, 51% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.06 (t, J = 7.1 Hz, 1H), 2.82 (t, J = 7.1 Hz, 2H), 2.65 (t, J = 7.1 Hz, 2H), 2.45 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.6, 132.6, 129.0, 124.2, 123.9, 120.7, 118.5, 92.0, 80.6, 17.7, 17.1, 15.0.

HRMS (CI+): Calculated for $C_{12}H_{11}SNH$ ($[M+H]^+$), 202.0690; found 202.0681.



***Methyl 3-iodo-1H-indole-2-carboxylate (SI-4.8)** was prepared according to a literature procedure[7] in 71% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.32 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.39–7.37 (m, 2H), 7.25–7.22 (m, 1H), 4.00 (s, 3H). This spectrum is in agreement with previously reported spectral data.[7]

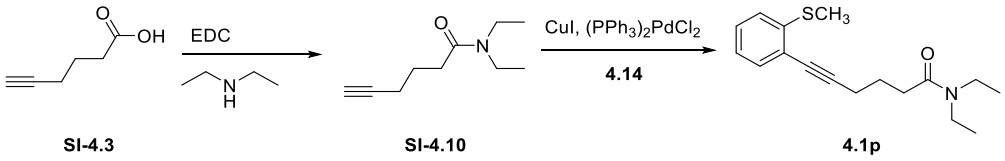
Methyl 3-iodo-1-methyl-1H-indole-2-carboxylate (SI-4.9) was prepared according to a literature procedure[7] in 63% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.57 (d, J = 8.1 Hz, 1H), 7.40 (ddd, J = 15.2, 6.8, 1.1 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.23 (ddd, J = 14.9, 6.9, 0.9 Hz, 1H), 4.07 (s, 3H), 3.99 (s, 3H). This spectrum is in agreement with previously reported spectral data.[7]

Methyl 1-methyl-3-((2-(methylthio)phenyl)ethynyl)-1H-indole-2-carboxylate (4.1o). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with **SI-4.9** (0.37 g, 1.2 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (17 mg, 0.024 mmol, 0.020 equiv), CuI (2.2 mg, 0.012 mmol, 0.010 equiv), Et_3N (1.5 mL), and a stir bar. In a separate dram vial, **SI-4.2** (0.21 g, 1.4 mmol, 1.2 equiv) and Et_3N (1 mL) were sequentially added. This solution was then added to the reaction mixture via pipette. The vial containing the resulting mixture was then capped and removed from the glovebox, and the solution was stirred for 18 h. The reaction mixture was then diluted with 200 mL of Et_2O and washed with saturated aqueous NH_4Cl (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 15% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1o** as a light yellow solid (330 mg, 69% yield).

^{1}H NMR ($CDCl_3$, 500.2 MHz): δ 7.88 (d, J = 8.0 Hz, 1H), 7.41 (dd, J = 7.6, 1.1 Hz, 1H), 7.28–7.25 (m, 2H), 7.18–7.11 (m, 2H), 7.07 (d, J = 7.9 Hz, 1H), 7.00 (dt, J = 7.5, 0.9 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 162.3, 141.2, 138.6, 132.5, 128.8, 128.6, 128.3, 126.1, 124.4, 124.2, 122.3, 122.2, 121.7, 110.5, 105.0, 93.1, 89.6, 52.1, 32.4, 15.3.

HRMS (ESI+): Calculated for $C_{20}H_{17}NO_2SNa$ ($[M+Na]^+$), 358.0878; found 358.0870.



SI-4.3 **SI-4.10** **4.1p**

***N*,*N*-Diethylhex-5-ynamide (SI-4.10)** was prepared according to a literature procedure[8] in 94% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.38–3.32 (m, 4H), 2.46–2.43 (m, 2H), 2.28–2.26 (m, 2H), 1.95–1.94 (m, 1H), 1.89–1.85 (m, 2H). 1.19 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[8]

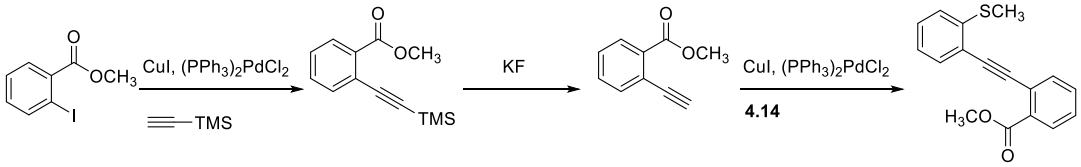
***N*,*N*-Diethyl-6-(2-(methylthio)phenyl)hex-5-ynamide (4.1p)**. A flask was charged with $(PPh_3)_2PdCl_2$ (42 mg, 0.060 mmol, 0.050 equiv), CuI (23 mg, 0.12 mmol, 0.10 equiv), and a stir bar. The flask was then connected to a Schlenk line and evacuated and refilled with N_2 three times before *o*-iodothioanisole **4.14** (0.17 mL, 1.2 mmol, 1.0 equiv) and Et_3N (3.6 mL) were added. Compound **SI-4.10** (0.30 g, 1.8 mmol, 1.5 equiv) was then added to the reaction mixture, and this solution was stirred for 18 h under dynamic N_2. At this time, analysis by TLC indicated full consumption of starting material. The reaction mixture was diluted with 200 mL DCM and washed with saturated NH_4Cl (1 × 30 mL), water (1 × 30 mL), and brine (1 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 20% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.1p** as a yellow oil (0.30 g, 87% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.29 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.19 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.99 (dt, *J* = 7.5, 1.0 Hz, 1H), 3.35–3.28 (m, 4H), 2.55–2.52

(m, 4H), 2.40 (s, 3H), 1,94 (quin, *J* = 6.8 Hz, 2H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 171.7, 141.3, 132.4, 128.3, 124.3, 123.9, 122.0, 96.7, 78.9, 42.1, 40.3, 21.9, 24.4, 19.4, 15.1, 14.5, 13.3.

HRMS (ESI+): Calculated for $C_{17}H_{23}SNONa$ ([M+Na]$^+$), 312.1398; found 312.1392.



SI-4.11 **SI-4.12** **SI-4.13** **4.1q**

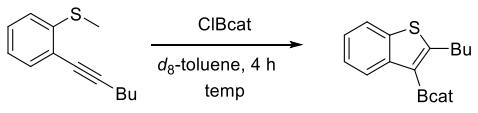
***Methyl 2-((trimethylsilyl)ethynyl)benzoate (SI-4.12)** was prepared according to a literature procedure[4] in 79% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.90 (app d, *J* = 7.6 Hz, 1H), 7.58 (app d, *J* = 7.5 Hz, 1H), 7.44 (td, *J* = 7.6, 0.8 Hz, 1H), 7.36 (app t, *J* = 7.6 Hz, 1H), 3.92 (s, 3H), 0.27 (s, 9H). This spectrum is in agreement with previously reported spectral data.[4]

***Methyl 2-ethynylbenzoate (SI-4.13)** was prepared according to a literature procedure[4] in 84% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 3.93 (s, 3H), 3.40 (s, 1H). This spectrum is in agreement with previously reported spectral data.[4]

***Methyl 2-((2-(methylthio)phenyl)ethynyl)benzoate (4.1q)** was prepared according to a literature procedure[4] in 70% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.94 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.73 (dd. *J* = 7.6, 1.1 Hz, 1H), 7.54 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.39 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.31 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.19 (d, *J* = 7.9

Hz, 1H), 7.13 (dt, *J* = 7.5, 0.9 Hz, 1H), 3.93 (s, 3H), 3.39 (s, 3H). This spectrum is in agreement with previously reported spectral data.[4]

*****Reaction Condition Optimization

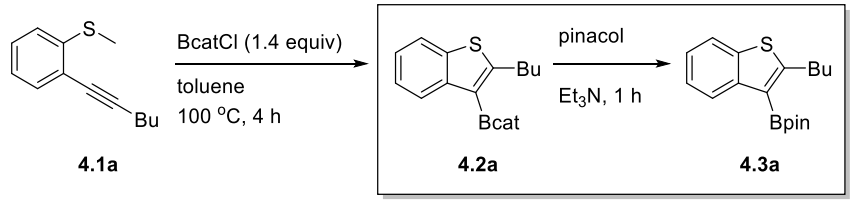


4.1a **4.2a**

In an N_2-filled glovebox, to a dram vial containing **4.1a** (80. mg, 0.39 mmol, 1.0 equiv) was added 1,3,5-triisopropylbenzene (20. μl, 0.083 mmol, 0.21 equiv) as an internal standard. To this mixture was added d_8-toluene (0.5–1.3 M with respect to **4.1a**). This mixture was then added to a dram vial containing *B*-chlorocatecholborane (1.0–1.4 equiv). After swirling to mix thoroughly, the reaction mixture was transferred to a J. Young NMR tube, which was capped, removed from the glovebox, and heated in a preheated oil bath for 4 h. The progress of the reaction was then examined at *t* = 4 h by single scan ^{1}H NMR spectroscopy, with the characteristic product (**4.2a**) peak at δ = 8.61 ppm in the ^{1}H NMR spectrum employed for integration relative to the internal standard. Entries 1–4 examined the effect of the equiv of ClBcat. Entries 5–8 examined the temperature dependence of the reaction, and entries 9–11 examined the effect of the concentration of **4.1a**. Entry 5 was found to be the best reaction conditions.

Table SI-4.1. Optimization of the Thioboration Reaction Conditions

Entry	ClBcat equiv	Concentration of 4.1a	Temp	^{1}H NMR Yield of 4.2a
1	1.0 equiv	1.3 M	100 °C	91
2	1.1 equiv	1.3 M	100 °C	91
3	1.2 equiv	1.3 M	100 °C	87
4	1.3 equiv	1.3 M	100 °C	91
5	1.4 equiv	1.3 M	100 °C	96
6	1.4 equiv	1.3 M	80 °C	78
7	1.4 equiv	1.3 M	60 °C	44
8	1.4 equiv	1.3 M	40 °C	27
9	1.4 equiv	0.5 M	100 °C	85
10	1.4 equiv	1.0 M	100 °C	86
11	1.4 equiv	1.5 M	100 °C	88



In an N_2-filled glovebox, a dram vial was charged with **4.1a** (100. mg, 0.491 mmol, 1.00 equiv), which was then dissolved in toluene (0.38 mL) and added to a dram vial containing *B*-chlorocatecholborane (106 mg, 0.690 mmol, 1.40 equiv). The reaction mixture was sealed with a cap and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and diluted with 0.38 mL of toluene. In a separate vial, pinacol (1.5–3.0 equiv) was dissolved in Et_3N (1.0 mL, 7.4 mmol, 15 equiv). This solution was then added to the reaction mixture and a stir bar was added. The reaction mixture was sealed with a cap, brought out of the glovebox, and stirred for 1 h at room temperature. The reaction mixture was then concentrated on a rotary evaporator (~10 Torr at 35 °C). An aliquot of this residue was removed and its mass was recorded as a fraction of the whole. To this aliquot was added 1,3,5-triisopropylbenzene, and this mixture was dissolved in $CDCl_3$. The ^{1}H NMR yield was calculated using the characteristic

product (**4.3a**) peak at δ = 8.30 ppm in the ^{1}H NMR spectrum. Entry 3 was identified to be the best isolation conditions.

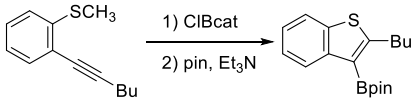
Table SI-4.2. Optimization of the Isolation Conditions of the Thioboration Reaction

Entry	Pinacol equiv	^{1}H NMR yield of 4.3a
1	1.5	72
2	2.0	81
3	2.5	95
4	3.0	85

Synthesis and Isolation of Thioboration Products **4.3a**–**4.3q**

General Remarks

For synthetic ease, all reactions were carried out in an N_2-filled glovebox unless otherwise specified. *B*-Chlorocatecholborane is water reactive and should be stored cool (0 ^{o}C or lower) when not in use. The ipso C–B bond is not detected by ^{13}C NMR spectroscopy.



4.1a **4.3a**

***2-(2-Butylbenzo[*b*]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3a)**. A dram vial was charged with **4.1a** (0.100 g, 0.490 mmol, 1.00 equiv) and 0.4 mL toluene. A separate vial was charged with *B*-chlorocatecholborane (0.106 g, 0.690 mmol, 1.40 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the borane-containing vial. This vial was then capped and then heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with 0.4 mL toluene. A separate vial was then charged with pinacol (0.174 g, 1.47 mmol, 2.50 equiv), Et_3N (1.0 mL, 7.4 mmol, 15 equiv), and a stir bar. The reaction mixture

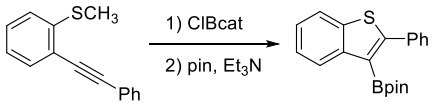
was added dropwise over ca. 1 min to this vial, which was then capped, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.3a** as a yellow oil (0.13 g, 82% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.33 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.35 (td, *J* = 7.1, 1.1 Hz, 1H), 7.27–7.25 (m, 1H), 3.26 (t, *J* = 7.6 Hz, 2H), 1.75 (q, *J* = 7.4 Hz, 2H), 1.46 (sext., *J* = 7.4 Hz, 2H), 1.40 (s, 12H), 0.98 (t, *J* = 7.4, Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 161.5, 144.7, 139.5, 125.0, 124.2, 123.4, 121.6, 83.2, 35.0, 30.7, 25.1, 22.5, 14.0.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.3.

HRMS (ESI+): Calculated for $C_{18}H_{25}SBO_2Na$ ([M+Na]$^+$), 339.1570; found 339.1572.



4.1b **4.3b**

4,4,5,5-Tetramethyl-2-(2-phenylbenzo[*b*]thiophen-3-yl)-1,3,2-dioxaborolane (4.3b). A dram vial was charged with **4.1b** (67 mg, 0.30 mmol, 1.0 equiv) and toluene (0.2 mL). A separate vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the borane-containing vial, and this vial was capped and heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.2 mL). A separate vial was then charged with pinacol (89 mg, 0.75 mmol, 2.5

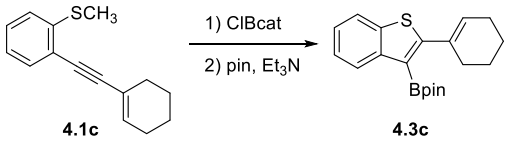
equiv), Et_3N (0.62 mL, 4.5 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was then capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified 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 ca. 10 mTorr for 18 h to afford **4.3b** as a yellow oil (81 mg, 80% yield).

^{1}H NMR ($CDCl_3$, 600MHz): δ 8.25 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.64–7.62 (m, 2H), 7.42–7.38 (m, 4H), 7.32 (td, J = 8.1, 1.1 Hz, 1H), 1.34 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.1, 144.9, 140.7, 135.6, 130.0, 128.5, 128.1, 125.3, 124.6, 124.1, 121.7, 83.8, 24.9.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.9.

HRMS (ESI+): Calculated for $C_{18}H_{25}SBO_2Na$ ([M+Na]$^+$), 339.1570; found 339.1572.



***2-(2-(Cyclohex-1-en-1-yl)benzo[*b*]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3c)**. A dram vial was charged with **4.1c** (69 mg, 0.30 mmol, 1.0 equiv) and 0.2 mL toluene. A separate vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the borane-containing vial, and this vial was then capped and heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with 0.5 mL toluene. A separate vial was then charged with

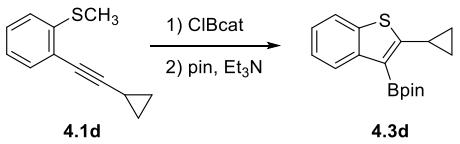
pinacol (89 mg, 0.75 mmol, 2.5 equiv), Et_3N (0.63 mL, 4.5 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was then capped, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified 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 ca. 10 mTorr for 18 h to afford **4.3c** as a yellow oil (88 mg, 86% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 7.1, 1.1 Hz, 1H), 7.2 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.10–6.08 (m, 1H), 2.54–2.51 (m, 2H), 2.26–2.23 (m, 2H), 1.85–1.81 (m, 2H), 1.75–1.71 (m, 2H), 1.42 (s, 12H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.4, 144.5, 139.5, 133.5, 129.4, 145.8, 124.2, 123.7, 121.6, 83.5, 30.7, 25.8, 25.0, 23.0, 22.0.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 30.1.

HRMS (CI+): Calculated for $C_{20}H_{25}SBO_2$ ($[M]^+$), 340.1672; found 340.1679.



4.1d **4.3d**

***2-(2-Cyclopropylbenzo[*b*]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3d)**. A dram vial was charged with **4.1d** (56 mg, 0.30 mmol, 1.0 equiv) and 0.2 mL toluene. A separate vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the borane-containing vial, and this vial was then capped and heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature and then diluted

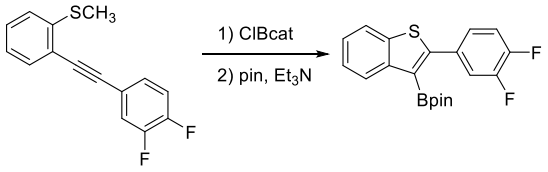
with 0.5 mL toluene. A separate vial was then charged with pinacol (89 mg, 0.75 mmol, 2.5 equiv), Et_3N (0.63 mL, 4.5 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3d** as a yellow solid (72 mg, 80% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.31 (d. J = 8.1 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 3.13–3.08 (m, 1H), 1.43 (s, 12H), 1.22–1.19 (m, 2H), 0.93–0.90 (m, 2H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 164.8, 144.9, 137.7, 124.6, 124.3, 123.3, 121.6, 83.2, 25.1, 13.3, 12.6.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.7.

HRMS (CI+): Calculated for $C_{17}H_{21}SBO_2$ ([M]$^+$), 300.1359; found 300.1361.



4.1e **4.3e**

***2-(2-(3,4-Difluorophenyl)benzo[*b*]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3e)**. A dram vial was charged with **4.1e** (104 mg, 0.400 mmol, 1.00 equiv) and toluene (0.3 mL). A separate vial was charged with *B*-chlorocatecholborane (86 mg, 0.56 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was

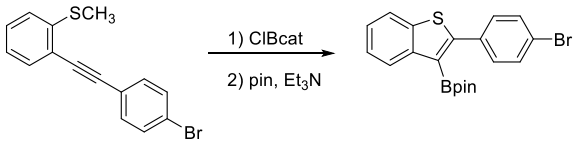
then added dropwise over ca. 1 min to the boron-containing vial, and this vial was then capped and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.3 mL). A separate vial was then charged with pinacol (118 mg, 1.00 mmol, 2.50 equiv), Et_3N (0.83 mL, 6.0 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3e** as a light yellow solid (130 mg, 86% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.27 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.49–7.45 (m, 1H), 7.40 (t. *J* = 8.0 Hz, 1H), 7.35–7.32 (m, 2H), 7.18 (dt, *J* = 10.0, 8.4 Hz, 1H), 1.34 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 152.6, 151.2 (dd, *J* = 126.2, 16.9 Hz), 149.2 (dd, *J* = 116.4, 17.0 Hz), 144.7, 140.5, 132.5 (dd, *J* = 6.7, 3.9 Hz), 126.1 (dd, *J* = 6.3, 3.5 Hz), 125.6, 124.8, 124.6, 121.7, 119.2 (d, *J* = 18.1 Hz), 116.9 (d, *J* = 17.4 Hz), 83.9, 24.9,

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.8.

HRMS (ESI+): Calculated for $C_{20}H_{19}SBF_2O_2Na$ ($[M+Na]^+$), 395.1068; found 395.1055.



4.1f **4.3f**

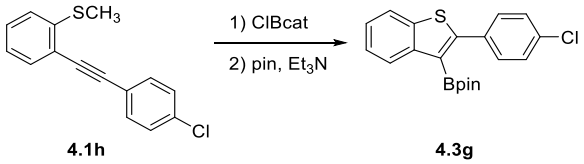
***2-(2-(4-Bromophenyl)benzo[*b*]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3f)**. A dram vial was charged with **4.1f** (91 mg, 0.30 mmol, 1.0 equiv) and toluene (0.2 mL). A separate vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the boron-containing vial, and this vial was then capped and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.2 mL). A separate vial was then charged with pinacol (89 mg, 0.75 mmol, 2.5 equiv), Et_3N (0.63 mL, 4.5 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3f** as a yellow solid (110 mg, 89% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.27 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.51 (q, J = 8.5 Hz, 4H), 7.40 (t, J = 7.9 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 1.34 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.7, 144.9, 140.6, 134.5, 131.5, 131.2, 125.5, 124.7, 124.4, 122.8, 121.7, 83.8, 24.9.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.8.

HRMS (ESI+): Calculated for $C_{20}H_{20}SBBrO_2Na$ ($[M+Na]^+$), 473.0362; found 473.0355.



4.1h **4.3g**

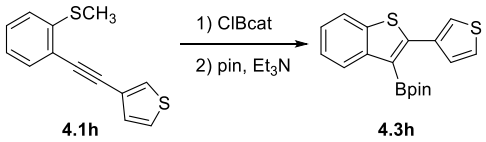
***2-(2-(4-Chlorophenyl)benzo[*b*]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3g)**. A dram vial was charged with **4.1g** (91 mg, 0.35 mmol, 1.0 equiv) and toluene (0.3 mL). A separate vial was charged with *B*-chlorocatecholborane (75 mg, 0.49 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the borane-containing vial, and this vial was then capped and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.3 mL). A separate vial was then charged with pinacol (104 mg, 0.880 mmol, 2.50 equiv), Et_3N (0.73 mL, 5.3 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3g** as a white solid (92 mg, 71% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.27 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.42–7.36 (m, 3H), 7.33 (t, *J* = 7.8 Hz, 1H), 1.34 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.7, 144.8, 140.6, 134.6, 134.1, 131.3, 128.2, 125.5, 124.7, 124.4, 121.7, 83.9, 24.9.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.6.

HRMS (ESI+): Calculated for $C_{20}H_{20}SBClO_2Na$ ($[M+Na]^+$), 393.0867; found 393.0864.



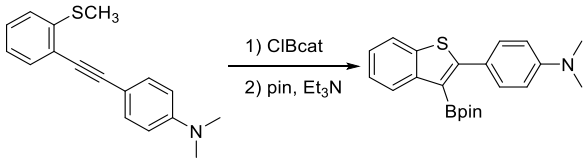
4.1h **4.3h**

***4,4,5,5-Tetramethyl-2-(2-(thiophen-3-yl)benzo[*b*]thiophen-3-yl)-1,3,2-dioxaborolane (4.3h)**. A dram vial was charged with **4.1h** (92 mg, 0.40 mmol, 1.0 equiv) and toluene (0.3 mL). A separate vial was charged with *B*-chlorocatecholborane (86 mg, 0.56 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the borane-containing vial, and this vial was then capped and heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.3 mL). A separate vial was then charged with pinacol (120 mg, 1.0 mmol, 2.5 equiv), Et_3N (0.83 mL, 6.0 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3h** as a brown solid (0.10 g, 76% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.25 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.69 (dd, J = 2.9, 1.3 Hz, 1H), 7.44 (dd, J = 5.0, 1.2 Hz, 1H), 7.34 (td, J = 7.3, 1.1 Hz, 1H), 7.33 (dd, J = 5.0, 3.0 Hz, 1H), 7.30 (app. t, J = 7.6 Hz, 1H), 1.38 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.0, 145.0, 139.9, 136.0, 129.4, 125.3, 125.0, 124.8, 124.6, 124.2, 121.6, 83.8, 25.0.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 30.0.

HRMS (ESI+): Calculated for $C_{18}H_{19}S_2BO_2Na$ ([M+Na]$^+$), 365.0821; found 365.0814.



4.1i **4.3i**

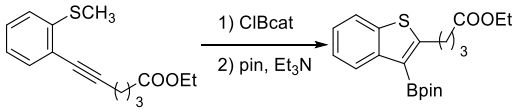
***N*,*N*-dimethyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)aniline (4.3i)**. A dram vial was charged with **4.1i** (80. mg, 0.30 mmol, 1.0 equiv) and toluene (0.2 mL). A separate vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the borane-containing vial, and this vial was then capped and heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.2 mL). A separate vial was then charged with pinacol (89 mg, 0.75 mmol, 2.5 equiv), Et_3N (0.62 mL, 4.5 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3i** as a yellow solid (68 mg, 60% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 6.3 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 2H), 3.02 (s, 6H), 1.37 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.2, 150.8, 145.4, 140.2, 130.7, 124.8, 124.3, 123.6, 123.5, 121.6, 111.8, 83.6, 40.6, 25.0.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.9.

HRMS (ESI+): Calculated for $C_{22}H_{26}SBNO_2Na$ ([M+Na]$^+$), 402.1679; found 402.1679.



4.1j **4.3j**

Ethyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)butanoate (4.3j). A dram vial was charged with **4.1j** (79 mg, 0.30 mmol, 1.0 equiv) and toluene (0.2 mL). A separate vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the borane-containing vial, and this vial was then capped and heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.2 mL). A separate vial was then charged with pinacol (89 mg, 0.75 mmol, 2.5 equiv), Et_3N (0.62 mL, 4.5 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified by column chromatography using an elution gradient from 100% hexanes to 10% EtOAc/hexanes. Product-containing fractions

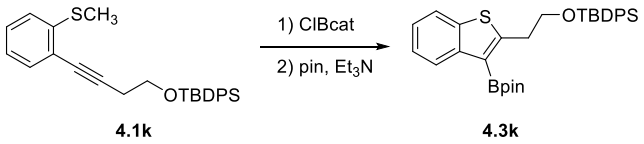
were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.3j** as a viscous oil (87 mg, 77% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.1 Hz, 1H), 7.27 (t, *J* = 7.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.30 (t, *J* = 7.4 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.09 (quin, *J* = 7.7 Hz, 2H), 1.40 (s, 12H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.4, 159.6, 144.5, 139.5, 125.1, 124.3, 123.6, 121.6, 83.2, 60.3, 33.7, 30.1, 27.7, 25.0, 14.3.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.3.

HRMS (ESI+): Calculated for $C_{20}H_{27}SBO_4Na$ ([M+Na]$^+$), 397.1625; found 397.1613.



4.1k **4.3k**

***tert*-Butyldiphenyl(2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)ethoxy)silane (4.3k)**. A dram vial was charged with **4.1k** (110 mg, 0.25 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (54 mg, 0.35 mmol, 1.4 equiv) and toluene (0.2 mL). The resulting homogenous solution from the borane-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1k**, and this vial was then capped and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.5 mL). A separate vial was then charged with pinacol (89 mg, 0.75 mmol, 2.5 equiv), Et_3N (0.63 mL, 4.5 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at

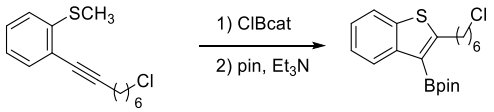
room temperature. The solution was concentrated in vacuo and the resulting residue was purified by column chromatography using an elution gradient from 100% hexanes to 5% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.3k** as a yellow oil (65 mg, 48% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (d. J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.9 Hz, 4H), 7.40 (d, J = 7.2 Hz, 2H), 7.35–7.32 (m, 5H), 7.23–7.25 (m, 1H), 3.98 (t, J = 6.7 Hz, 2H), 3.53 (t, J = 6.4 Hz, 2H), 1.32 (s, 12H), 1.07 (s, 9H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 156.9, 144.4, 140.0, 135.7, 133.9, 129.6, 127.7, 125.1, 124.1, 123.5, 121.5, 83.2, 65.3, 34.4, 27.0, 25.0, 19.3.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 28.9.

HRMS (ESI+): Calculated for $C_{32}H_{39}SBO_3SiNa$ ([M+ Na]$^+$), 565.2386; found 565.2408.



4.1m **4.3m**

***2-(2-(6-chlorohexyl)benzo[*b*]thiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.3m)**. A dram vial was charged with **4.1m** (80. mg, 0.30 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv) and toluene (0.2 mL). The resulting homogenous solution from the borane-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1m**, and this vial was then capped and heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.2 mL). A separate vial was then charged with pinacol (89 mg, 0.75 mmol, 2.5 equiv), Et_3N (0.63 mL, 4.5 mmol, 15

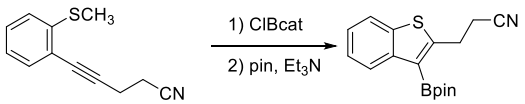
equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified by column chromatography using an elution gradient from 100% hexanes to 15% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.3m** as a yellow oil (0.10 g, 89% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.31 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.34 (td, J = 7.3, 1.0 Hz, 1H), 7.26–7.23 (m, 1H), 3.54 (t, J = 6.7 Hz, 2H), 3.23 (t, J = 7.5 Hz, 2H), 1.81–1.73 (m, 4H), 1.51–1.42 (m, 4H), 1.39 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 161.0, 144.6, 139.4, 125.0, 124.2, 123.5, 121.6, 83.2, 45.3, 32.7, 32.6, 30.8, 28.5, 26.7, 25.1.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.2.

HRMS (ESI+): Calculated for $C_{20}H_{28}SBO_2ClNa$ ([M+ Na]$^+$), 401.1493; found 401.1486.



4.1n **4.3n**

***3-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)propanenitrile (4.3n)**. A dram vial was charged with **4.1n** (60. mg, 0.30 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv) and toluene (0.2 mL). The resulting homogenous solution from the borane-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1n**, and this vial was then sealed and heated at 100 ^{o}C for 4 h. The reaction mixture was then

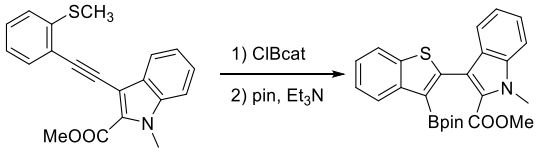
cooled to room temperature and then diluted with toluene (0.2 mL). A separate vial was then charged with pinacol (89 mg, 0.75 mmol, 2.5 equiv), Et_3N (0.63 mL, 4.5 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3n** as a yellow solid (64 mg, 65% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.36 (app. d, *J* = 8.0 Hz, 1H), 7.78 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.37 (ddd, *J* = 15.2, 6.8, 1.2 Hz, 1H), 7.30 (ddd, *J* = 15.1, 6.9, 1.3 Hz, 1H), 3.55 (t, *J* = 7.5 Hz, 2H), 2.76 (t, *J* = 7.7 Hz, 2H), 1.39 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 154.7, 144.3, 139.5, 125.6, 124.7, 124.3, 121.8, 119.0, 83.7, 27.0, 25.1, 20.1.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.0

HRMS (ESI+): Calculated for $C_{17}H_{20}SBNO_2Na$ ([M+ Na]$^+$), 336.1209; found 336.1206.



1o **3o**

***Methyl 1-methyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)-1*H*-indole-2-carboxylate (4.3o)**. A dram vial was charged with **4.1o** (116 mg, 0.350 mmol, 1.00 equiv). A separate vial was charged with

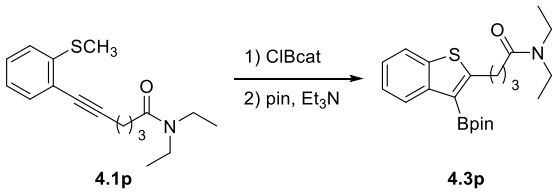
B-chlorocatecholborane (75 mg, 0.49 mmol, 1.4 equiv) and toluene (0.3 mL). The resulting homogenous solution from the borane-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1o**, and this vial was then capped and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.3 mL). A separate vial was then charged with pinacol (103 mg, 0.880 mmol, 2.50 equiv), Et_3N (0.73 mL, 5.3 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3o** as a yellow solid (98 mg, 63% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.33 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.44–7.34 (m, 4H), 7.14 (td, *J* = 7.3, 0.8 Hz, 1H), 4.14 (s, 3H), 3.68 (s, 3H), 1.18 (s, 6H), 1.07 (s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 163.0, 147.5, 144.4, 141.2, 138.3, 128.0, 126.6, 125.4, 125.2, 124.2, 123.8, 122.1, 121.6, 120.9, 117.3, 110.0, 83.1, 51.6, 32.2, 25.0, 24.7.

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

HRMS (ESI+): Calculated for $C_{25}H_{26}SBNO_4Na$ ($[M+ Na]^+$), 470.1578; found 470.1559.



4.1p 4.3p

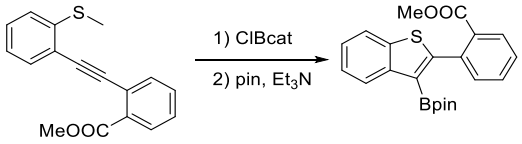
***N*,*N*-Diethyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)butanamide (4.3p)**. A dram vial was charged with **4.1p** (170 mg, 0.58 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (130 mg, 0.81 mmol, 1.4 equiv) and toluene (0.5 mL). The resulting homogenous solution from the borane-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1q**, and this vial was then capped and heated at 100 °C for 24 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.5 mL). A separate vial was then charged with pinacol (170 mg, 1.5 mmol, 2.5 equiv), Et_3N (1.1 mL, 7.9 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. At this time, the reaction mixture was diluted with 100 mL EtOAc and washed with water (3 × 10 mL) and brine (1 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography using an elution gradient from 100% hexanes to 40% EtOAc/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.3p** as a yellow solid (163 mg, 70% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.24 (dd, *J* = 7.4, 1.1 Hz, 1H), 3.36 (q, *J* = 7.1 Hz, 2H), 3.31 (t, *J* = 7.2 Hz, 2H), 3.23 (q, *J* = 7.1 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.10 (quint., *J* = 7.3 Hz, 2H), 1.38 (s, 12H), 1.11–1.08 (m, 6H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 171.9, 160.2, 144.6, 139.5, 125.1, 124.2, 123.5, 121.6, 83.2, 42.0, 40.1, 32.4, 30.4, 28.1, 25.1, 14.4, 13.2.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.3.

HRMS (ESI+): Calculated for $C_{22}H_{32}SNBO_3Na$ ([M+ Na]$^+$), 424.2098; found 424.2085.



4.1q **4.3q**

Methyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)benzoate (4.3q). A dram vial was charged with **4.1q** (93 mg, 0.33 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (71 mg, 0.46 mmol, 1.4 equiv) and toluene (0.3 mL). The resulting homogenous solution from the borane-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1q**, and this vial was then capped and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.3 mL). A separate vial was then charged with pinacol (97 mg, 0.83 mmol, 2.5 equiv), Et_3N (0.69 mL, 5.0 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.3q** as a solid (69 mg, 53% yield).

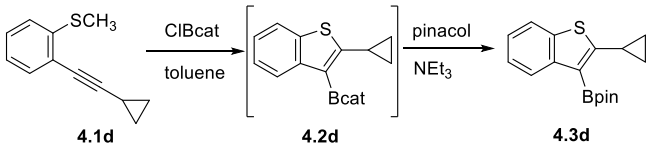
^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.32 (d. J = 8.0 Hz, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.52–7.45 (m, 3H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 3.64 (s, 3H), 1.18 (s, 12H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 167.6, 154.7, 143.9, 140.6, 136.8, 132.3, 131.8, 130.7, 129.8, 128.2, 125.6, 124.5, 124.0, 121.5, 83.2, 52.0, 24.8.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 29.2.

HRMS (ESI+): Calculated for $C_{22}H_{23}SBO_4Na$ ([M+ Na]$^+$), 417.1312; found 417.1305.

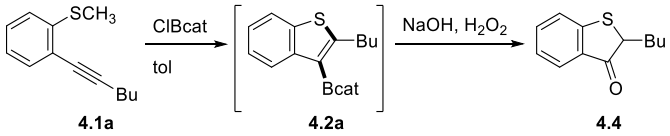
Multigram Scale Preparation of **4.3d**



In an N_2-filled glovebox, a Schlenk bomb was charged with a solution of **4.1d** (1.8 g, 9.7 mmol, 1.0 equiv) in toluene (3 mL) via pipette. A solution of *B*-chlorocatecholborane (2.1 g, 14 mmol, 1.4 equiv) in toluene (4.5 mL) was then added via pipette. The Schlenk bomb was then sealed, removed from the glovebox, and cooled to –78 °C using an isopropanol/dry ice bath. The headspace in the Schlenk bomb was then removed under reduced pressure (ca. 10 mTorr for 10 sec) before resealing. The solution was then stirred under static vacuum for 4 h at 100 °C in an oil bath. At this time, the reaction mixture was exposed to dynamic N_2 and cooled to room temperature before additional toluene (7 mL) was added. A solution of pinacol (2.9 g, 24 mmol, 3.0 equiv) in Et_3N (20. mL, 150 mmol, 15 equiv) was then added to the reaction mixture over 5 min and the resulting solution was stirred for 1 h at room temperature. The contents of the Schlenk bomb were then filtered over a bed of celite and rinsed with toluene (3 × 20 mL), and the filtrate was

concentrated in vacuo. The resulting 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 ca. 10 mTorr for 18 h to afford **4.3d** as a yellow solid (2.0 g, 69% yield). Spectral data were identical to those previously obtained for this compound.

In Situ Downstream Functionalization Reactions (Compounds **4.4**–**4.8**)



4.1a **4.2a** **4.4**

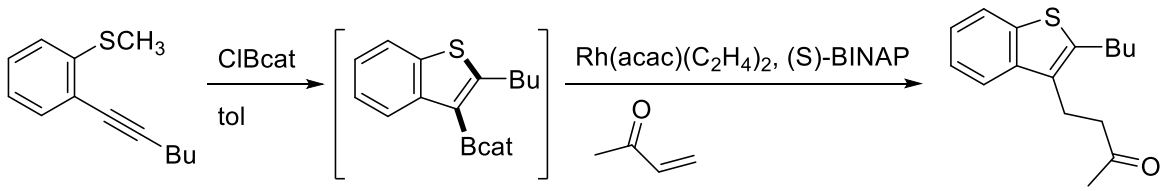
***2-Butylbenzo[*b*]thiophen-3(2*H*)-one (4.4)**. In an N_2-filled glovebox, a dram vial was charged with **4.1a** (0.10 g, 0.49 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (106 mg, 0.690 mmol, 1.40 equiv) and toluene (0.4 mL). The resulting homogenous solution from the borane-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1a**, and this vial was sealed, removed from the glovebox, and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and MeOH (1 mL) and a stir bar were added. NaOH (0.26 mL of a 3.0 M solution, 0.78 mmol, 1.6 equiv) and H_2O_2 (80. μL of a 30. wt% solution in H_2O, 0.78 mmol, 1.6 equiv) were then sequentially added. The reaction-containing vial was then capped and the solution was stirred for 1.5 h. The reaction mixture was then diluted with 100 mL EtOAc and washed with saturated NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution

gradient of 0% to 10% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.4** as a viscous yellow oil (73 mg, 72% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.54 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 3.20 (s, 1H), 2.07–2.03 (m, 1H), 1.95–1.90 (m, 1H), 1.64–1.58 (m, 1H), 1.36–1.33 (m, 3H), 0.88 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 202.5, 150.6, 136.9, 128.4, 127.6, 125.3, 124.4, 93.5, 39.5, 26.7, 22.8, 14.0.

HRMS (CI+): Calculated for $C_{12}H_{15}SO$ ($[M+H]^+$), 207.0844; found 207.0844.



4.1a **4.2a** **4.5**

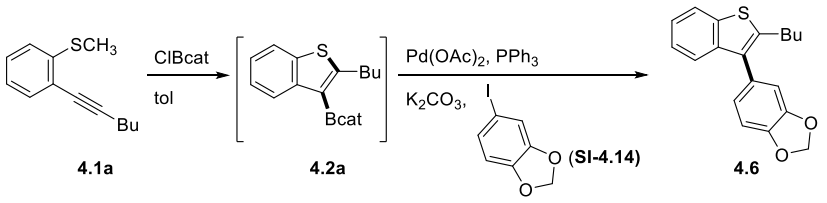
4-(2-Butylbenzo[*b*]thiophen-3-yl)butan-2-one (4.5). In an N_2-filled glovebox, a dram vial was charged with **4.1a** (0.200 g, 0.980 mmol, 2.00 equiv) and 0.8 mL toluene. A separate vial was charged with *B*-chlorocatecholborane (0.212 g, 1.37 mmol, 2.80 equiv). The resulting homogenous solution from the first vial was then added dropwise over ca. 1 min to the boron-containing vial, and this mixture was heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature. A separate dram vial was charged with (S)-BINAP (15 mg, 0.25 mmol, 0.050 equiv) and a stir bar. A third dram vial was charged with $Rh(acac)(C_2H_4)_2$ (3.8 mg, 0.15 mmol, 0.030 equiv) and dioxane (0.5 mL). This solution was then added to the vial containing (S)-BINAP via pipette. To this vial was added the cooled reaction mixture, which was subsequently rinsed with dioxane (0.5 mL)

to ensure quantitative transfer. The vial containing the resulting reaction mixture was then sealed with a septum vial cap, removed from the glovebox, and placed under dynamic N_2. Et_3N (0.34 mL, 2.5 mmol, 5.0 equiv), H_2O (0.1 mL), and methyl vinyl ketone (40. μL, 0.49 mmol, 1.0 equiv) were sequentially added via syringe. The vial was then removed from dynamic N_2, sealed with electrical tape, and heated to 100 °C. The reaction mixture then stirred for 3 h before being cooled to room temperature. The reaction mixture was diluted with 200 mL DCM and washed with saturated aqueous $NaHCO_3$ (1 × 20 mL), and water (3 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 20% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.5** as a yellow oil (91 mg, 71% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 7.1, 1.1 Hz, 1H), 7.28 (dd, *J* = 7.1, 1.1 Hz, 1H), 3.08 (t, *J* = 7.7 Hz, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.74 (t, *J* = 7.7 Hz, 2H), 2.15 (s, 3H), 1.73–1.68 (m, 2H), 1.49–1.43 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 207.9, 141.3, 139.8, 138.5, 129.6, 123.9, 123.5, 122.4, 120.9, 43.4, 33.8, 30.1, 28.2, 22.5, 20.3, 14.0.

HRMS (ESI+): Calculated for $C_{16}H_{20}SONa$ ($[M+Na]^+$), 283.1133; found 283.1141.

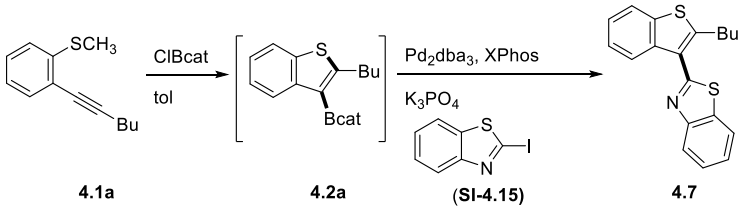


5-(2-Butylbenzo[*b*]thiophen-3-yl)benzo[*d*][1,3]dioxole (4.6). In an N_2-filled glovebox, a dram vial was charged with **4.1a** (82 mg, 0.40 mmol, 1.3 equiv). A separate vial was charged with *B*-chlorocatecholborane (86 mg, 0.56 mmol, 1.8 equiv) and toluene (0.3 mL). The resulting homogenous solution from the boron-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1a**, and this vial was sealed and heated at 100 ^{o}C for 4 h. The reaction mixture was then cooled to room temperature. A separate dram vial was charged with $Pd(OAc)_2$ (9 mg, 0.04 mmol, 0.1 equiv), PPh_3 (21 mg, 0.080 mmol, 0.25 equiv), K_2CO_3 (0.20 mL of a 2.0 M solution, 0.40 mmol, 1.3 equiv), and EtOH (0.5 mL). This solution was then added to the vial containing the reaction mixture via pipette. A third dram vial was charged with **SI-4.14** (79 mg, 0.32 mmol, 1.0 equiv) and toluene (0.5 mL). This solution was then added to the vial containing the reaction mixture, and a stir bar was added. This vial was sealed and removed from the glovebox, and heated at 80 ^{o}C while stirring for 24 h. The reaction mixture was then diluted with 150 mL DCM and washed with saturated NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.6** as a viscous yellow oil (65 mg, 66% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.83 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.52–7.51 (m, 1H), 7.33–7.30 (m, 2H), 7.0 (d, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 1.3 Hz, 1H), 6.86 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.06 (s, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 1.71 (q, *J* = 7.7 Hz, 2H), 1.49–1.43 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 147.8, 146.9, 142.6, 140.6, 138.2, 133.1, 129.3, 124.2, 123.8, 123.6, 122.6, 122.2, 110.6, 108.6, 101.2, 34.0, 28.7, 22.4, 13.9.

HRMS (CI+): Calculated for $C_{19}H_{18}SO_2$ ($[M]^+$), 310.1028; found 310.1028.



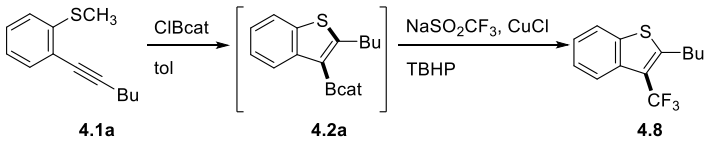
2-(2-Butylbenzo[*b*]thiophen-3-yl)benzo[*d*]thiazole (4.7). In an N_2-filled glovebox, a dram vial was charged with **4.1a** (123 mg, 0.600 mmol, 2.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (129 mg, 0.84 mmol, 2.8 equiv) and toluene (0.5 mL). The resulting homogenous solution from the boron-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1a**, and this vial was sealed and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature. A separate 20 mL scintillation vial was charged with Pd_2dba_3 (9 mg, 0.02 mmol, 0.05 equiv), XPhos (14 mg, 0.030 mmol, 0.10 equiv), **SI-4.15** (78 mg, 0.30 mmol, 1.0 equiv), K_3PO_4 (127 mg, 0.600 mmol, 1.00 equiv), and a stir bar. To this scintillation vial was added the contents from the dram vial, and 1-butanol (1.0 mL) was subsequently added. This vial was sealed and removed from the glovebox, and heated at 100 °C while stirring for 21 h. The reaction mixture was then diluted with 150 mL Et_2O, filtered over celite, washed with water (2 × 10

mL), and brine (1 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.7** as a yellow solid (56 mg, 58% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.26 (d, *J* = 8.1 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.2 Hz, 1H), 7.46 (t, *J* = 7.1 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.1 Hz, 1H), 3.25 (t, *J* = 7.7 Hz, 2H) 1.80 (q, *J* = 7.7 Hz, 2H), 1.49–1.43 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 161.5, 153.5, 149.8, 139.0, 137.9, 135.4, 126.3, 125.5, 125.3, 125.0, 124.5, 123.5, 123.2, 122.1, 121.5, 33.8, 29.5, 22.6, 13.9.

HRMS (CI+): Calculated for $C_{19}H_{17}S_2N$ ([M]$^+$), 323.0802; found 323.0800.



4.1a **4.2a** **4.8**

***2-Butyl-3-(trifluoromethyl)benzo[*b*]thiophene (4.8)**. In an N_2-filled glovebox, a dram vial was charged with **4.1a** (0.10 g, 0.49 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (76 mg, 0.49 mmol, 1.0 equiv) and toluene (0.4 mL). The resulting homogenous solution from the boron-containing vial was then added dropwise over ca. 1 min to the vial containing **4.1a**, and this vial was sealed and heated at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and the vial was removed from the glovebox. A round bottom flask was charged with $NaSO_2CF_3$ (230 mg, 1.5 mmol, 3.0 equiv), CuCl (49 mg, 0.49 mmol, 1.0 equiv), MeOH (1.0 mL), H_2O (0.8 mL),

and a stir bar. To this flask was added the contents of the reaction-mixture containing vial, and this vial was rinsed with DCM (0.8 mL) and added to the flask. The flask was then sparged for 1 minute with N_2 before being cooled to 0 °C. *tert*-Butyl hydrogen peroxide (TBHP, 0.34 mL of a 70. wt% in H_2O solution, 2.5 mmol, 5.0 equiv) was added via syringe over 2 min. The reaction mixture was stirred while warming to room temperature under dynamic N_2 for 18 h. The reaction mixture was then diluted with 150 mL Et_2O, filtered over celite, washed with saturated aqueous $NaHCO_3$ (1 × 15 mL), saturated aqueous NaS_2O_3 (1 × 15 mL), water (1 × 15 mL), and brine (1 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using 100% pentane as the eluent. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.8** as a white solid (47 mg, 37% yield).

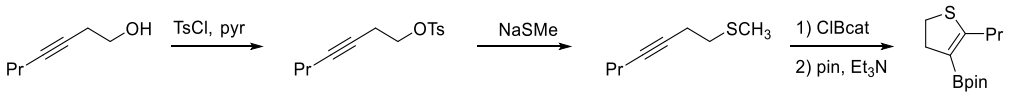
^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.90 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.41 (td, J = 7.2, 1.1 Hz, 1H), 7.35 (td, J = 7.2, 1.1 Hz, 1H), 3.09–3.06 (m, 2H), 1.75 (q, J = 7.5 Hz, 2H), 1.46 (sext., J = 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 150.9 (q, J = 34 Hz), 137.7, 136.7, 125.1, 124.6, 123.6 (q, J = 272.3 Hz), 122.6 (q, J = 2.7 Hz), 122.0,120.1 (q, J = 32.8 Hz), 33.9, 29.1 (app. d, J = 2.0 Hz), 22.6, 13.9.

^{19}F NMR ($CDCl_3$, 565 MHz): δ 56.2 (s, 3F).

HRMS (CI+): Calculated for $C_{13}H_{13}SF_3$ ($[M]^+$), 258.0690; found 258.0697.

Borylated Dihydrothiophene Syntheses (Compounds **4.21a** and **4.21b**)



SI-4.16 **SI-4.17** **4.18** **4.21a**

***Hept-3-yn-1-yl 4-methylbenzenesulfonate (SI-4.17)** was synthesized using a literature procedure[9] in 58% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.80 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 2H), 4.06 (q, *J* = 7.3 Hz, 2H), 2.51 (d, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 2.5 (d, *J* = 7.9 Hz, 2H), 1.44 (quin, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). This spectrum is in agreement with previously reported spectral data.[9]

***Hept-3-yn-1-yl(methyl)sulfane (4.18)**. A round bottom flask was charged with NaSMe (620 mg, 8.8 mmol, 2.0 equiv) and a stir bar. The flask was then sealed with a rubber septum and placed under dynamic N_2. To this flask was added DMF (5.5 mL). A separate flask was charged with **SI-4.17** (1.2 g, 4.4 mmol, 1.0 equiv), and DMF (5.5 mL). This solution was then transferred via syringe to the NaSMe-containing flask. The solution was then stirred for 18 h under dynamic N_2. At this time, the reaction mixture was diluted with 200 mL Et_2O, and the organic layer was washed with H_2O (8 × 15 mL) and brine (1 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford **4.18** as a yellow liquid that was used without further purification (260 mg, 41% yield).

^{1}H NMR (CDCl3, 600 MHz): δ 2.63 (t, *J* = 8.0 Hz, 2H), 2.47–2.44 (m, 2H), 2.14–2.11 (m, 5H), 1.50 (sext., *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 81.4, 78.6, 33.9, 22.5, 20.9, 20.0, 15.8, 13.6.

HRMS (CI+): Calculated for $C_8H_{14}SH$ ($[M+H]^+$), 143.0894; found 143.0896.

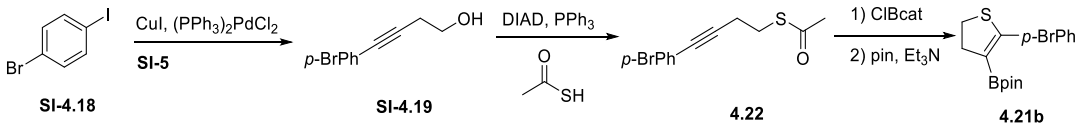
***4,4,5,5-tetramethyl-2-(2-propyl-4,5-dihydrothiophen-3-yl)-1,3,2-dioxaborolane (4.21a)**. In an N_2-filled glovebox, a dram vial was charged with **4.18** (77 mg, 0.54 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (120 mg, 0.76 mmol, 1.4 equiv) and toluene (0.4 mL). The resulting homogenous solution from the boron-containing vial was then added dropwise over ca. 1 min to the vial containing **4.18**, and this vial was then capped and heated at 100 ^oC for 4 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.4 mL). A separate vial was then charged with pinacol (96 mg, 0.81 mmol, 1.5 equiv), Et_3N (0.37 mL, 2.7 mmol, 5 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting 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 ca. 10 mTorr for 18 h to afford **4.21a** as a yellow oil (83 mg, 60% yield).

^1H NMR ($CDCl_3$, 600 MHz): δ 3.13 (t, J = 8.6 Hz, 2H), 2.90 (t, J = 8.4 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 1.53 (q, J = 7.4 Hz, 2H), 1.24 (s, 12H), 0.90 (t, J = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 161.8, 82.8, 39.9, 33.5, 32.8, 24.9, 23.2, 13.6.

^{11}B NMR (CDCl3, 193 MHz): δ 28.5.

HRMS (ESI+): Calculated for $C_{13}H_{24}SBO_2$ ($[M+H]^+$), 255.1593; found 255.1597.



SI-4.18 SI-4.19 4.22 4.21b

***4-(4-bromophenyl)but-3-yn-1-ol (SI-4.19)** was synthesized using a literature procedure[10] in 82% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.42 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 3.82 (q, J = 5.6 Hz, 2H), 2.68 (t, J = 6.3 Hz, 2H), 1.76 (d, J = 6.3 Hz, 1H). This spectrum is in agreement with previously reported spectral data.[10]

S-(4-(4-bromophenyl)but-3-yn-1-yl) ethanethioate (4.22) was synthesized using an adapted procedure.[11] A round bottom flask was charged with PPh_3 (3.6 g, 14 mmol, 1.6 equiv) and a stir bar. This flask was sealed with a rubber septum and then THF (36 mL) was added. This solution was then cooled to 0 ^{o}C with an ice water bath. To this flask was added diisopropyl azodicarboxylate (DIAD, 2.7 mL, 14 mmol, 1.6 equiv) via syringe over ca. 10 min. This reaction mixture stirred at 0 ^{o}C for 30 min before a solution of **SI-4.19** (2.0 g, 8.9 mmol, 1.0 equiv) and thioacetic acid (1.0 mL, 14 mmol, 1.6 equiv) in THF (12 mL) was added over ca. 5 min. The reaction mixture was then stirred under dynamic N_2 for 18 h while warming to room temperature. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 150 mL Et_2O, and the organic layer was washed with saturated aqueous NH_4Cl (1 × 30 mL), water (1 × 30 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. To the resulting solid/oil mixture was added 50 mL of hexanes, and the resulting solution was filtered over a bed of celite to remove the precipitated PPh_3O. The filtrate was then concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 10% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and

volatiles were removed at ca. 10 mTorr for 18 h to afford **4.22** as a yellow solid (2.1 g, 85% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 3.10 (t, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 195.5, 133.2, 131.6, 122.5, 122.2, 89.0, 80.9, 30.8, 28.4, 20.7.

HRMS (CI+): Calculated for $C_{12}H_{12}BrOS$ ($[M+H]^+$), 282.9792; found 282.9804.

2-(2-(4-bromophenyl)-4,5-dihydrothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.21b). In an N_2-filled glovebox, a dram vial was charged with **4.22** (110 mg, 0.39 mmol, 1.0 equiv). A separate vial was charged with *B*-chlorocatecholborane (83 mg, 0.54 mmol, 1.4 equiv) and toluene (0.3 mL). The resulting homogenous solution from the borane-containing vial was then added dropwise over ca. 1 min to the vial containing **4.22**, and this vial was then capped and heated at 100 ^{o}C for 2 h. The reaction mixture was then cooled to room temperature and then diluted with toluene (0.3 mL). A separate vial was then charged with pinacol (170 mg, 1.4 mmol, 3.5 equiv), Et_3N (0.83 mL, 6.0 mmol, 15 equiv), and a stir bar. The reaction mixture was added dropwise over ca. 1 min to this vial, which was capped, removed from the glovebox, and then stirred for 1 h at room temperature. The solution was concentrated in vacuo and the resulting residue was purified by column chromatography using an elution gradient from 100% hexanes to 40% DCM/hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **4.21b** as a yellow solid (76 mg, 52% yield).

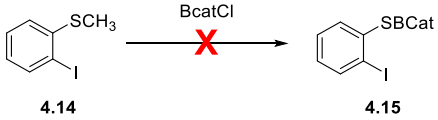
^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.41 (app. d, J = 8.5 Hz, 2H), 7.36 (app. d, J = 8.5 Hz, 2H), 3.27 (t, J = 8.9 Hz, 2H), 3.12 (t, J = 8.3 Hz, 2H), 1.20 (s, 12H).

^{13}C NMR (CDCl3, 151 MHz): δ 155.4, 134.5, 130.9, 130.8, 122.7, 83.3, 42.1, 34.1, 24.7.

^{11}B NMR ($CDCl_3$, 193 MHz): δ 28.8.

HRMS (ESI+): Calculated for $C_{16}H_{20}SBBrO_2Na$ ($[M+Na]^+$), 389.0361; found 389.0376.

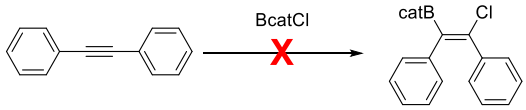
*****Procedure for ^{1}H NMR Spectroscopic characterization of the rate of demethylation of 2-iodothioanisole **4.14**



4.14 **4.15**

This procedure was performed in an N_2-filled glovebox. A dram vial was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv) and 0.3 mL of d_8-toluene. To this vial was sequentially added **4.14** (75 μL, 0.50 mmol, 1.0 equiv) and mesitylene (40. μL, 0.17 mmol, 0.33 equiv) via syringe. The contents of this vial were then transferred to a J. Young NMR tube, which was sealed, and then removed from the glovebox and heated to 100 °C. Single-scan ^{1}H and ^{11}B NMR spectra were taken at time points *t* = 0 h, 2 h, and 4 h for which the tube was briefly removed from the heating bath. The resonances corresponding to **4.14** were compared to the internal standard to determine the percent of **4.14** remaining at *t* = 4 h (>95% **4.14** remaining at *t* = 4 h).

*****Procedure for ^{1}H NMR spectroscopic characterization of the rate of chloroboration of diphenylacetylene **4.16**



4.16 **4.17**

This procedure was performed in an N_2-filled glovebox. A dram vial was charged with *B*-chlorocatecholborane (0.108 g, 0.700 mmol, 1.40 equiv) and 0.3 mL of d_8-toluene. To this vial was sequentially added **4.16** (75 μL, 0.50 mmol, 1.0 equiv) and mesitylene (40. μL, 0.17 mmol, 0.33 equiv) via syringe. The contents of this vial were then transferred to a J. Young NMR tube, which was sealed, and then removed from the glovebox and heated to 100 ^{o}C. Single-scan ^{1}H and ^{11}B NMR spectra were taken at time points t = 0 h, 2 h, and 4 h for which the tube was briefly removed from the heating bath. The resonances corresponding to **4.16** were compared to the internal standard to determine the percent of **4.16** remaining at t = 4 h (>95% **4.16** remaining at t = 4 h).

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Chapter 5

Mechanistic Insight into the Thioboration Reaction

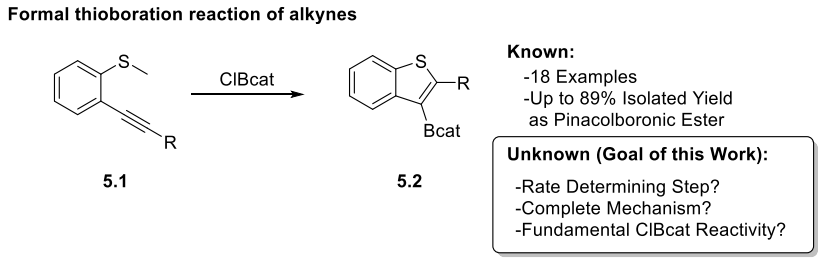
Abstract: The catalyst-free formal thioboration reaction of alkynes is explored to gain mechanistic insight into *B*-chlorocatecholborane (ClBcat) in its mechanistically new role as an alkynophilic Lewis acid in electrophilic cyclization reactions. Hammett σ+ correlation parameters show electronic effects dominating the reaction rate with product formation accelerated by electron donating groups. The commercially available ClBcat reagent activates alkynes despite being less electrophilic than other known alkyne-activating boron reagents (e.g., $B(C_6F_5)_3$). The experiments in this chapter are part of a larger mechanistic story that is being worked on with graduate student Adena Issaian. All experiments described in this chapter are my own work.

Introduction

Addition of boron/sulfur, boron/oxygen, and boron/nitrogen formal equivalents to C–C π bonds is an underdeveloped area of methodology, despite its promising efficiency in route to the synthesis of synthetically and biologically useful heterocycles.[1–3] Early work showed that highly electrophilic $B(C_6F_5)_3$ could activate alkynes towards nucleophilic cyclization with oxygen.[4–6] The resulting zwitterionic heterocycles, however, are unreactive for downstream reactivity and thus were limited in their use as synthetic building blocks. Development of methods that effect such additions using practical regents and resulting in products capable of participating in the rich downstream chemistry of boron would thus be of high impact. We recently reported the first two examples of employing readily available *B*-chlorocatecholborane (ClBcat) as the cyclization reagent for boron/oxygen and boron/sulfur additions.[1,2] This reaction is catalyst free and the first to produce synthetically useful building blocks from formal boron/sulfur and boron/oxygen additions to alkynes.

Our previous reports open the possibility of a suite of related new reactions employing additional synthetically amenable boron reagents. Ingleson showed that BCl_3 can also induce such cyclizations, although it cannot demethylate without additional reagents, beginning the expansion of such reactivity to other reagents.[7] Now pressing questions arise: do these more synthetically useful boron reagents proceed through activation of the alkyne despite their attenuated electrophilicity compared to $B(C_6F_5)_3$? Experiments herein provide preliminary insight towards the answer to this question as guiding principles for developing a family of related reactions (Figure 5.1).

Figure 5.1. Recently developed formal thioboration reaction of alkynes, and what is known about this reaction (chapter four) and unknown (this work).



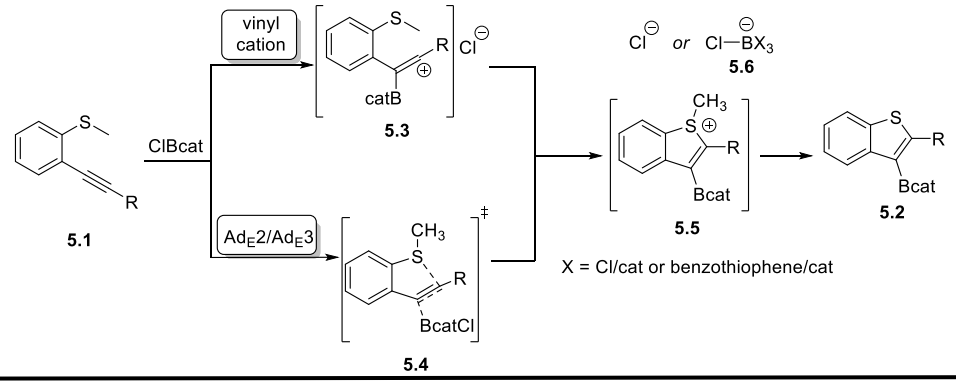
The outcomes of this study are significant because they provide information about the fundamental reactivity of ClBcat—and by extension, other practical, readily available, and synthetically useful boron reagents—towards alkynes and their potential in the emerging area of electrophilic cyclization of heteroatoms with alkynes.

Results and Discussion

The mechanistic pathways considered here for the thioboration reaction in the synthesis of borylated benzothiophenes are shown in Scheme 5.1. Both of these possible reaction routes take advantage of Lewis acidic boron-induced activation of the alkyne in thioanisole **5.1**. In the top pathway, this carbophilic activation is sufficiently strong to generate a formal vinyl carbocation in intermediate **5.3**. Cyclization then proceeds through

nucleophilic attack by sulfur, which gives rise to the intermediate **5.5**, which is common to both pathways. In the bottom pathway, ClBcat is insufficiently electrophilic to activate the alkyne in the absence of electronically mitigating simultaneous nucleophilic attack by sulfur. Simultaneous attack leads to an Ad_E2/Ad_E3[8] mechanistic pathway (via transition state **5.4**) to form the shared intermediate **5.5**. In both pathways, **5.5** is then demethylated by chloride ion or possibly a boron-based chloride delivery agent **5.6**.[9] Demethylation yields the final 3-borylated-benzothiophene product **5.2**. Previous experiments ruled out alternative mechanistic pathways that proceed through either B–S σ-bond formation/cyclization or haloboration/cyclization routes.[1]

Scheme 5.1. Possible mechanistic pathways for the formal thioboration of alkynes.

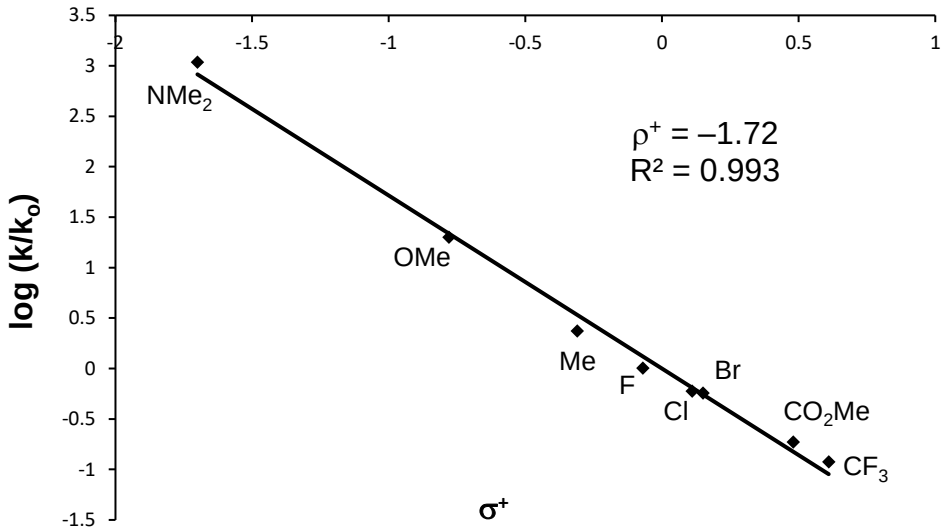


The major remaining mechanistic questions in this system are: 1) is ClBcat sufficiently electrophilic to produce a formal carbocation or is the cyclization concerted, 2) which step is rate-determining, and 3) how does substrate structure affect activation by boron?

A Hammett study was conducted to aid in determination of the degree of positive charge build up on the alkyne and possibly also to identify the rate-determining step in the reaction (Figure 5.2). The relative reaction rates of *para*-substituted alkynylthioanisole derivatives **5.1** were assessed via competition experiments in which a solution of ClBcat

was added to a solution of 3.0 equiv of a *para*-substituted alkynylthioanisole and 3.0 equiv of the parent unsubstituted alkynylthioanisole in toluene-d_8. These reactions were monitored by ^{1}H NMR spectroscopy using mesitylene as an internal standard and found to be complete in 2–4 h. The product ratios did not change upon standing.

Figure 5.2. Hammett study showing correlation between log(k/k$_o$) and σ$^+$.



A variety of substituents were tested, including electron-withdrawing (*p*-CF_3, *p*-CO_2Me), neutral (*p*-F), and electron-donating (*p*-NMe_2, *p*-OMe, *p*-Me) substituents. The product ratios obtained through this series of competition experiments were then plotted against σ$^+$ and σ$_p$. A better fit was obtained when the log of the relative reaction rates were plotted against σ$^+$ (R^2 = 0.993) than against σ$_p$ (R^2 = 0.957) (see Experimental Section for plot of log(k/k$_o$) vs σ$_p$), providing a ρ^+ value of –1.72 (Figure 5.2). The negative slope indicates that there is positive charge character buildup in the rate-determining step.

Importantly, the opposite effect would be expected if dealkylation were rate-determining, because dealkylation decreases the positive character by neutralizing the sulfur. Therefore, the data rules out dealkylation as the rate-determining step. We next

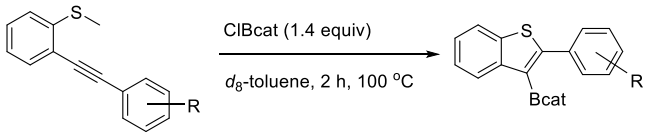
considered if the rate-determining step involved formation of a vinylic cation or a simultaneous boron activation sulfur ring-closing event to form the sulfonium species. The low absolute value of ρ^+ suggests that electronic resonance stabilization effects are not as significant as that previously obtained in systems with formal carbocations (e.g., ρ^+ values that generate benzylic carbocations are typically greater than 4.0).[10,11] Thus, we hypothesize that the mechanistic pathway for the formal thioboration reaction proceeds through the Ad_E2/Ad_E3 pathway (Scheme 5.1, bottom).

The substituent pattern was varied on the phenyl ring to probe steric effects on rate of cyclization in the thioboration reaction (Table 5.1). Two substituents (R = Me, Cl) were selected to incorporate both a moderate electron-donating group and a moderate electron-withdrawing group. These 2-alkynylthioanisole derivatives were subjected to standard thioboration conditions (1.3 M toluene-d_8 with respect to starting material, 1.4 equiv ClBcat, 100 °C) and examined by ^{1}H NMR spectroscopy at t = 2 h using mesitylene as an internal standard. Each reaction was run in duplicate and yields are reported with the standard deviation of two runs.

If sterics were the dominating factor on rate of the thioboration reaction, then *ortho*-substituted phenyl rings would result in lower yields at a given reaction time. When R = Me, however, all three substitution patterns provided statistically comparable yields (~88%). This indicates a minimal steric influence in this system. Yet the corresponding chloride system displayed a moderate steric effect. When R = Cl, the *p*-Cl provided the highest ^{1}H NMR yield (73 ± 1%), and both *o*-Cl and *m*-Cl provided comparable yields (57 ± 3% and 54 ± 3%, respectively). Given that the A-value for methyl is 1.7 and the A-value

for chloride is 0.43 (i.e. methyl is sterically larger than chloride),[12] the direction of this effect is clearly subtle.

Table 5.1. Varying the substituents: sterics vs. electronic effects in the thioboration reaction.



5.1 **5.2**

Entry	R Group	^{1}H NMR Yield (%)[a] **5.2**
1	*o*-Cl	57 ± 3
2	*m*-Cl	54 ± 3
3	*p*-Cl	73 ± 1
4	*o*-Me	85 ± 2
5	*m*-Me	89 ± 3
6	*p*-Me	88 ± 1

[a]Yield is reported as an average of two runs, and the error is reported as standard deviation of two runs.

In addition to the mechanistic insight gained from the aforementioned experiments, efforts were made to isolate a catecholboronic ester thioboration product **5.2**. The purpose of this experiment is to probe the stability of the catecholboronic ester derivatives to see if the previously employed transesterification step to the pinacolboronic ester was necessary prior to downstream functionalization. Alkynylthioanisole **5.1** (R = *p*-BrPh) was subjected to the standard thioboration conditions to yield catecholboronic ester **5.2**, which was then isolated by filtration to give an analytically pure white solid in 69% yield. This compound did not exhibit air or moisture sensitivity during short term handling (1–2 days).

Conclusions

Experiments towards the understanding of the complete mechanistic picture of the formal thioboration reaction of alkynes to generate borylated benzothiophenes have been

conducted. On the basis of Hammett studies, cyclization is determined to be the rate determining step; the demethylation step is ruled out due to the negative ρ^+ slope of the Hammett graph. It is also concluded from the magnitude of the ρ^+ value that the likely cyclization pathway is not through a vinyl cation, but rather through an Ad_E2/Ad_E3 concerted pathway. Steric and electronic effects were probed to see how they influenced the rate of reaction. Electronic effects were found to have a marked effect on reaction rate, and steric effects played a subtle role. These studies contribute to a broader mechanistic picture that can serve as a springboard for future formal electrophilic cyclization reaction design strategies.

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Experimental

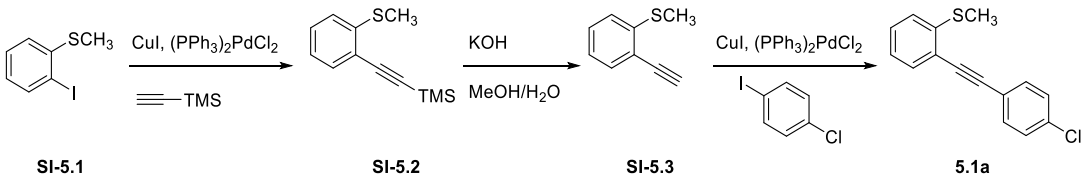
General Considerations

All chemicals were used as received from commercial sources unless otherwise noted. Triethylamine, acetonitrile, toluene, tetrahydrofuran, *N*,*N*-dimethylformamide, and dichloromethane were purified by passage through an alumina column under argon pressure on a push-still solvent system. d_8-Toluene was dried over CaH_2, degassed using three freeze-pump-thaw cycles, and vacuum transferred prior to use. All manipulations were conducted 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-500 spectrometer outfitted with a cryoprobe, or a Bruker AVANCE-600 spectrometer outfitted with a cryoprobe. All boron nuclear magnetic resonance (^{11}B NMR) spectra and fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker AVANCE-600 spectrometer. 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 = 2.08 ppm for d_8-toluene; δ = 77.2 ppm for $CDCl_3$ or δ = 20.4 ppm for d_8-toluene 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.

Synthetic Procedures

Preparation of Substrates **5.1a**–**5.1f** for the Hammett Study

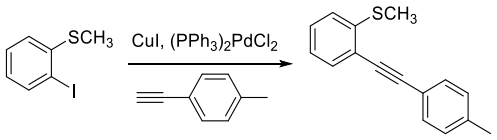


SI-5.1 **SI-5.2** **SI-5.3** **5.1a**

Trimethyl((2-(methylthio)phenyl)ethynyl)silane (SI-5.2) was synthesized using a literature procedure[1] in 98% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.42 (dd, J = 7.6, 0.2 Hz, 1H), 7.27 (td, J = 8.0, 1.5 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.06 (td, J = 7.6, 1.1 Hz, 1H), 2.48 (s, 3H), 0.30 (s, 9H). This spectrum is in agreement with previously reported spectral data.[1]

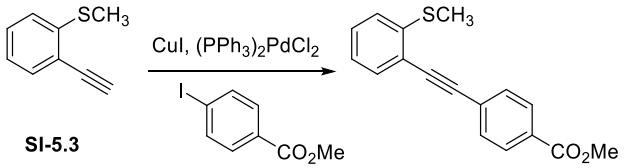
(2-Ethynylphenyl)(methyl)sulfane (SI-5.3) was synthesized using a literature procedure[1] in 99% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.46 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 3.48 (s, 1H), 2.49 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]

(2-((4-Chlorophenyl)ethynyl)phenyl)(methyl)sulfane (5.1a) was synthesized using a literature procedure[1] in 99% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.50 (d, J = 10.2 Hz, 2H), 7.47 (d, J = 9.1 Hz, 1H), 7.33–7.30 (m, 3H), 7.18 (d, J = 9.6Hz, 1H), 7.12 (t, J = 9.1 Hz, 1H), 2.52 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]



SI-5.1 **5.1b**

Methyl(2-(p-tolylethynyl)phenyl)sulfane (5.1b) was synthesized using a literature procedure[2] in 99% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48–7.46 (m, 3H), 7.29 (td, *J* = 7.7, 1.4 Hz, 1H), 7.18–7.15 (m, 3H), 7.11 (td, *J* = 7.5, 1.2 Hz, 1H), 2.51 (s, 3H), 2.37 (s, 3H). This spectrum is in agreement with previously reported spectral data.[2]



SI-5.3 **5.1c**

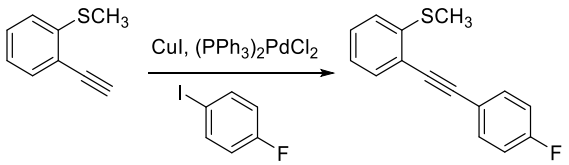
Methyl 4-((2-(methylthio)phenyl)ethynyl)benzoate (5.1c). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with methyl 4-iodobenzoate (580 mg, 2.2 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (77 mg, 0.011 mmol, 0.050 equiv), CuI (42 mg, 0.22 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-5.3** (420 mg, 2.9 mmol, 1.3 equiv) was dissolved in Et_3N (6.1 mL). This solution was then added to the reaction vial via pipette, and the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 15% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and

volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1c** as a yellow solid (470 mg, 75% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.02 (dt, *J* = 8.4, 1.7 Hz, 2H), 7.63 (dt, *J* = 8.4, 1.7 Hz, 2H), 7.49 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.33 (td, *J* = 8.0, 1.5 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.13 (td, *J* = 7.6, 1.1 Hz, 1H), 3.93 (s, 3H), 2.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 166.7, 142.2, 132.5, 131.6, 129.7, 129.6, 129.4, 128.0, 124.4, 124.3, 120.8, 95.1, 89.9, 52.4, 15.2.

HRMS (CI+): Calculated for $C_{17}H_{14}O_2S$ ($[M]^+$), 282.0714; found 282.0714.



SI-5.3 **5.1d**

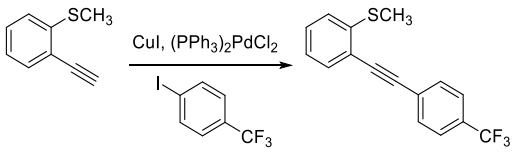
(2-((4-Fluorophenyl)ethynyl)phenyl)(methyl)sulfane (5.1d). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with methyl 4-fluoroiodobenzoate (0.24 mL, 2.1 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (77 mg, 0.011 mmol, 0.050 equiv), CuI (40. mg, 0.21 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-5.3** (370 mg, 2.5 mmol, 1.2 equiv) was dissolved in Et_3N (6.4 mL). This solution was then added to the reaction vial via pipette, and the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer

was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1d** as a yellow solid (493 mg, 97% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.56 (ddd, *J* = 8.8, 5.4, 2.2 Hz, 2H), 7.47 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.31 (td, *J* = 7.9, 1.4 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.11 (td, *J* = 7.6, 1.1 Hz, 1H), 7.05 (tt, *J* = 8.8, 2.1 Hz, 2H), 2.51 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 162.8 (d, *J* = 249.8 Hz), 141.8, 133.6 (d, *J* = 8.3 Hz), 132.3, 129.0, 124.3 (d, *J* = 28.3 Hz), 121.3, 119.4 (d, *J* = 3.5 Hz), 115.9, 115.7, 94.9, 86.7, 15.2.

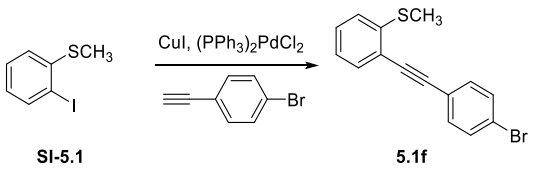
HRMS (CI+): Calculated for $C_{15}H_{11}SF$ ($[M]^+$), 242.0565; found 242.0557.



SI-5.3 **5.1e**

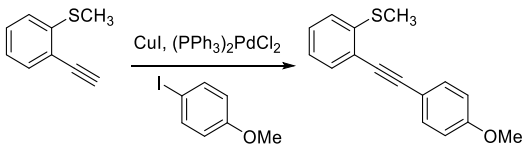
Methyl(2-((4-(trifluoromethyl)phenyl)ethynyl)phenyl)sulfane (5.1e). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with methyl 4-iodobenzotrifluoride (0.31 mL, 2.1 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (77 mg, 0.011 mmol, 0.050 equiv), CuI (40. mg, 0.21 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-5.3** (373 mg, 2.5 mmol, 1.2 equiv) was dissolved in Et_3N (6.4 mL). This solution was then added to the reaction

vial via pipette, and the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL EtOAc and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1e** as a yellow oil (540 mg, 88% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.50 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.34 (td, *J* = 7.8, 1.4 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.13 (td, *J* = 7.5, 1.0 Hz, 1H), 2.53 (s, 3H). This spectrum is in agreement with previously reported spectral data.[3]



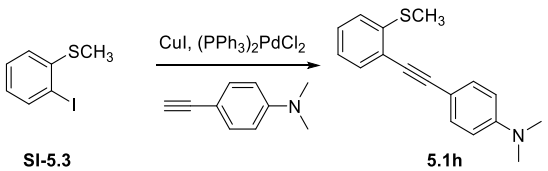
SI-5.1 **5.1f**

(2-((4-Bromophenyl)ethynyl)phenyl)(methyl)sulfane (5.1f) was synthesized using a literature procedure[1] in 86% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.50–7.46 (m, 3H), 7.44–7.43 (m, 2H), 7.32 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 2.51 (s, 3H). This spectrum is in agreeance with previously reported spectral data.[1]



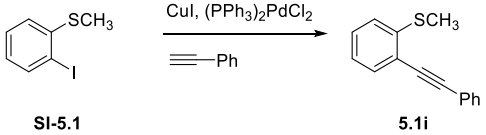
SI-5.3 **5.1g**

(2-((4-methoxyphenyl)ethynyl)phenyl)(methyl)sulfane (5.1g). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with 4-iodoanisole (740 mg, 3.2 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (110 mg, 0.16 mmol, 0.050 equiv), CuI (61 mg, 0.32 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-5.3** (570 mg, 3.8 mmol, 1.2 equiv) was dissolved in Et_3N (9.6 mL). This solution was then added to the reaction vial via pipette, and the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL Et_2O and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 10% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1g** as a yellow oil (540 mg, 67% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 7.6 Hz, 1H), 7.29 (td, J = 7.9 Hz, 1.4 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.09 (td, J = 7.6, 1.0 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.51 (s, 3H). This spectrum is in agreement with previously reported spectral data[2]



SI-5.3 5.1h

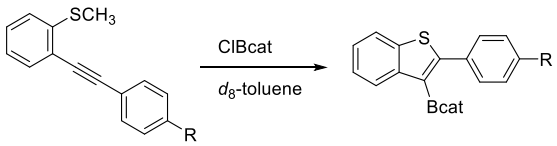
***N,N*-Dimethyl-4-((2-(methylthio)phenyl)ethynyl)aniline (5.1h)** was synthesized using a literature procedure[1] in 97% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47 (d, J = 10.9 Hz, 3H), 7.26 (t, J = 9.5 Hz, 1H), 7.16 (d, J = 9.3 Hz, 1H), 7.10 (t, J = 9.0 Hz, 1H), 6.66 (d, J = 10.7 Hz, 2H), 2.99 (s, 6H), 6.51 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]



SI-5.1 5.1i

Methyl(2-(phenylethynyl)phenyl)sulfane (5.1i) was synthesized using a literature procedure[2] in 79% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.59–7.57 (m, 2H), 7.48 (dd, J = 7.6, 1.4 Hz, 1H), 7.37–7.32(m, 3H), 7.31–7.29 (m, 1H), 7.18 (d, J = 7.9 Hz, 1H), 7.11 (td, J = 7.5, 1.1 Hz, 1H), 2.52 (s, 3H). This spectrum is in agreement with previously reported spectral data.[1]

Procedure for Reference Cyclizations of Thioanisoles **5.1a**–**5.1i**.

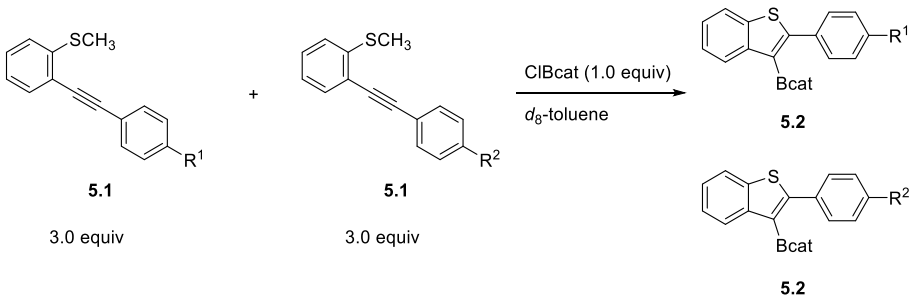


5.1 **5.2**

In order to monitor the competition reactions by ^{1}H NMR spectroscopy, it was necessary to run the individual substrates (**5.1a–5.1i**) under thioboration conditions.

This procedure was performed in an N_2-filled glovebox. A dram vial was charged with *B*-chlorocatecholborane (42 mg, 0.27 mmol, 1.4 equiv) and 0.15 mL of d_8-toluene. A separate dram vial was charged with **5.1a–5.1i** (0.20 mmol, 1.0 equiv). The ClBcat/d_8-toluene containing solution was then transferred via pipette to the vial containing compound **5.1**. The vial was sealed and placed in a pre-heated aluminum block at 100 ^{o}C. The mixture was heated for 4 h. The mixture was then cooled to room temperature before the contents of this vial were then transferred to a J. Young NMR tube and 0.3 mL of d_8-toluene was added. The tube was then sealed and removed from the glovebox. ^{1}H NMR spectroscopy was used to identify the resonances corresponding to the desired thioboration products **5.2a–5.2i**.

Procedure for Competition Experiments to Determine the Hammett Plot

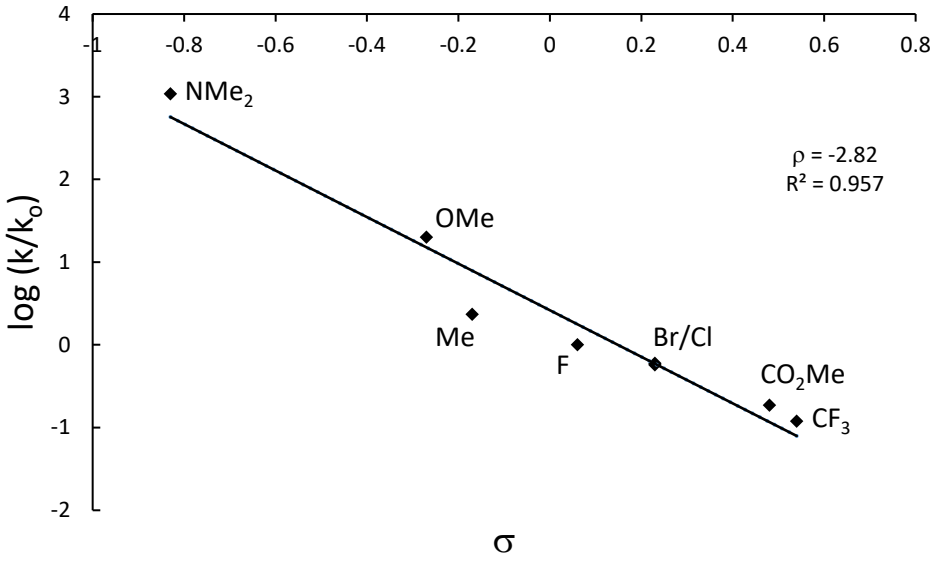


This procedure was performed in an N_2-filled glovebox. A dram vial was charged with *B*-chlorocatecholborane (13 mg, 0.087 mmol, 1.0 equiv) and 0.4 mL of d_8-toluene. A separate dram vial was charged with mesitylene (6.0 μL, 0.043 mmol, 0.50 equiv) as an internal standard, **5.1** (R^1) (0.26 mmol, 3.0 equiv) and **5.1** (R^2) (0.26 mmol, 3.0 equiv). The ClBcat/d_8-toluene containing solution was then transferred via pipette to the vial containing compounds **5.1**. The contents of this vial were then transferred to a J. Young NMR tube, sealed, and removed from the glovebox. The tube was then placed in a preheated oil bath at 100 °C. Single-scan ^{1}H NMR spectra were taken at time points t = 0 h, 2 h, and 4 h for which the tube was briefly removed from the heating bath for the latter two points. The resonances corresponding to **5.2** (R^1) and **5.2** (R^2) or **5.1** (R^1) and **5.1** (R^2) were compared to the internal standard to determine the relative reaction rates (k) for each competition experiment. The product ratios did not change upon standing. Resonances listed after the trial number below were used to determine product ratios.

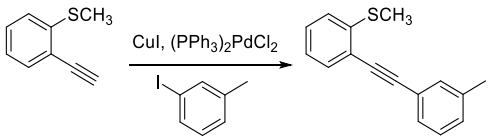
Trial 1: R^1 = H (**5.1i**), R^2 = F (**5.1d**); used resonances at δ = 8.68 and 8.69 ppm.
Trial 2: R^1 = H (**5.1i**), R^2 = CF_3 (**5.1e**); used resonances at δ = 7.52 and 7.42 ppm.
Trial 3: R^1 = F (**5.1d**), R^2 = Me (**5.1b**); used resonances at δ = 7.58 and 7.42 ppm.
Trial 4: R^1 = F (**5.1d**), R^2 = COOMe (**5.1c**); used resonances at δ = 8.66 and 8.04 ppm.
Trial 5: R^1 = H (**5.1i**), R^2 = Br (**5.1f**); used resonances at δ = 8.67 and 7.57 ppm.
Trial 6: R^1 = H (**5.1i**), R^2 = OMe (**5.1g**); used resonances at δ = 8.50 and 3.30 ppm.

Trial 7: R^1 = NMe_2 (**5.1h**), R^2 = OMe (**5.1g**); used resonances at δ = 3.32 and 2.50 ppm.
Trial 8: R^1 = H (**5.1i**), R^2 = Cl (**5.1a**); used resonances at δ = 8.67, 7.33 and 7.24 ppm.

Figure SI-5.1. Graph of $\log(k/k_0)$ vs σ to determine Hammett correlation.



Preparation of Substrates **5.1j**–**5.1n** for Sterics vs. Electronics Study



SI-5.3 **5.1j**

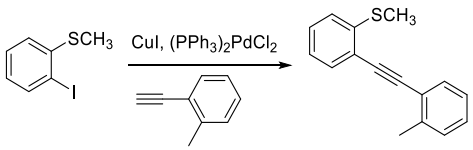
Methyl(2-(m-tolylethynyl)phenyl)sulfane (5.1j). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with 3-iodotoluene (0.27 mL, 2.1 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (73 mg, 0.010 mmol, 0.050 equiv), CuI (39 mg, 0.20 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-5.3** (370 mg, 2.5 mmol, 1.2 equiv) was dissolved in Et_3N (12 mL). This solution was then added to the reaction vial via pipette, and the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material.

The reaction mixture was diluted with 100 mL Et_2O and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1j** as a yellow oil (475 mg, 95% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.48 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.41–7.38 (m, 2H), 7.30 (td, *J* = 7.9, 1.5 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.11 (td, *J* = 7.5, 1.1 Hz, 1H), 2.52 (s, 3H), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 141.8, 138.1, 132.4, 132.3, 129.5, 128.83, 128.82, 128.4, 124.4, 124.2, 123.1, 121.6, 96.2, 86.7, 21.4, 15.2.

HRMS (CI+): Calculated for $C_{16}H_{14}S$ ([M]$^+$), 238.0816; found 238.0821.



SI-5.1 **5.1k**

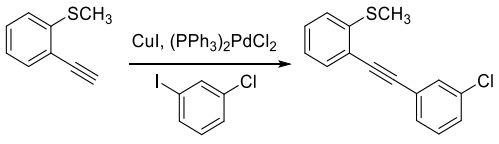
Methyl(2-(o-tolylethynyl)phenyl)sulfane (5.1k). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with compound **SI-5.1** (0.49 mL, 3.5 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (120 mg, 0.18 mmol, 0.050 equiv), CuI (67 mg, 0.35 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, 2-ethynyltoluene (0.57 mL, 4.6 mmol, 1.3 equiv) was diluted in Et_3N (11 mL). This solution was then added to the reaction vial via pipette, and

the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL Et_2O and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 5% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1k** as a yellow liquid (420 mg, 50% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.55 (d, *J* = 7.4 Hz, 1H), 7.51 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.31 (td, *J* = 7.7, 1.4 Hz, 1H), 7.24 (dd, *J* = 4.8, 1.0 Hz, 2H), 7.19–7.16 (m, 2H), 7.12 (td, *J* = 7.5, 1.1 Hz, 1H), 2.58 (s, 3H), 2.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 141.6, 140.5, 132.5, 132.2, 129.6, 128.8, 128.6, 125.7, 124.4, 124.2, 123.1, 121.7, 95.0, 90.8, 21.2, 15.2.

HRMS (CI+): Calculated for $C_{16}H_{14}S$ ([M]$^+$), 238.0816; found 238.0815.



SI-5.3 **5.1m**

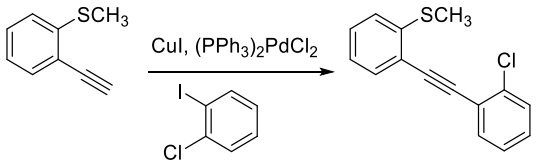
(2-((3-Chlorophenyl)ethynyl)phenyl)(methyl)sulfane (5.1m). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with 3-chloro-iodobenzene (0.15 mL, 1.2 mmol, 1.0

equiv), $(PPh_3)_2PdCl_2$ (42 mg, 0.060 mmol, 0.050 equiv), CuI (23 mg, 0.12 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-5.3** (230 mg, 1.6 mmol, 1.3 equiv) was dissolved in Et_3N (3.6 mL). This solution was then added to the reaction vial via pipette, and the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL Et_2O and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 3% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1m** as a yellow oil (390 mg, 94% yield).

^1H NMR ($CDCl_3$, 600 MHz): δ 7.57–7.56 (m, 1H), 7.48 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.45 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.34–7.27 (m, 3H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.12 (td, *J* = 7.5, 1.1 Hz, 1H), 2.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 142.1, 134.3, 132.5, 131.5, 129.8, 129.7, 129.3, 128.8, 125.1, 124.4, 124.3, 120.9, 94.4, 88.2, 15.1.

HRMS (CI+): Calculated for $C_{15}H_{11}SClNH_4$ ($[M+NH_4]^+$), 276.0614; found 276.0602.



SI-5.3 **5.1n**

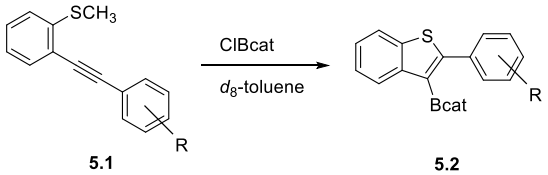
(2-((2-Chlorophenyl)ethynyl)phenyl)(methyl)sulfane (5.1n). In an N_2-filled glovebox, a 20 mL scintillation vial was charged with 2-chloro-iodobenzene (0.16 mL, 1.3 mmol, 1.0 equiv), $(PPh_3)_2PdCl_2$ (46 mg, 0.065 mmol, 0.050 equiv), CuI (25 mg, 0.13 mmol, 0.10 equiv), and a stir bar. In a separate dram vial, **SI-5.3** (250 mg, 1.7 mmol, 1.3 equiv) was dissolved in Et_3N (3.9 mL). This solution was then added to the reaction vial via pipette, and the mixture-containing vial was capped and removed from the glovebox, and the solution was stirred for 18 h. At this time, TLC indicated complete consumption of starting material. The reaction mixture was diluted with 100 mL Et_2O and washed with saturated aqueous NH_4Cl (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography using an elution gradient of 0% to 3% EtOAc in hexanes. Product-containing fractions were combined and concentrated in vacuo, and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.1n** as a yellow oil (330 mg, 98% yield).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.62–7.61 (m, 1H), 7.54 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.44–7.43 (m, 1H), 7.33 (td, *J* = 7.9, 1.4 Hz, 1H), 7.28–7.23 (m, 2H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.13 (td, *J* = 7.5, 1.1 Hz, 1H), 2.53 (s, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 142.0, 136.0, 133.6, 132.8, 129.5, 129.5, 129.3, 126.6, 124.4, 124.4, 123.3, 121.2, 92.6, 92.0, 15.3.

HRMS (CI+): Calculated for $C_{15}H_{11}SCl$ ([M]$^+$), 258.0270; found 258.0262.

Procedure for Cyclizations of Thionasioles **5.1a**, **5.1b**, **5.1j**–**5.1n**.



5.1 **5.2**

This procedure was performed in an N_2-filled glovebox. A dram vial was charged with *B*-chlorocatecholborane (99 mg, 0.64 mmol, 1.4 equiv) and 0.35 mL of d_8-toluene. A separate dram vial was charged with **5.1a**, **5.1b**, **5.1j–5.1n** (0.46 mmol, 1.0 equiv) and mesitylene (20. μL, 0.14 mmol, 0.33 equiv). The ClBcat/d_8-toluene containing solution was then transferred via pipette to the vial containing compound **5.1a**, **5.1b**, **5.1j–5.1n**. The contents of the vial were then transferred to a J. Young NMR tube. The tube was then sealed, removed from the glovebox, and placed into a preheated 100 ^{o}C oil bath. Single-scan ^{1}H spectra were taken at time points t = 0 h and 2 h for which the tube was briefly removed from the heating bath. The resonances corresponding to thioboration products **5.2a**, **5.2b**, **5.2j–5.2n** were compared to the internal standard to determine ^{1}H NMR yields.

Isolation of Catecholboronic Ester Thioboration Product **5.2f**

This reaction setup was performed in an N_2-filled glovebox. A dram vial was charged with *B*-chlorocatecholborane (65 mg, 0.42 mmol, 1.4 equiv) and 0.23 mL of toluene. A separate dram vial was charged with **5.1f** (91 mg, 0.30 mmol, 1.0 equiv). The ClBcat/ toluene-containing solution was then transferred via pipette to the vial containing compound **5.1f**. The mixture-containing vial was then sealed and placed in a preheated aluminum heating block at 100 ^{o}C and was subsequently heated for 4 h. At this time, the vial was removed from the heating block and the contents were cooled to room temperature; a white solid began precipitating out. Toluene (0.42 mL) was then added to the vial, the vial was resealed and placed back in the heating block at 110 ^{o}C for 25 min. The vial was then removed from the heating block and subsequently removed from the glovebox and cooled to room temperature over 3 h. The resulting slurry was filtered over a Büchner funnel and rinsed with chilled toluene (3 × 0.5 mL, 0 ^{o}C). The crystals were collected and volatiles were removed at ca. 10 mTorr for 18 h to afford **5.2f** as a white solid with trace solvent impurities (toluene) (84 mg, 69% yield).

^{1}H NMR (CD_2Cl_2, 600 MHz): δ 8.60 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.62 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.57 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.54–7.51 (m, 1H), 7.44–7.42 (m, 1H), 7.29 (dd, *J* = 5.8, 3.3 Hz, 2H), 7.14 (dd, *J* = 5.8, 3.3 Hz, 2H).

^{13}C NMR (CD_2Cl_2, 151 MHz): δ 157.8, 148.2, 144.6, 140.8, 134.4, 132.0, 131.8, 125.8, 125.6, 125.2, 123.8, 123.3, 122.2, 112.9.

^{11}B NMR (CD_2Cl_2, 193 MHz): δ 30.5.

HRMS (CI+): Calculated for $C_{20}H_{12}SBBrO_2$ ($[M]^+$), 405.9838; found 405.9847.

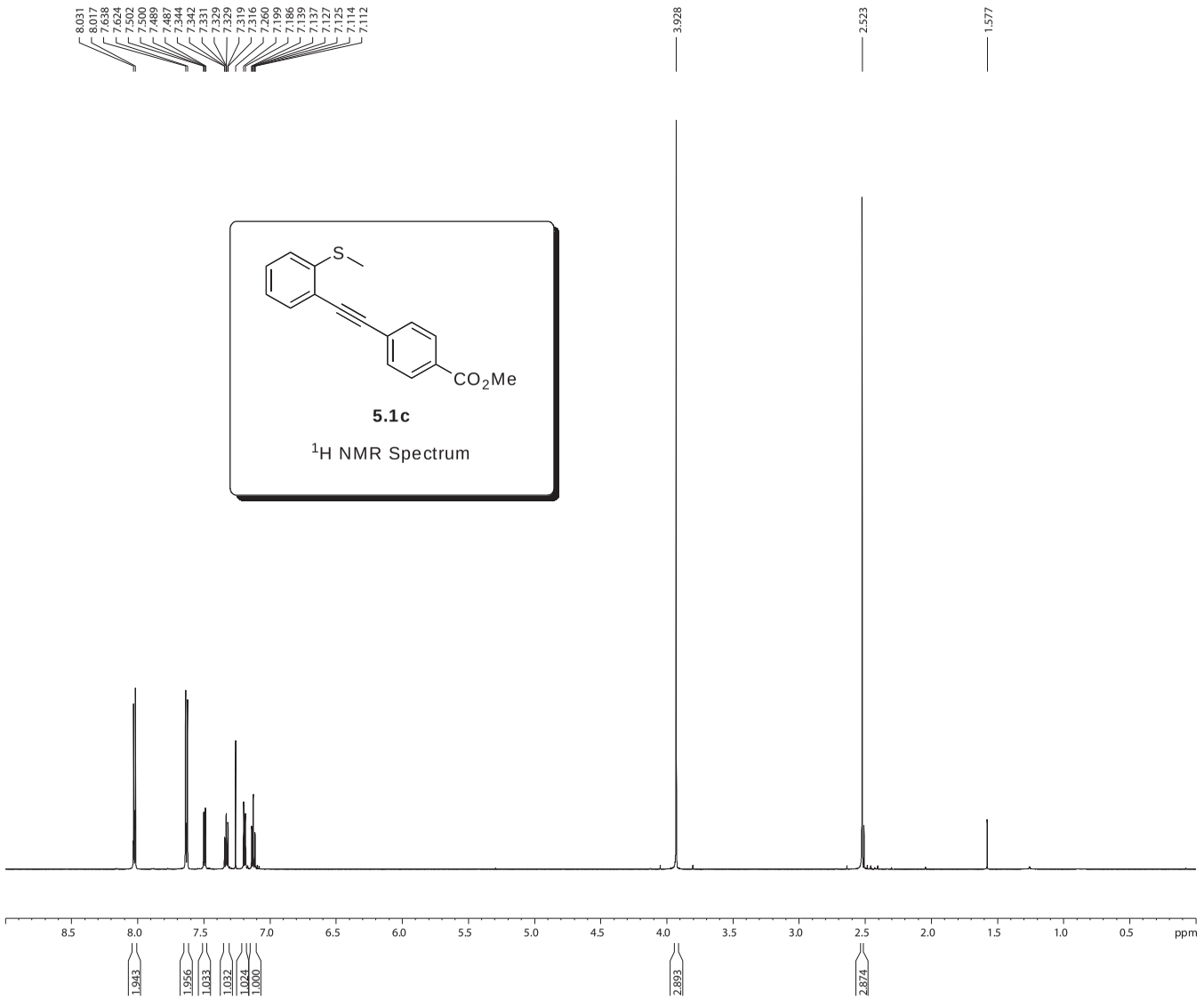
References for Experimental Section

1. Faizi, D. J.; Davis, A. J.; Meany, F. B.; Blum, S. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 14286.
2. Lin, C. -H.; Chen, C. -C.; WWu, M. -J. *Chem. Eur. J.* **2013**, *19*, 2578.
3. Yamauchi, T.; Shibahara, F.; Murai, T. *Tetrahedron Lett.* **2016**, *57*, 2945.

Appendix A

NMR Spectra (for Chapter 5)

This appendix contains unpublished ^{1}H, ^{11}B, and ^{13}C NMR spectra for compounds from chapter 5.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7.329
7.319
7.316
7.260
7.199
7.186
7.139
7.137
7.127
7.125
7.114
7.112
3.928
2.523
1.577
S
CO2Me
5.1c
1H NMR Spectrum
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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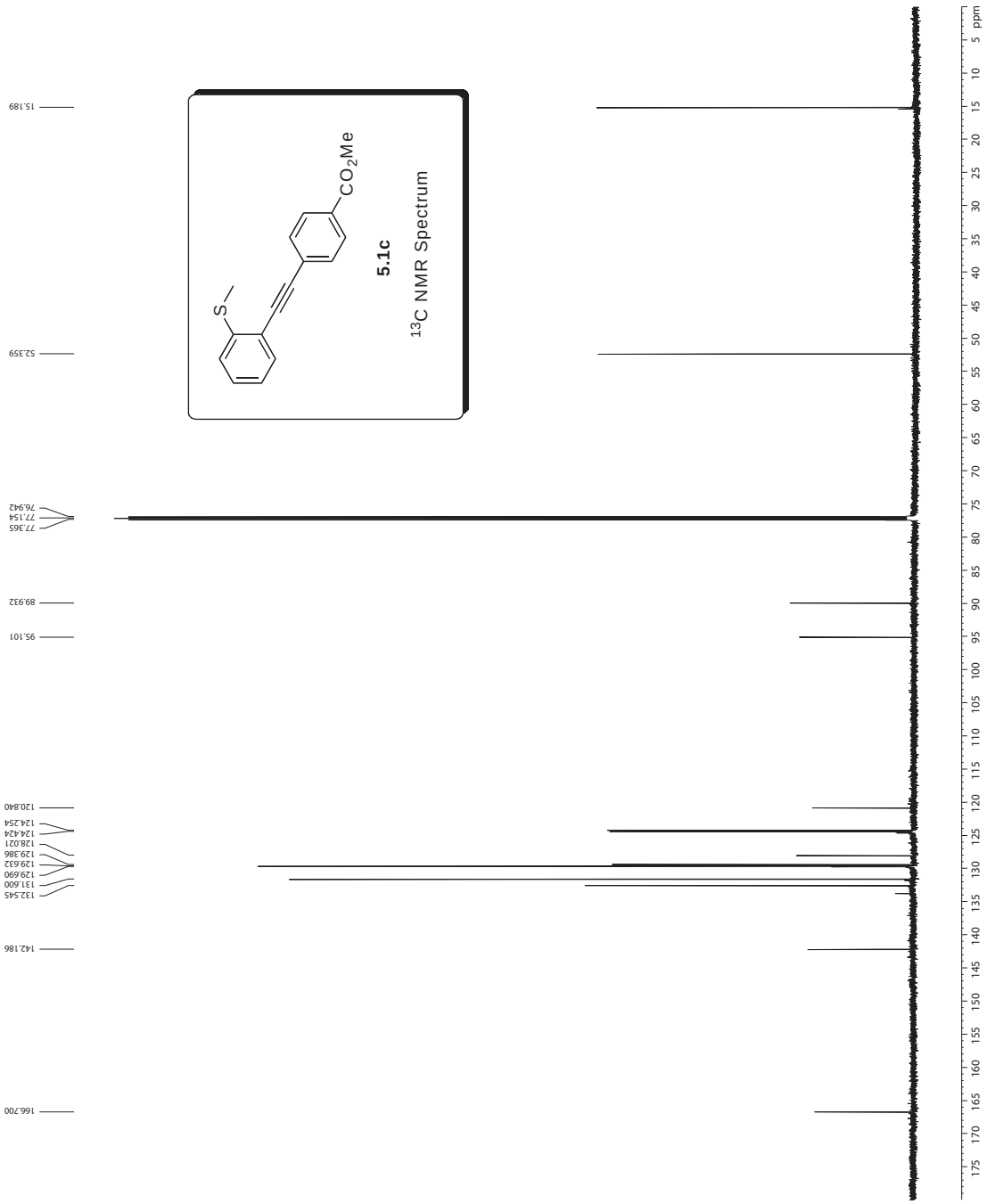
1.000
2.893
2.874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76.942
77.154
77.365
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95.101
120.840
124.254
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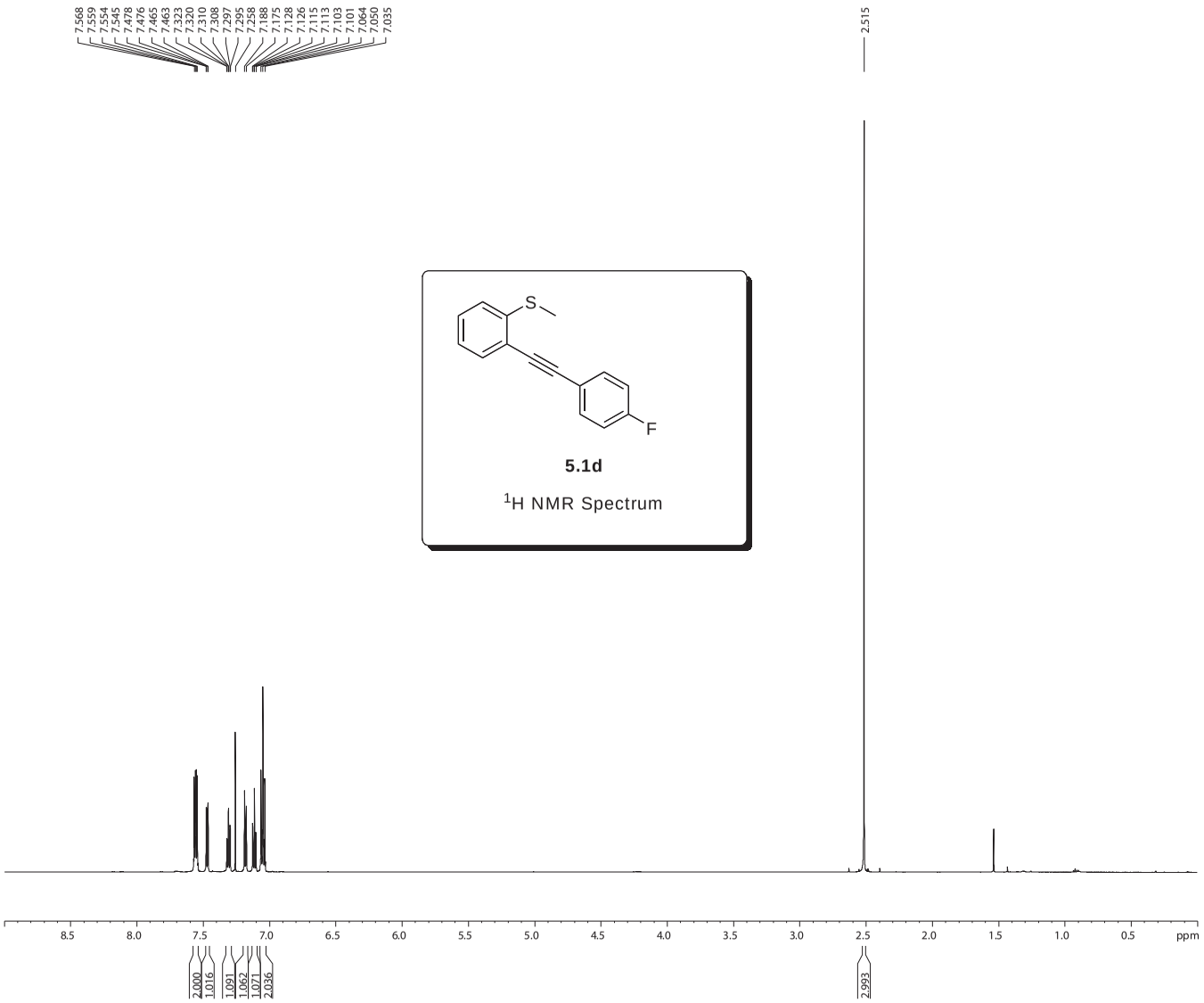
129.386
129.632
129.690
131.600
132.545
142.186
166.700
S
CO2Me
5.1c
13C NMR Spectrum
5 ppm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7.308
7.297
7.295
7.258
7.188
7.175
7.128
7.126
7.115
7.113
7.103
7.101
7.064
7.050
7.035
2.515
S
F
5.1d
1H NMR Spectrum
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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1.0
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ppm
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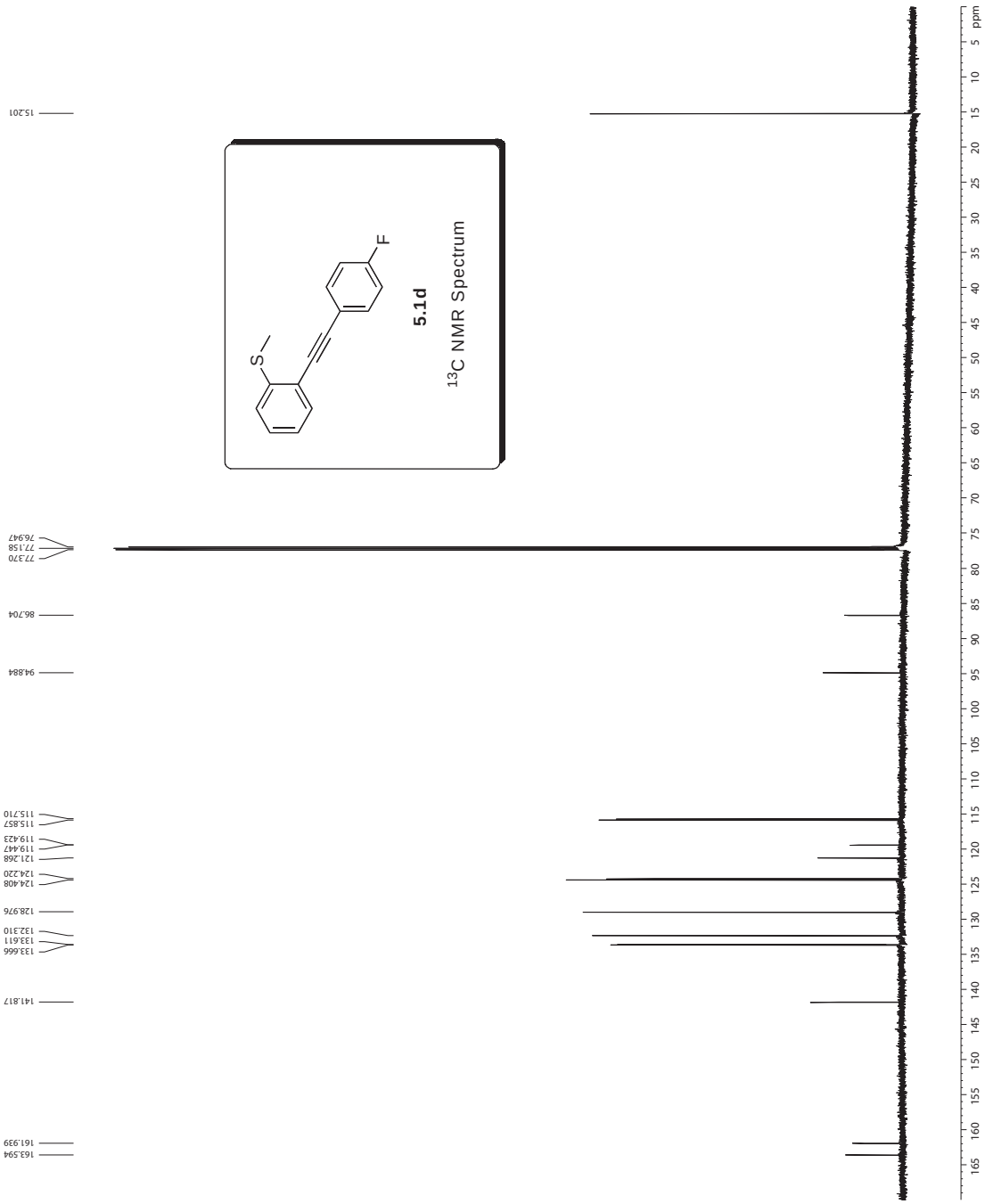
2.036
2.993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F
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119.447
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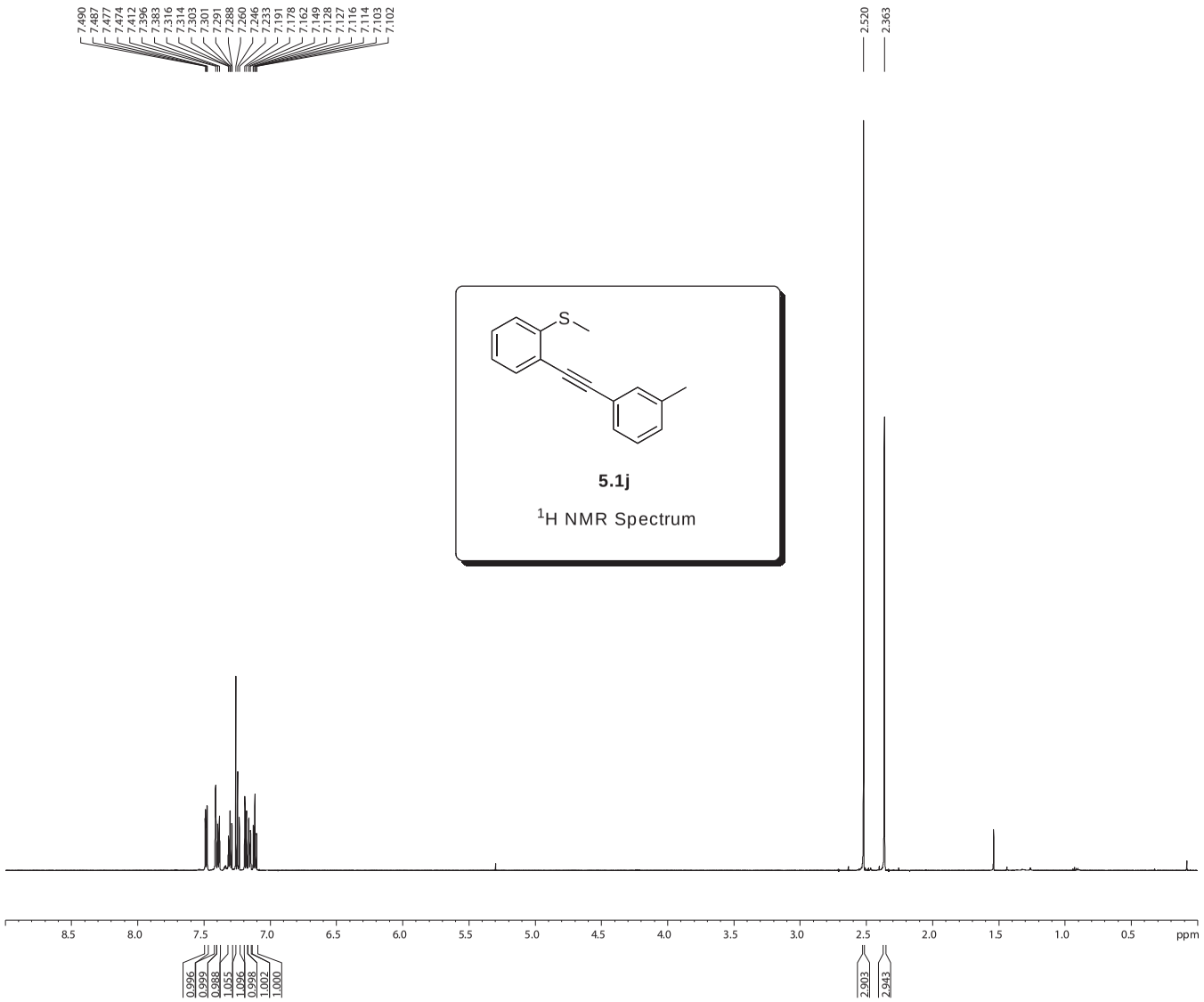
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7.288
7.260
7.246
7.233
7.191
7.178
7.162
7.149
7.128
7.127
7.116
7.114
7.103
7.102
2.520
2.363
S
5.1j
1H NMR Spectrum
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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0.998
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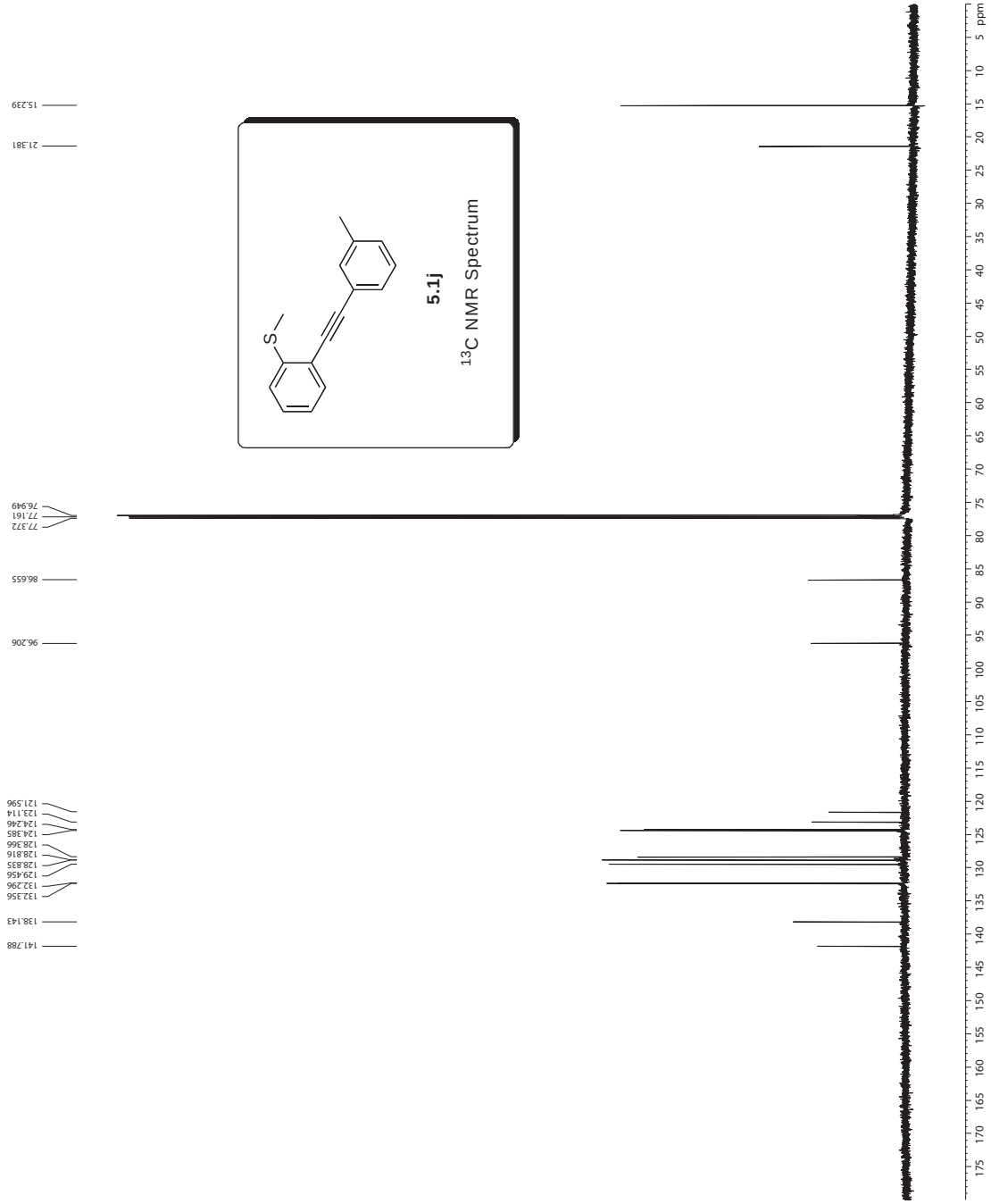
1.000
2.903
2.943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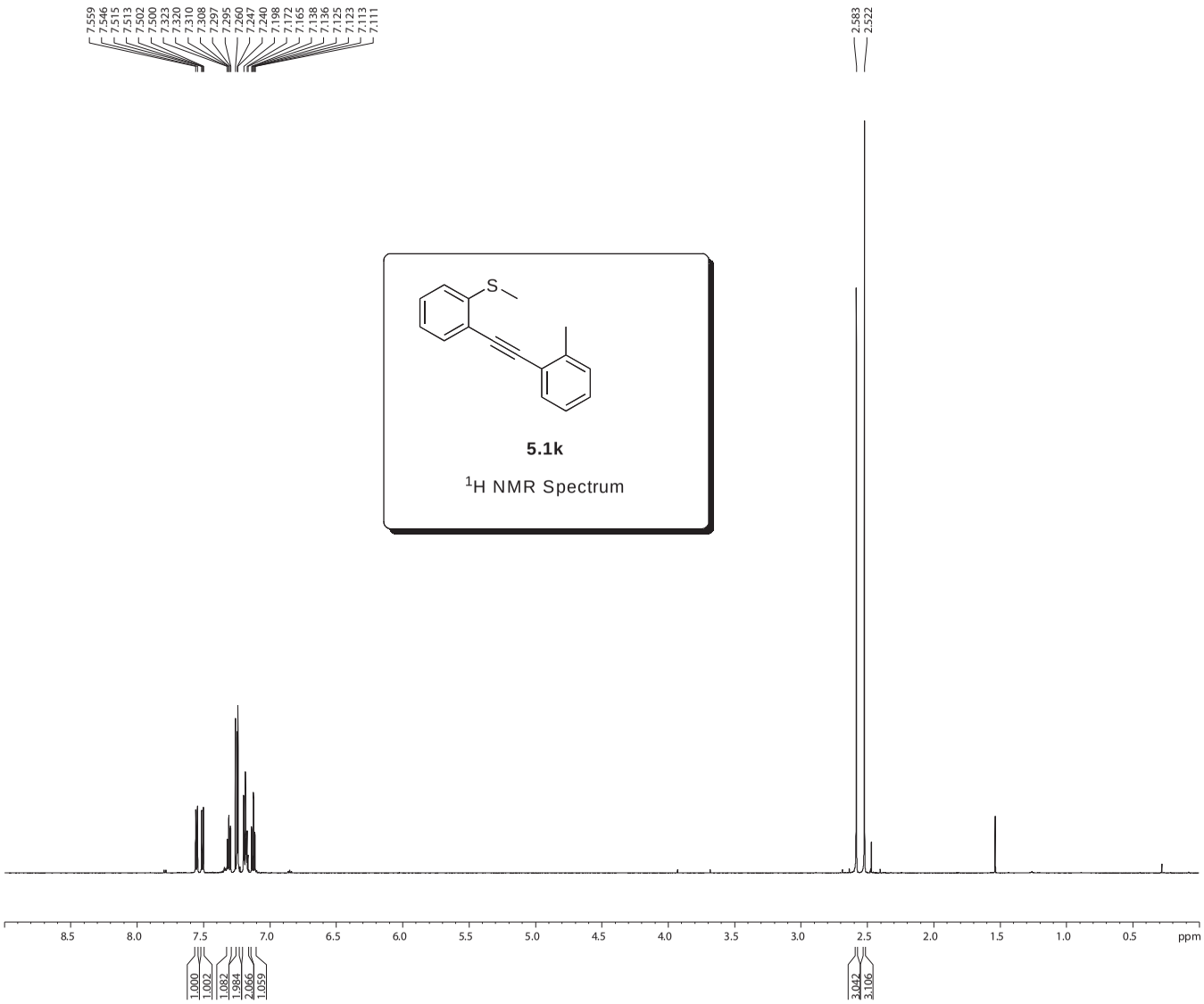
^{13}C NMR Spectrum
S
ppm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7.247
7.240
7.198
7.172
7.165
7.138
7.136
7.125
7.123
7.113
7.111
2.583
2.522
S
5.1k
1H NMR Spectrum
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
2.5
2.0
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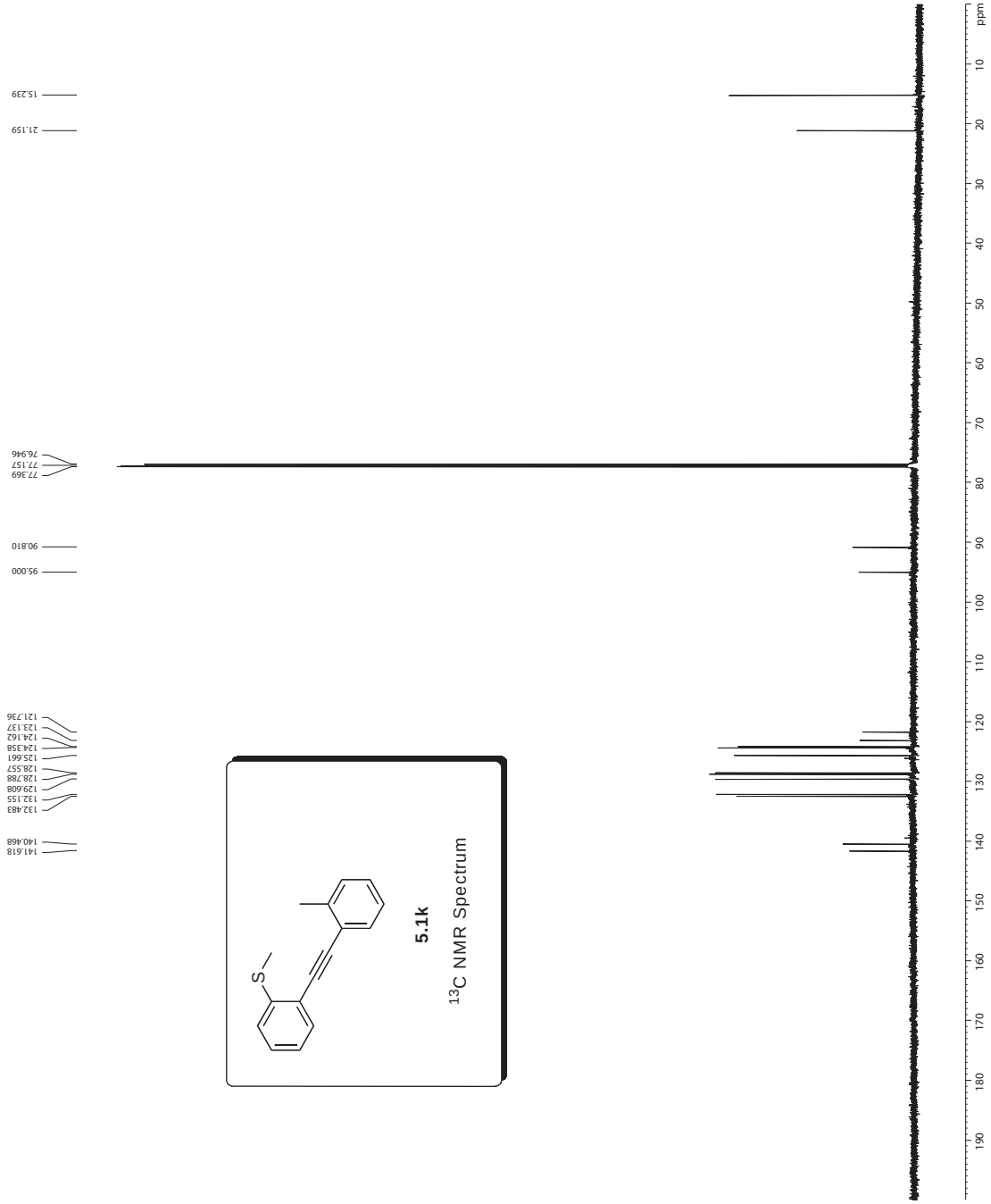
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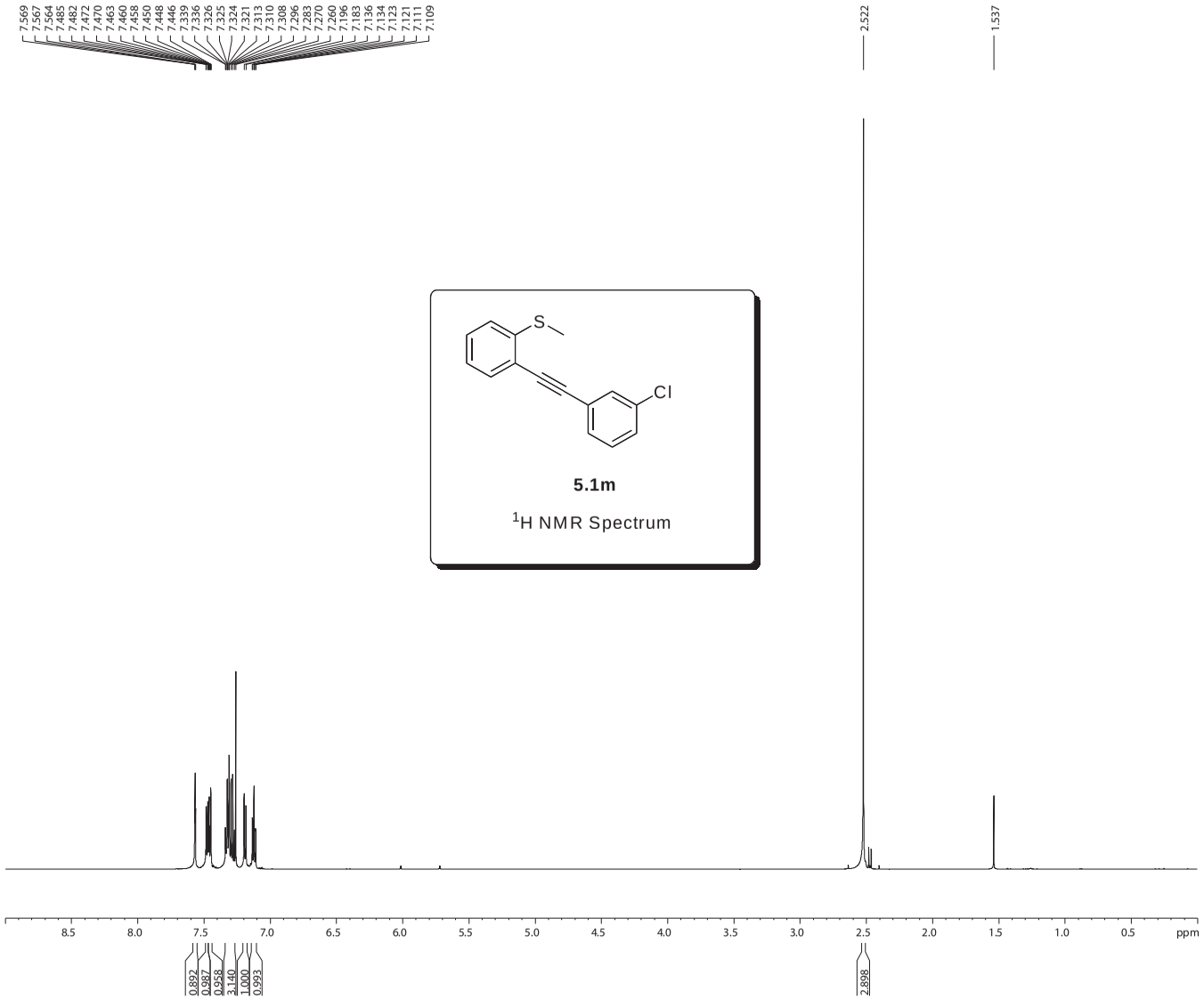
S
5.1k
^{13}C NMR Spectrum
ppm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7.134
7.123
7.121
7.111
7.109
2.522
1.537
S
Cl
5.1m
1H NMR Spectrum
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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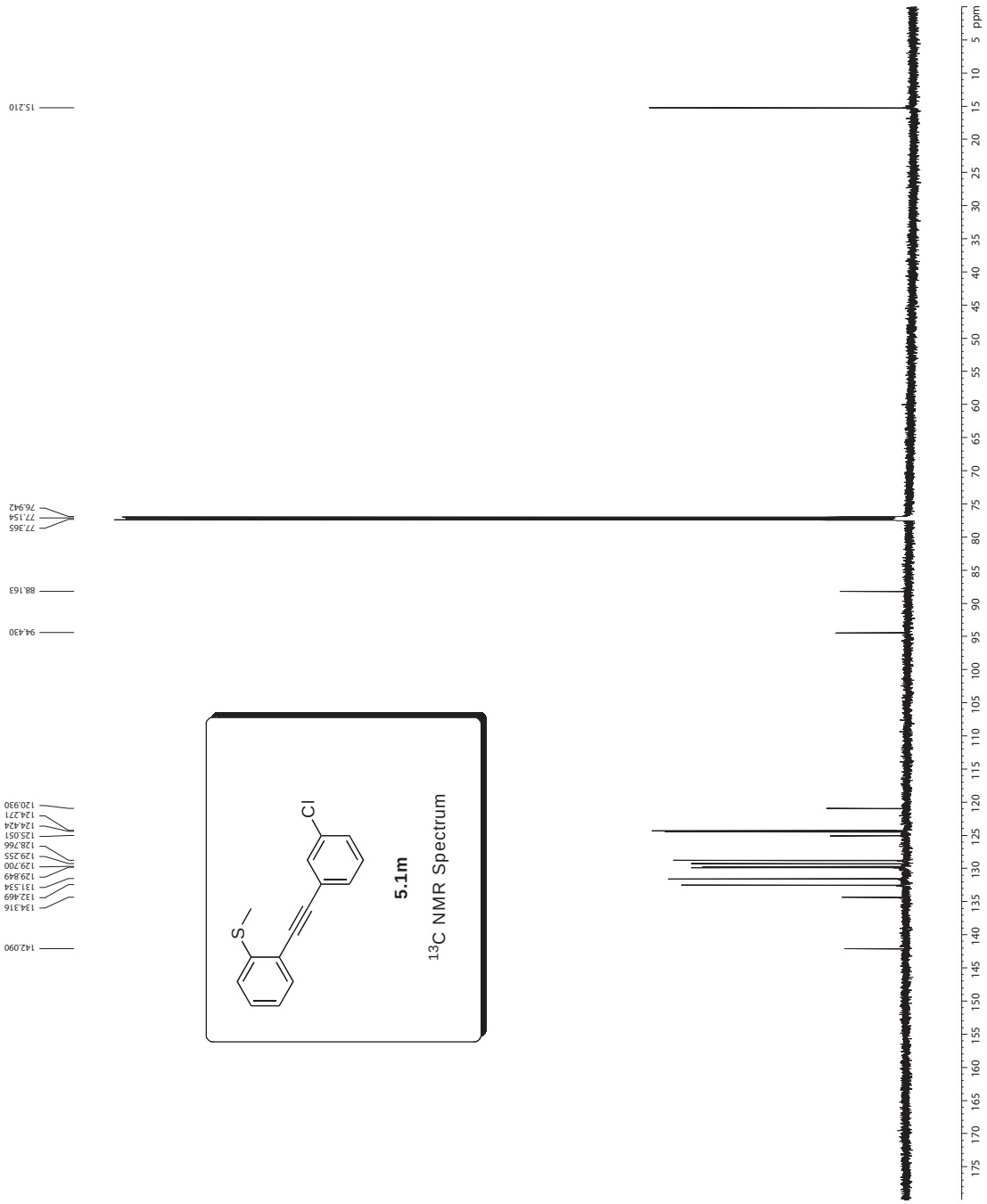
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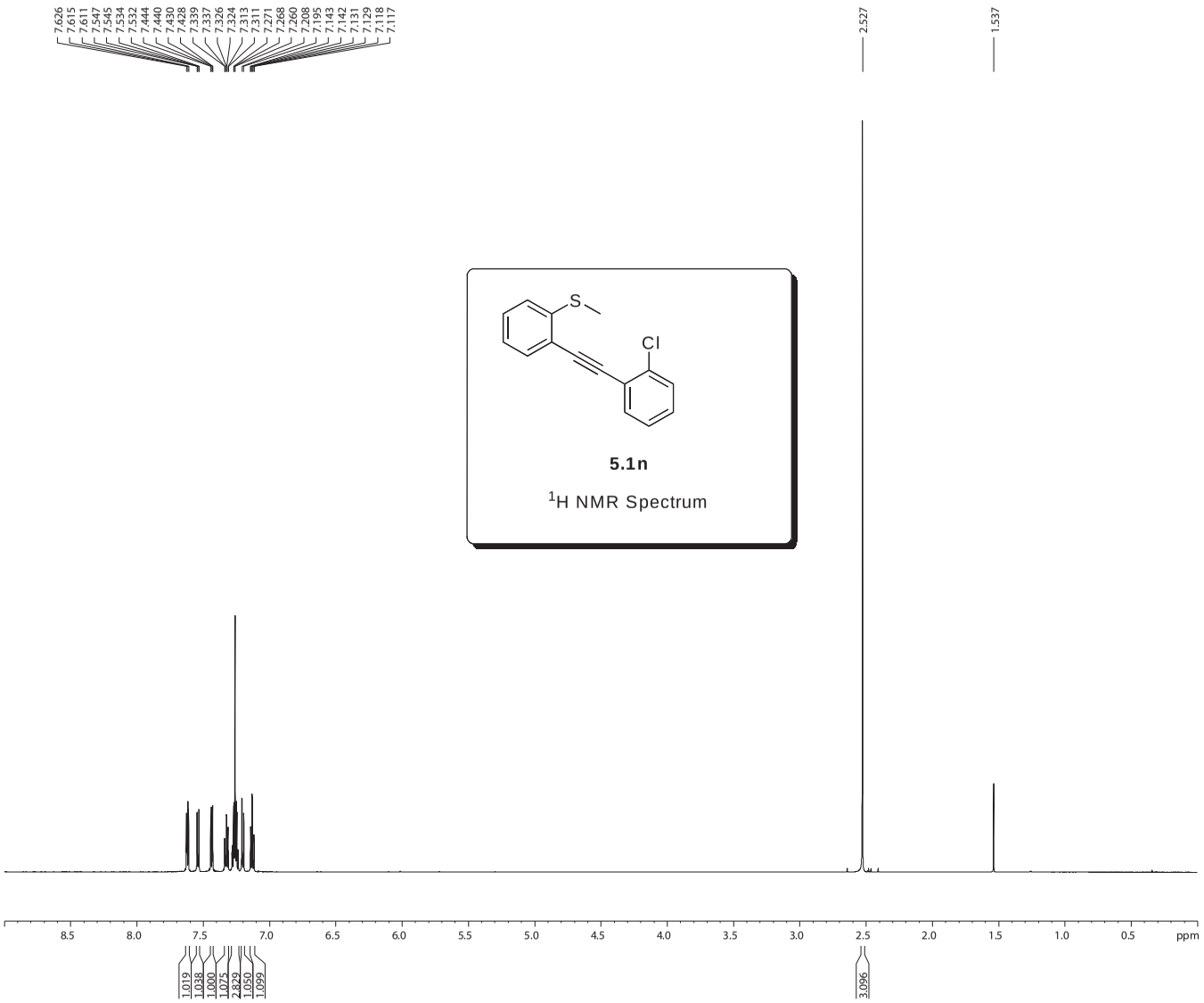
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7.131
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S
Cl
5.1n
1H NMR Spectrum
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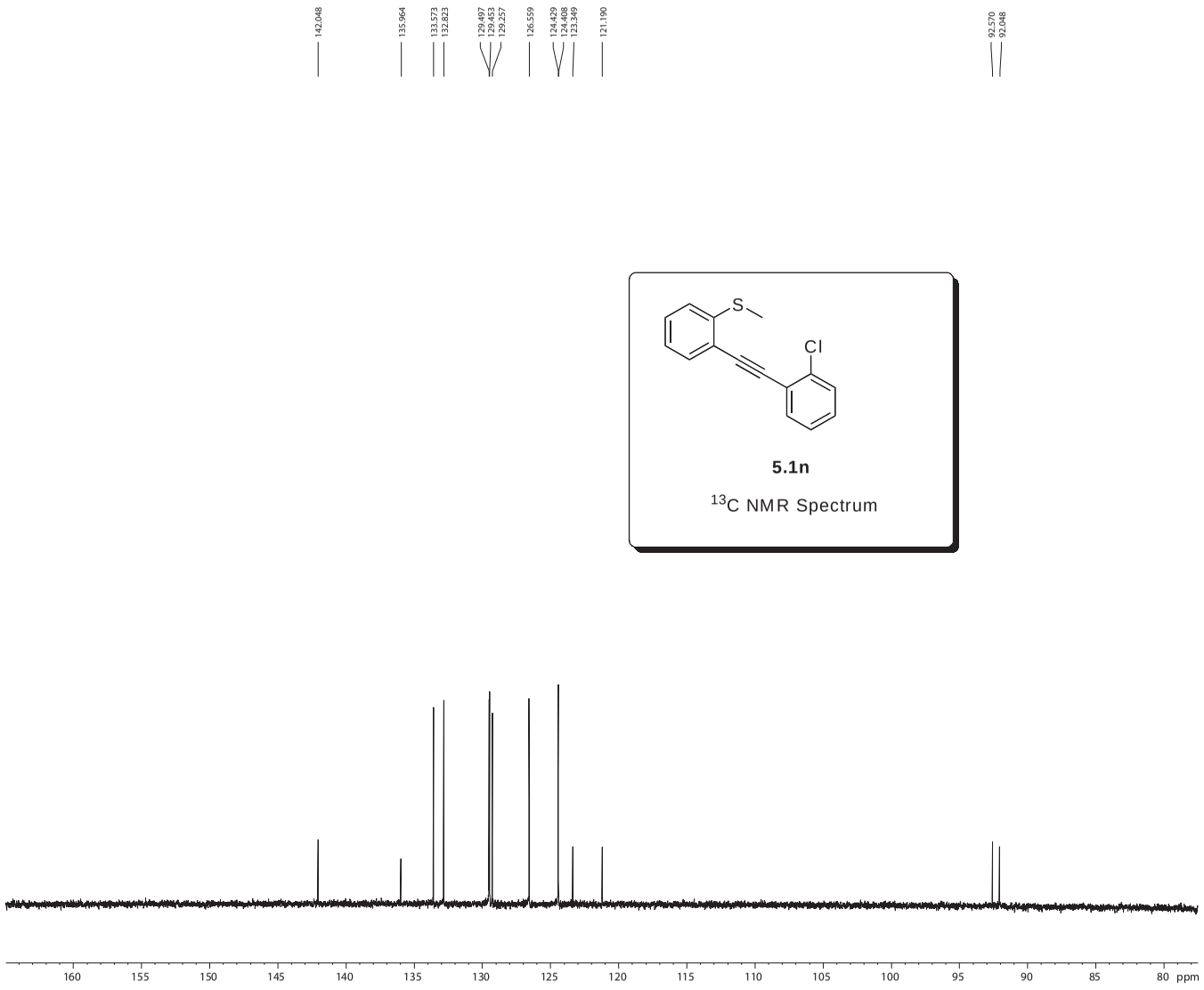
1.099
3.096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135.964
133.573
132.823
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129.453
129.257
126.559
124.429
124.408
123.349
121.190
92.570
92.048
S
Cl
5.1n
13C NMR Spectrum
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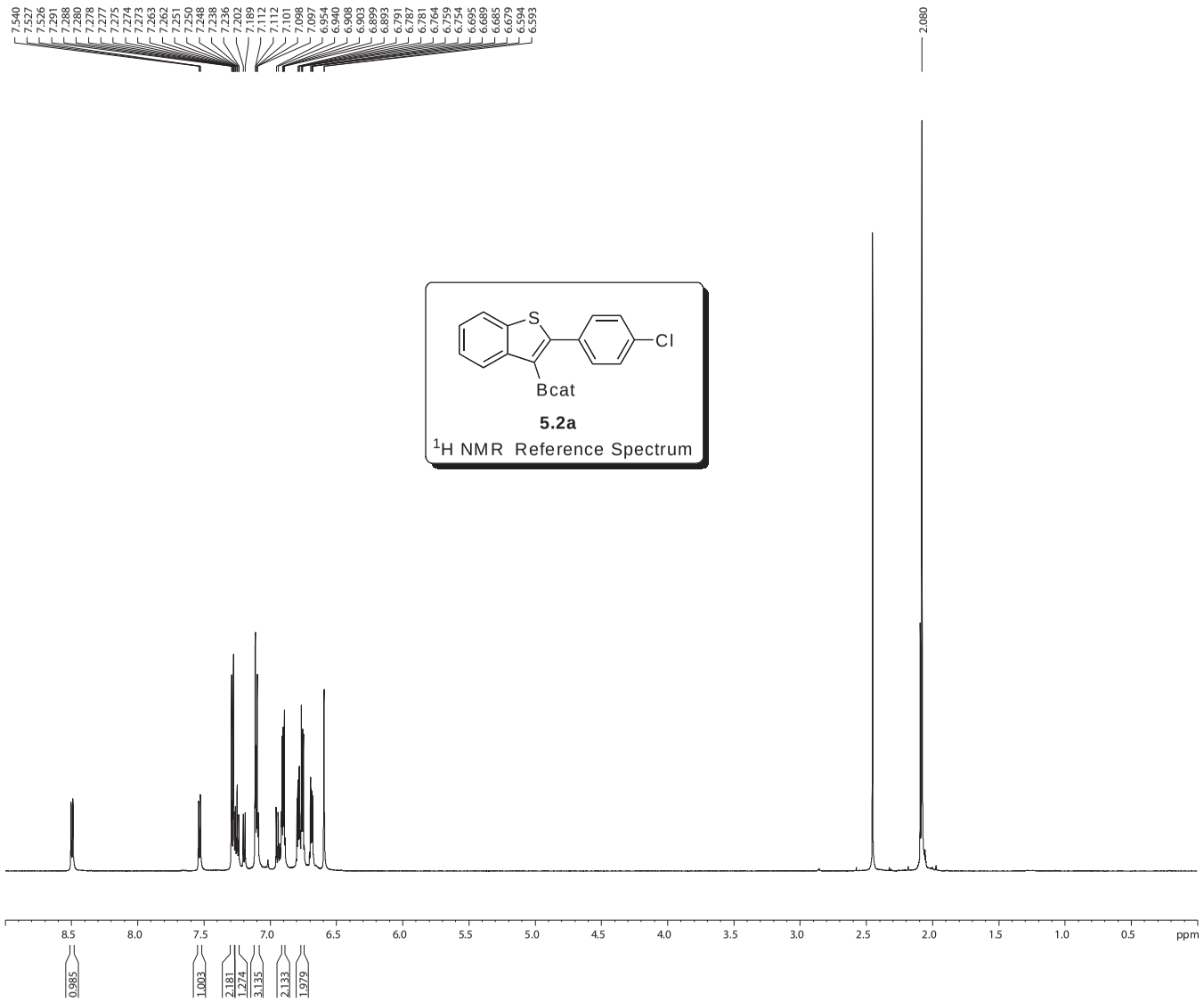
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80 ppm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7.277
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7.274
7.273
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7.262
7.251
7.250
7.248
7.238
7.236
7.202
7.189
7.112
7.112
7.101
7.098
7.097
6.954
6.940
6.908
6.903
6.899
6.893
6.791
6.787
6.781
6.764
6.759
6.754
6.695
6.689
6.685
6.679
6.594
6.593
2.080
S
Cl
Bcat
5.2a
1H NMR Reference Spectrum
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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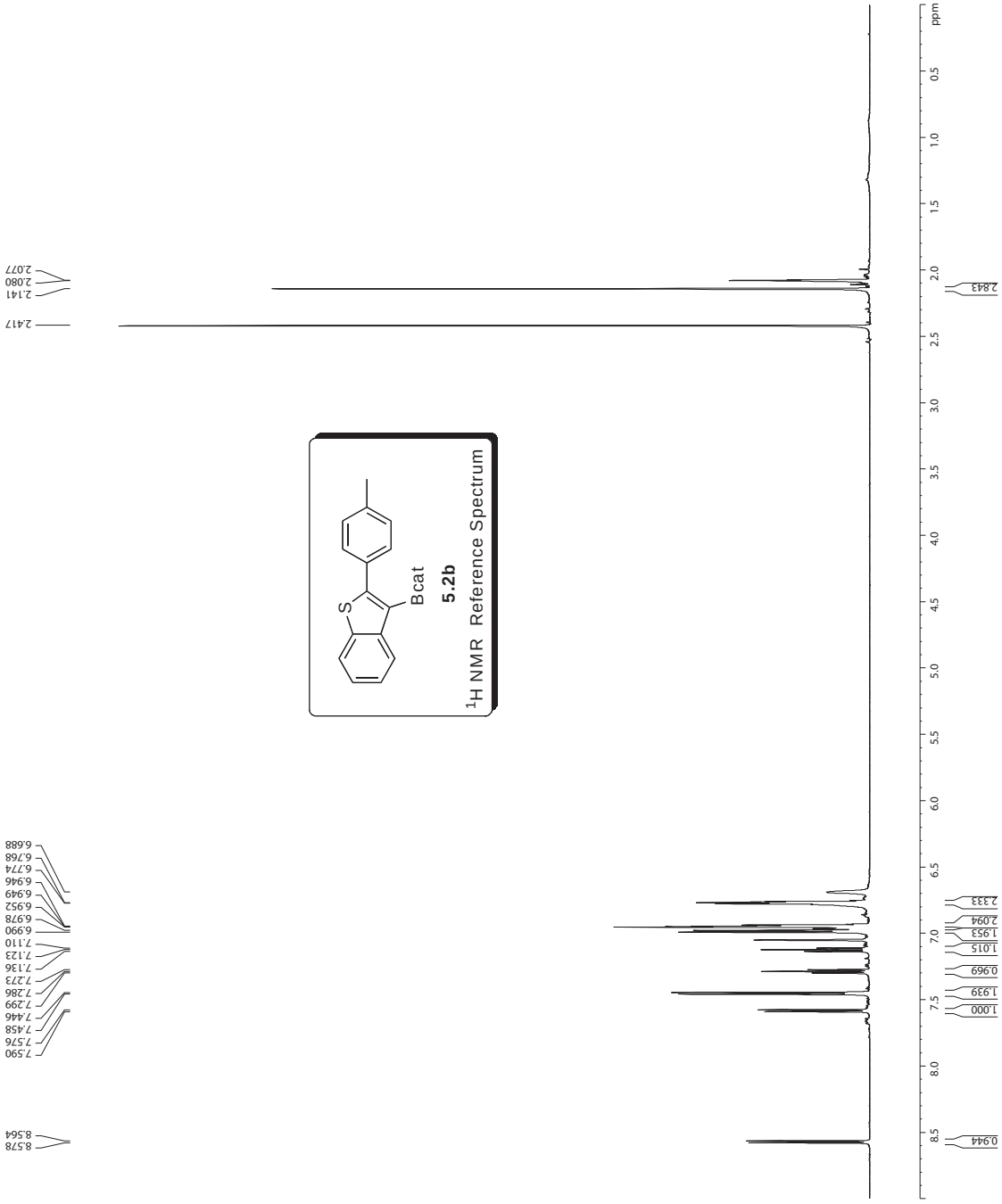
1.979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7.110
6.990
6.978
6.952
6.949
6.946
6.774
6.768
6.688
2.417
2.141
2.080
2.077
2.843
2.333
2.094
1.953
1.015
0.969
1.939
1.000
0.944
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
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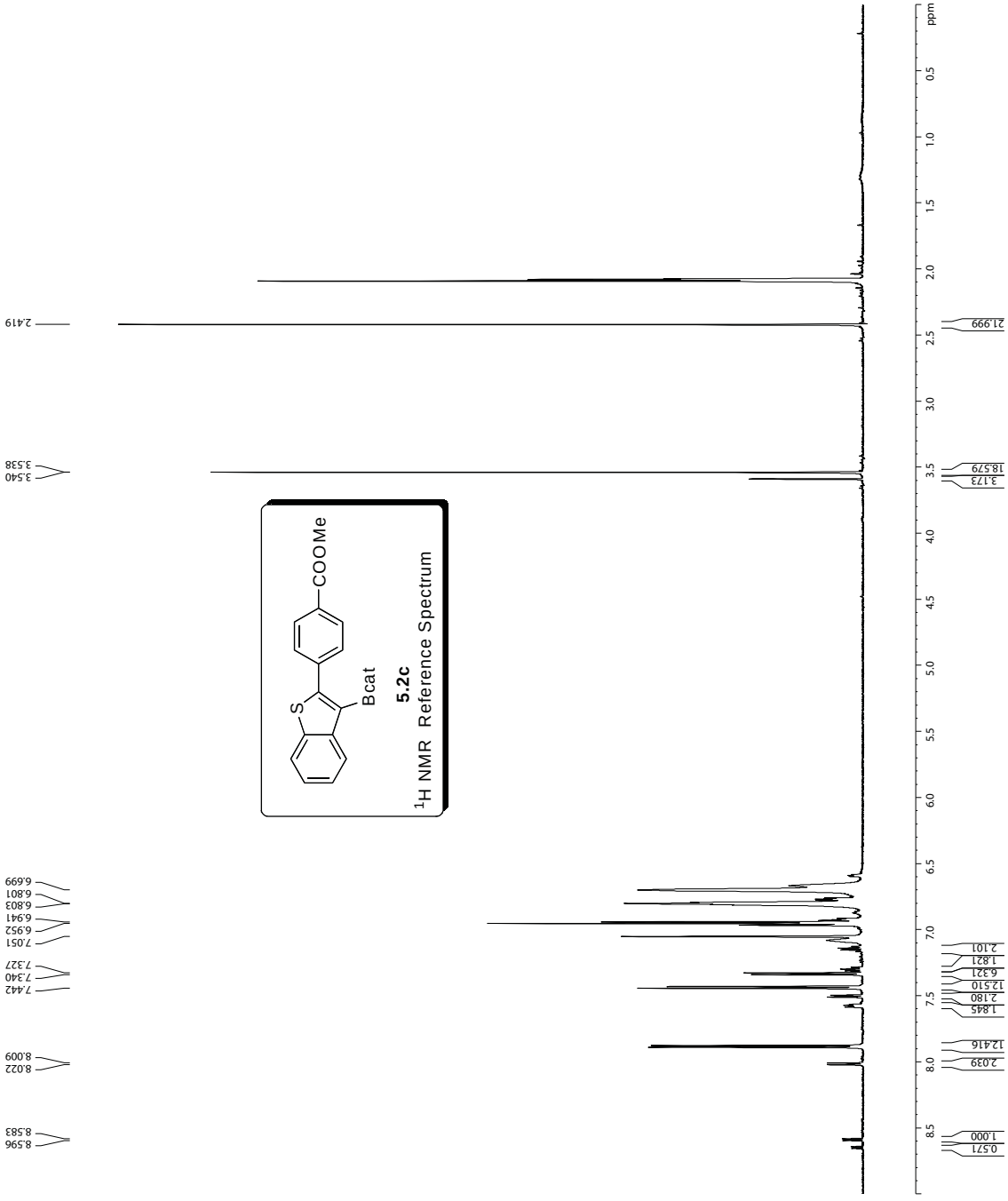
S
Bcat
5.2b
^{1}H NMR Reference Spectrum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12.510
6.321
1.821
2.101
21.999
3.173
18.579
2.419
3.540
3.538
8.596
8.583
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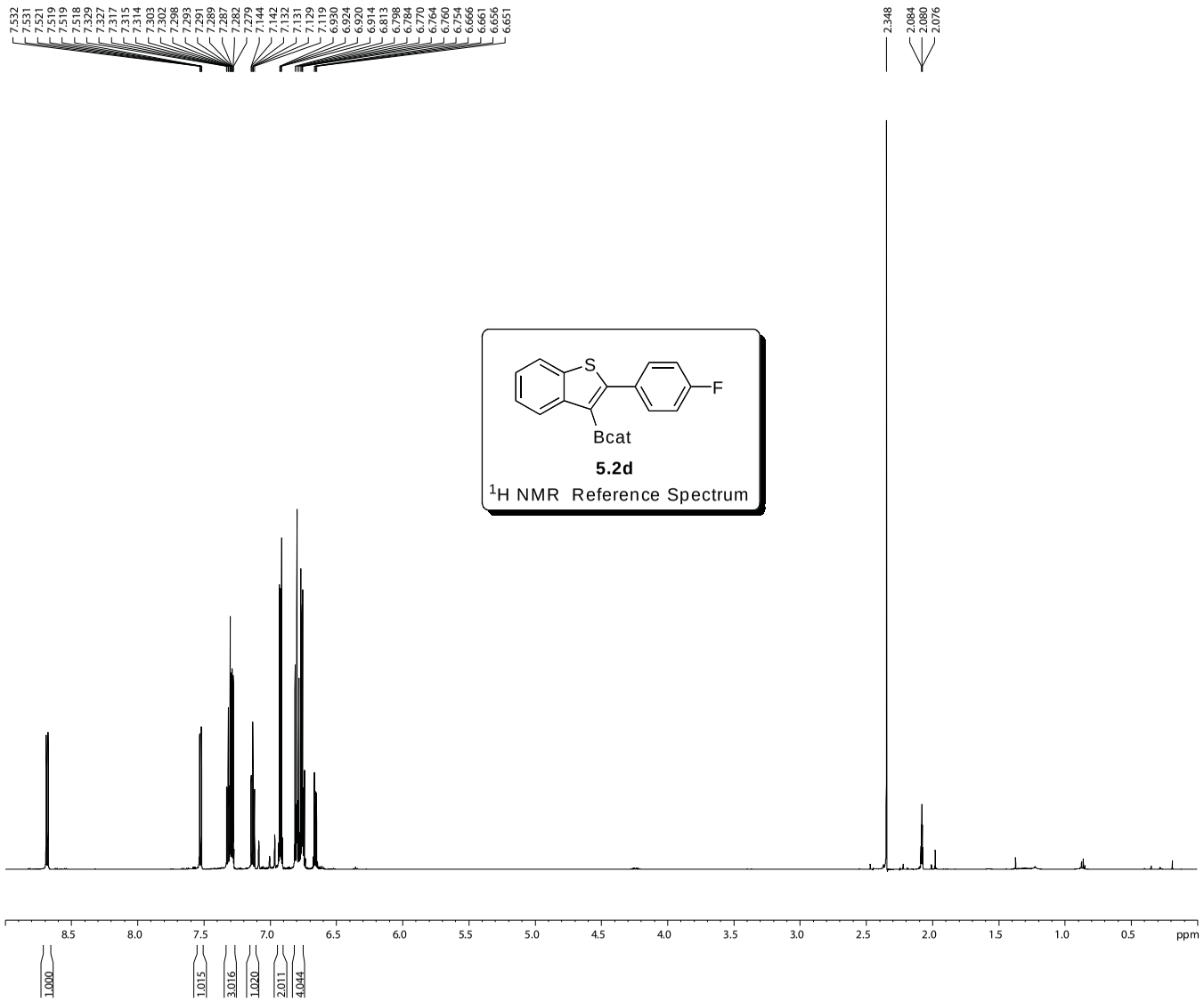
8.009
7.442
7.327
7.340
7.051
6.952
6.941
6.803
6.801
6.699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7.531
7.521
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7.519
7.518
7.329
7.327
7.317
7.315
7.314
7.303
7.302
7.298
7.293
7.291
7.289
7.287
7.282
7.279
7.144
7.142
7.132
7.131
7.129
7.119
6.930
6.924
6.920
6.914
6.813
6.798
6.794
6.784
6.770
6.764
6.760
6.754
6.666
6.661
6.656
6.651
2.348
2.084
2.080
2.076
S
F
Bcat
5.2d
1H NMR Reference Spectrum
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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1.015
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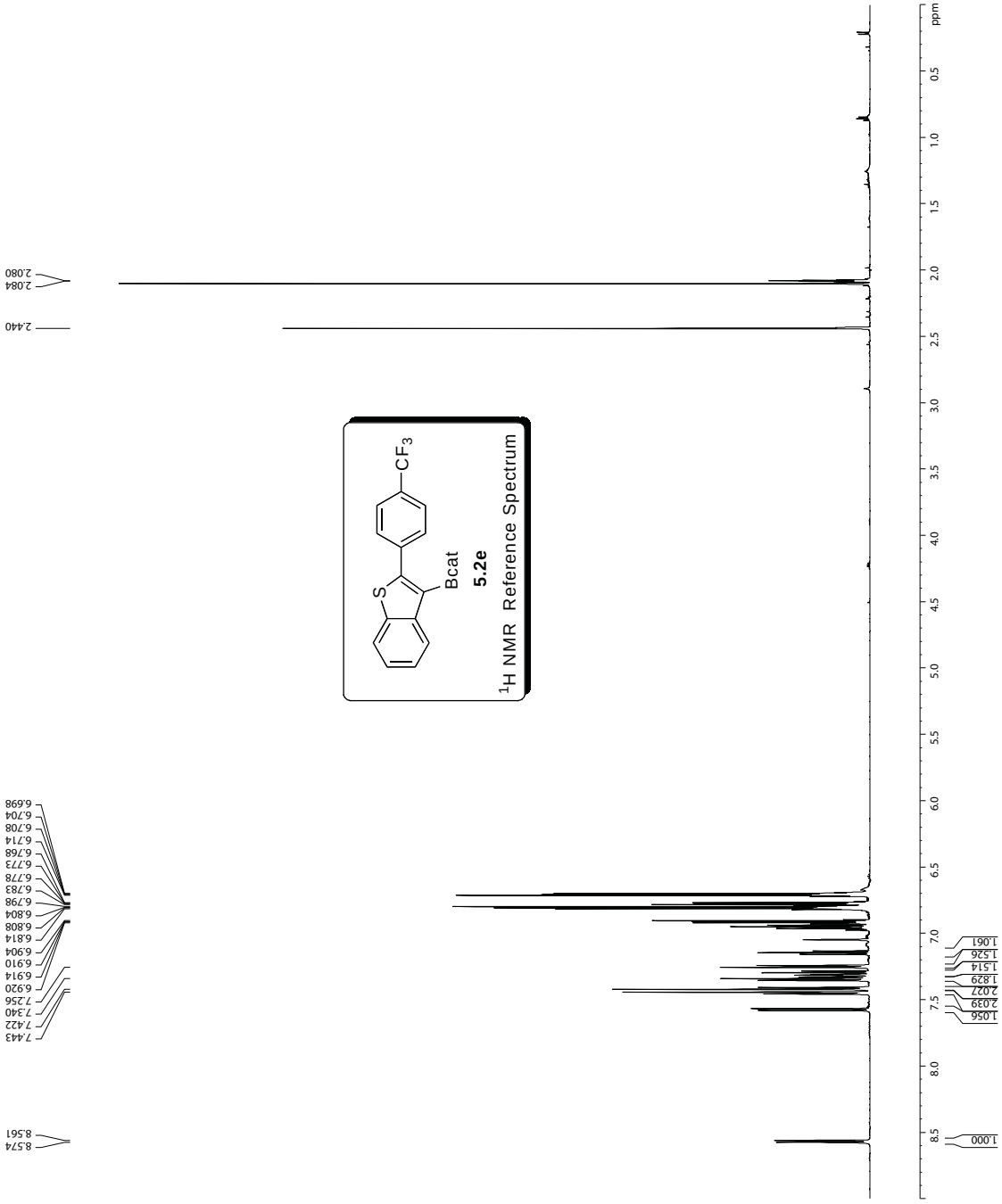
1.020
2.011
4.044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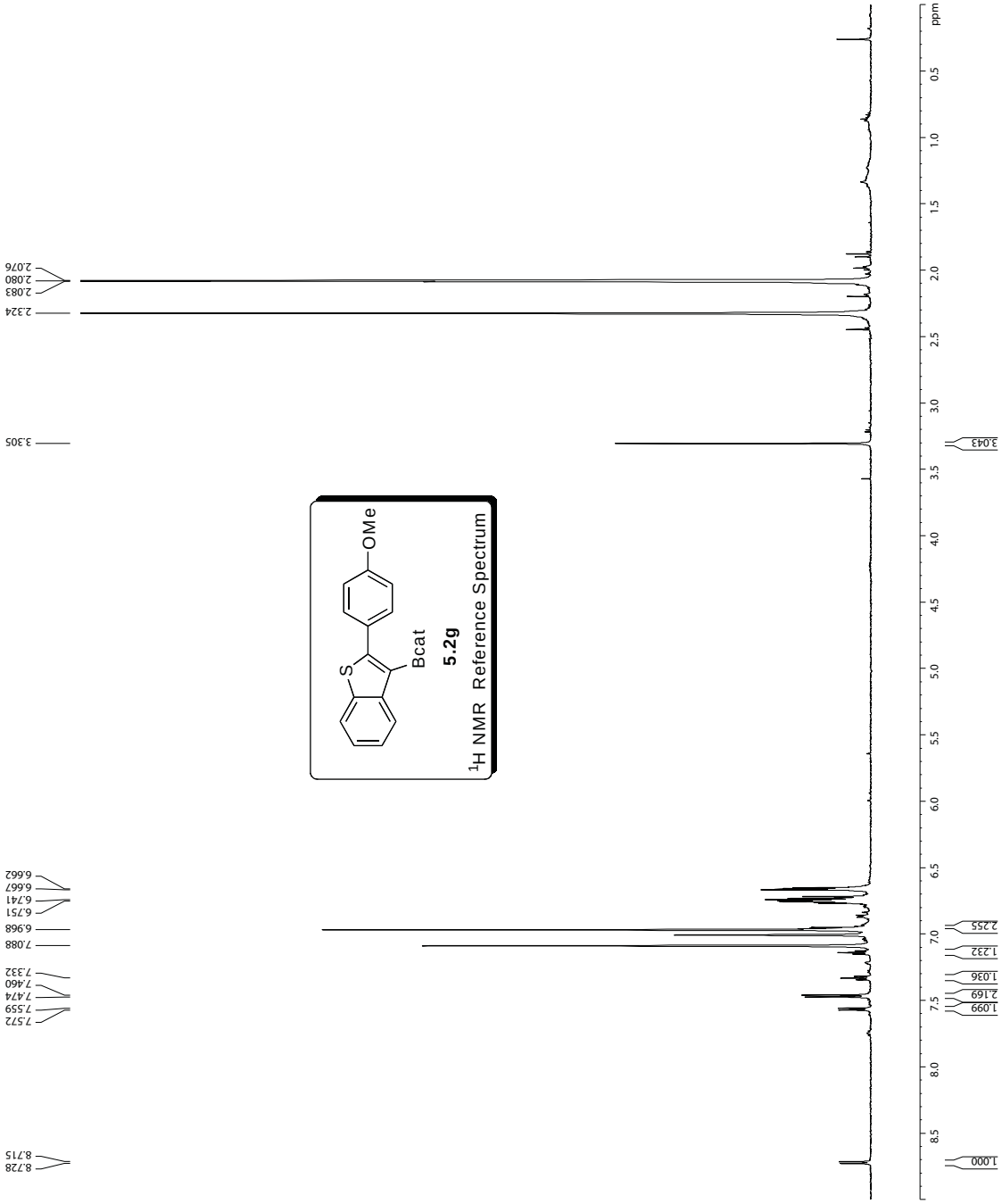
6.768
6.773
6.778
6.783
6.798
6.804
6.808
6.814
6.904
6.910
6.914
6.920
7.256
7.340
7.422
7.443
8.561
8.574
1.000
1.056
2.039
2.027
1.829
1.514
1.526
1.061

8.708
8.695
7.544
7.543
7.541
7.531
7.529
7.528
7.372
7.369
7.368
7.359
7.358
7.356
7.320
7.253
7.242
7.239
7.169
7.154
7.140
7.063
7.049
6.915
6.910
6.906
6.900
6.795
6.782
6.750
6.744
6.671
6.665
6.661
6.655
2.080
1.000
1.063
2.161
1.022
1.998
3.451
2.096
ppm
Br
Bcat
S
5.2f
1H NMR Reference Spectrum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7.559
7.474
7.460
7.332
7.088
6.968
6.751
6.741
6.667
6.662
3.305
2.324
2.083
2.080
2.076
1.000
1.099
2.169
1.036
1.232
2.255
3.043
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
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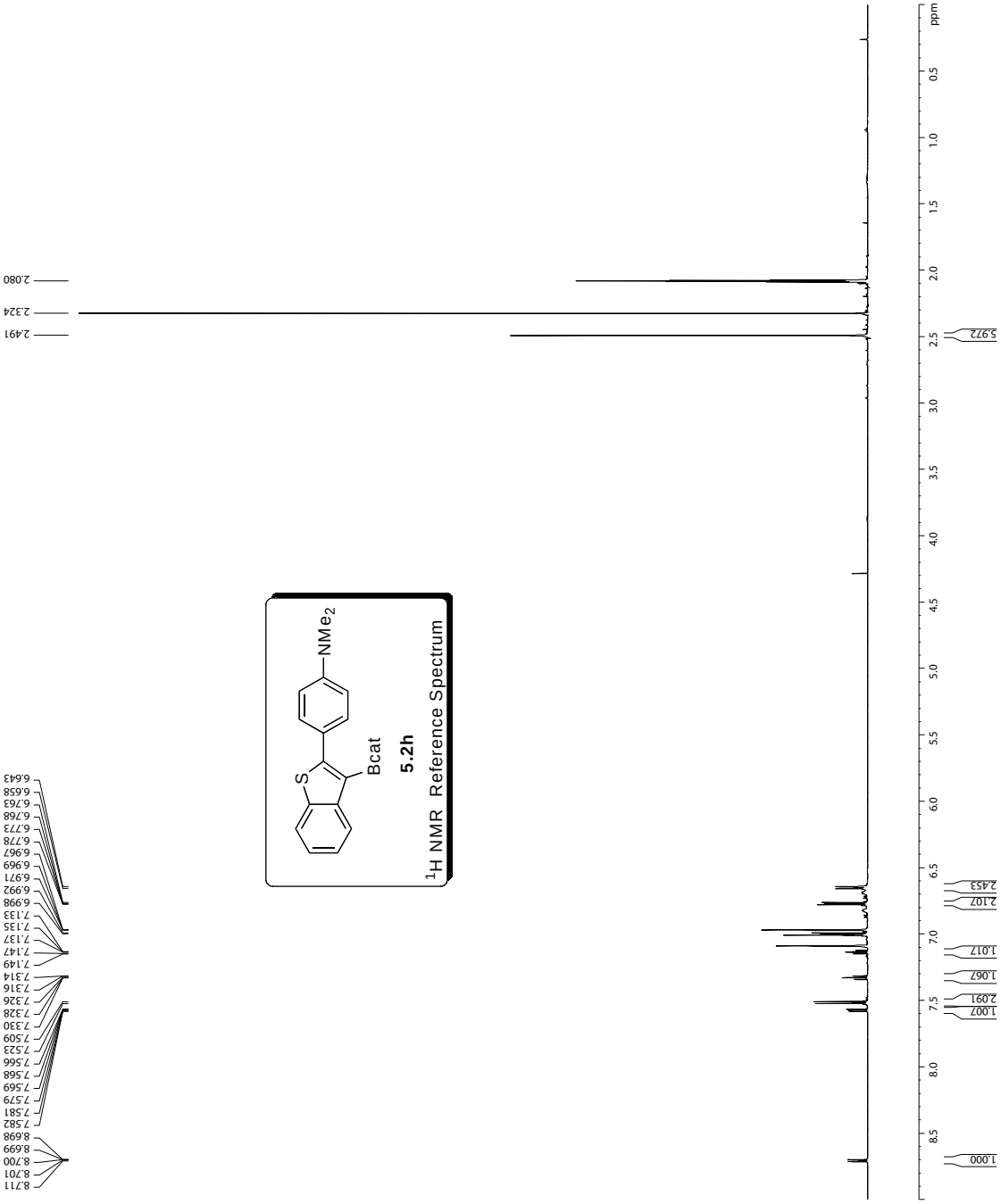
6.5
7.0
7.5
8.0
8.5
OMe
S
Bcat
5.2g
^{1}H NMR Reference Spectrum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8.701
8.700
8.699
8.698
7.582
7.581
7.579
7.569
7.568
7.566
7.523
7.509
7.330
7.328
7.326
7.316
7.314
7.149
7.147
7.137
7.135
7.133
6.998
6.992
6.971
6.969
6.967
6.778
6.773
6.768
6.763
6.658
6.643
2.491
2.324
2.080
NMe2
S
Bcat
5.2h
1H NMR Reference Spectrum
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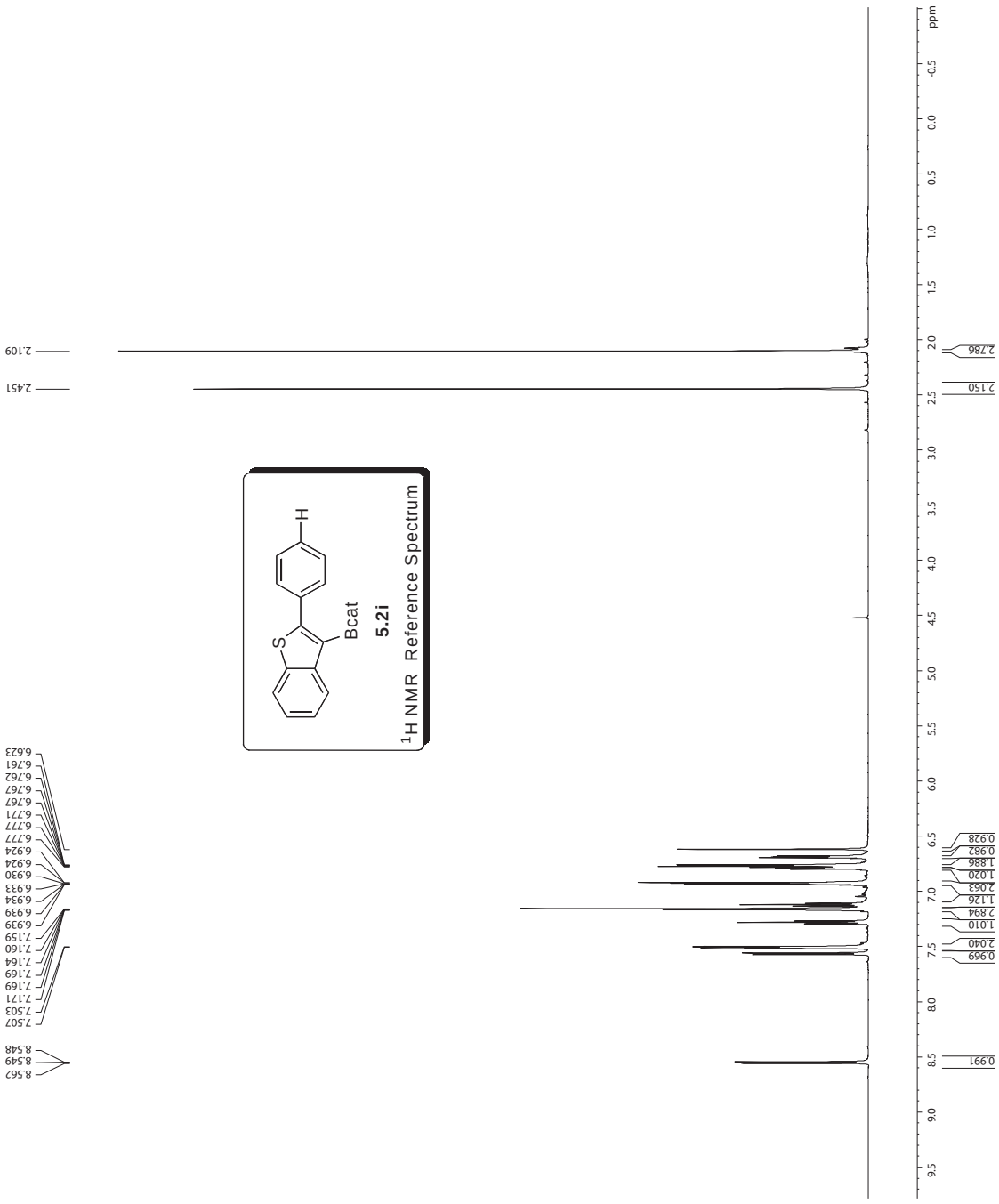
2.107
1.017
1.067
2.091
1.007
5.922
ppm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7.507
7.503
7.171
7.169
7.169
7.164
7.160
7.159
6.939
6.934
6.933
6.930
6.924
6.924
6.777
6.777
6.771
6.767
6.767
6.762
6.761
6.623
2.786
2.150
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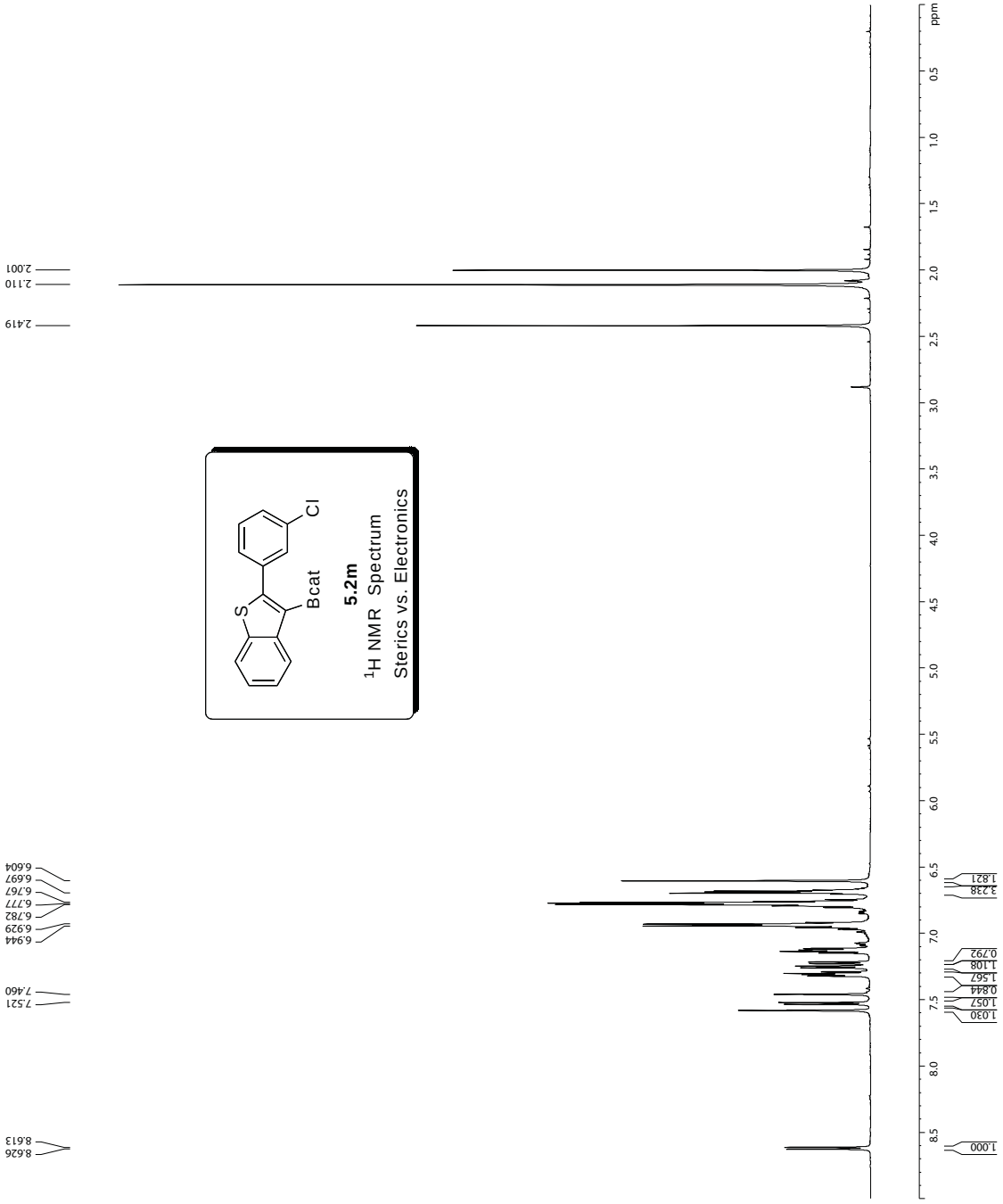
1.886
1.020
2.063
1.126
2.894
1.010
2.040
0.969
0.991
ppm


Cl
Bcat
S
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^{1}H NMR Spectrum
Sterics vs. Electronics
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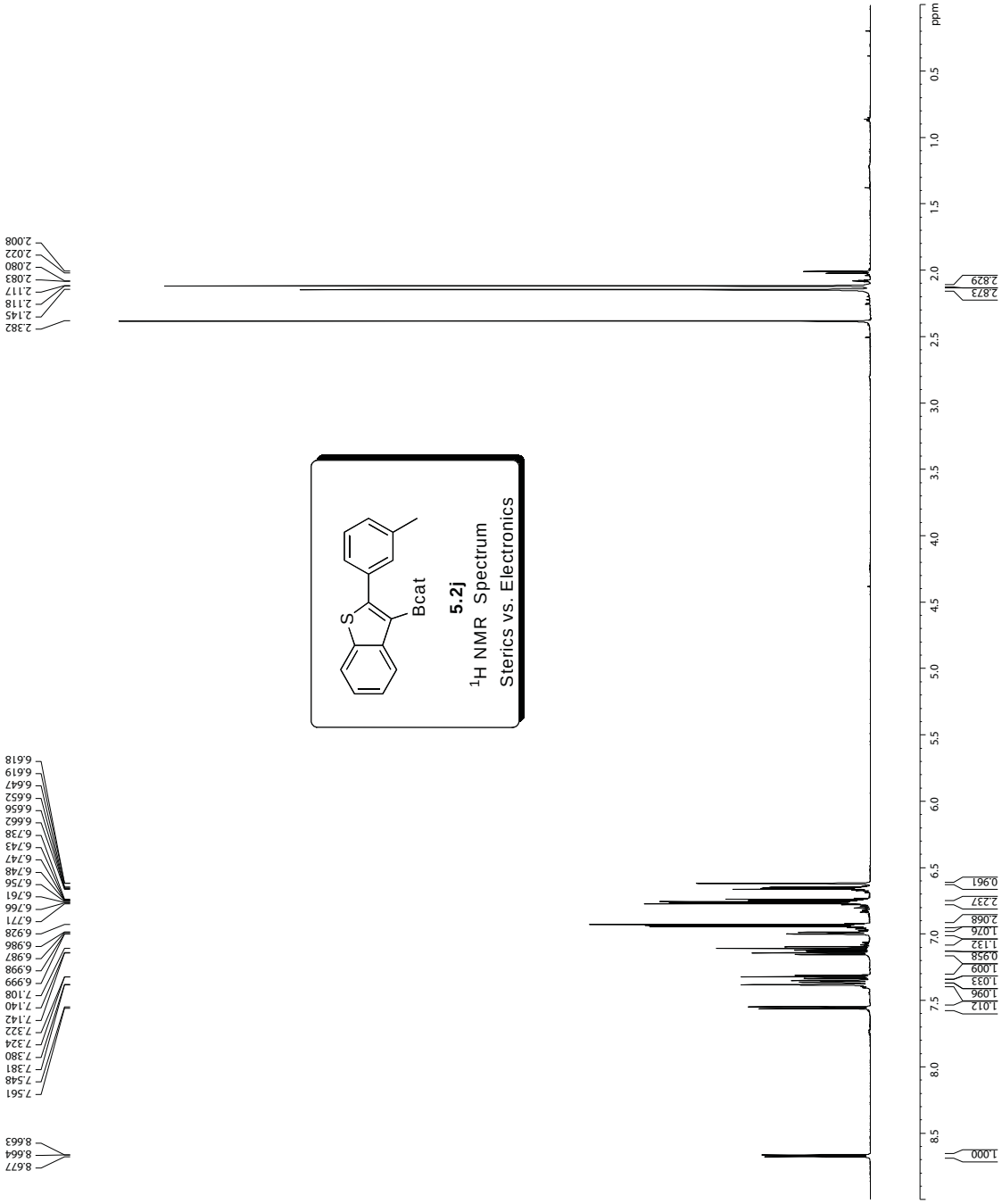
2.110
2.419
6.604
6.697
6.767
6.777
6.782
6.929
6.944
7.460
7.521
8.613
8.626
1.000
1.030
1.057
0.844
1.567
1.108
0.792
3.238
1.821
ppm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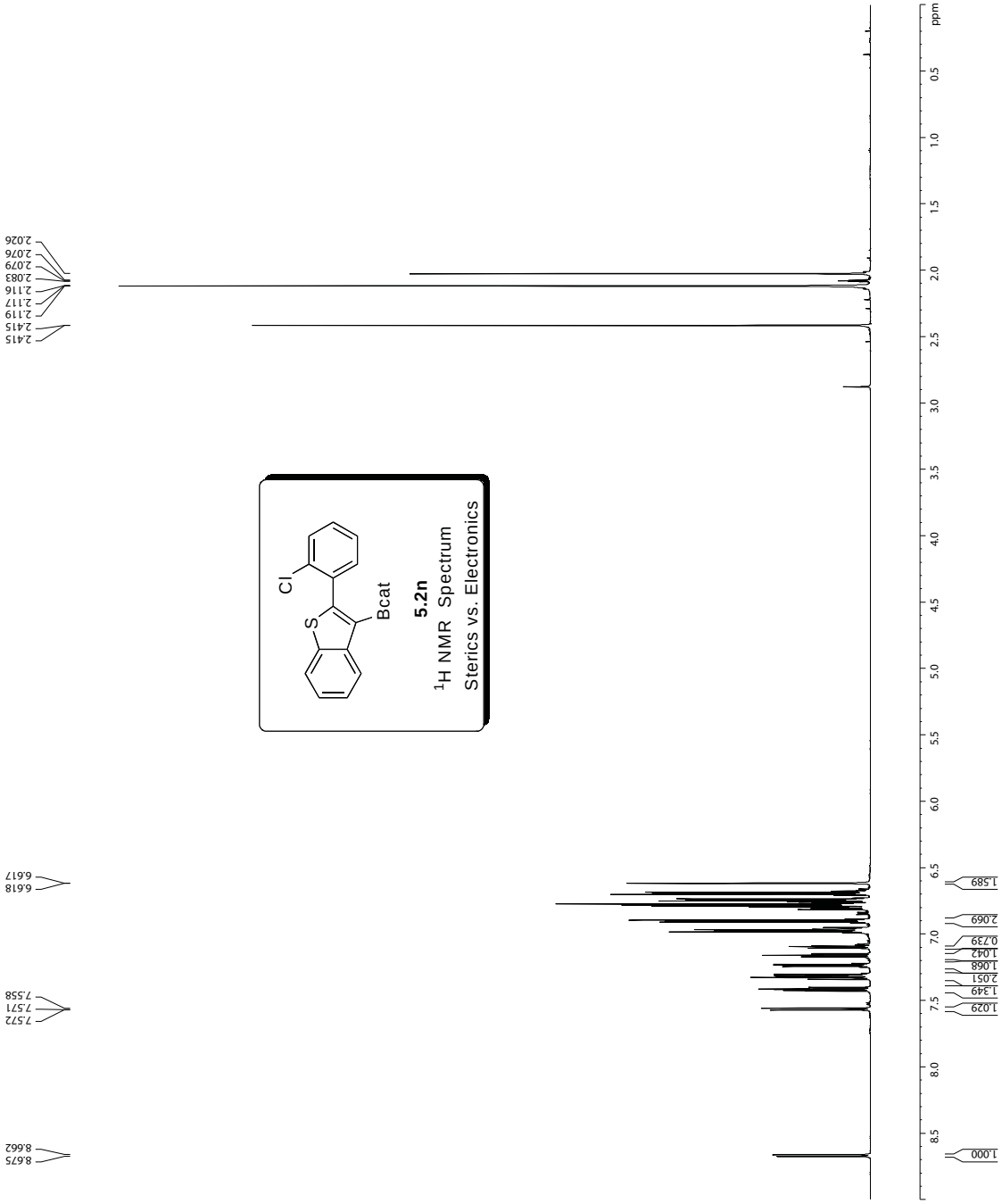
^{1}H NMR Spectrum
Sterics vs. Electronics
S
ppm


Cl
S
Bcat
5.2n
1H NMR Spectrum
Sterics vs. Electronics
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2.076
2.079
2.083
2.116
2.117
2.119
2.415
2.415
6.617
6.618
7.558
7.571
7.572
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1.029
1.349
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1.042
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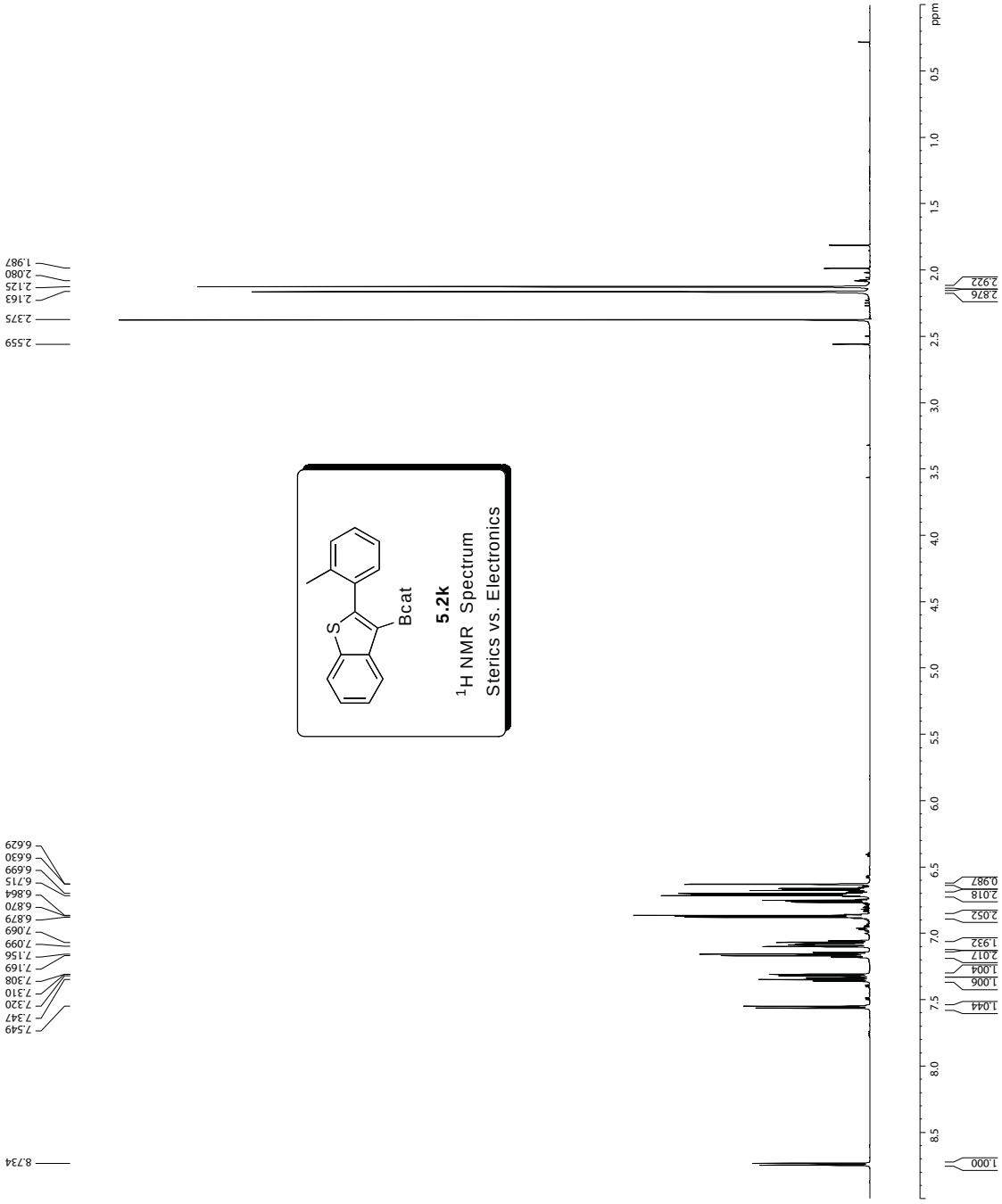
1.589
ppm


Bcat
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Sterics vs. Electronics
S
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7.549
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7.308
7.169
7.156
7.099
7.069
6.879
6.870
6.864
6.715
6.699
6.630
6.629
2.559
2.375
2.163
2.125
2.080
1.987
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1.006
1.004
2.017
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2.052
2.018
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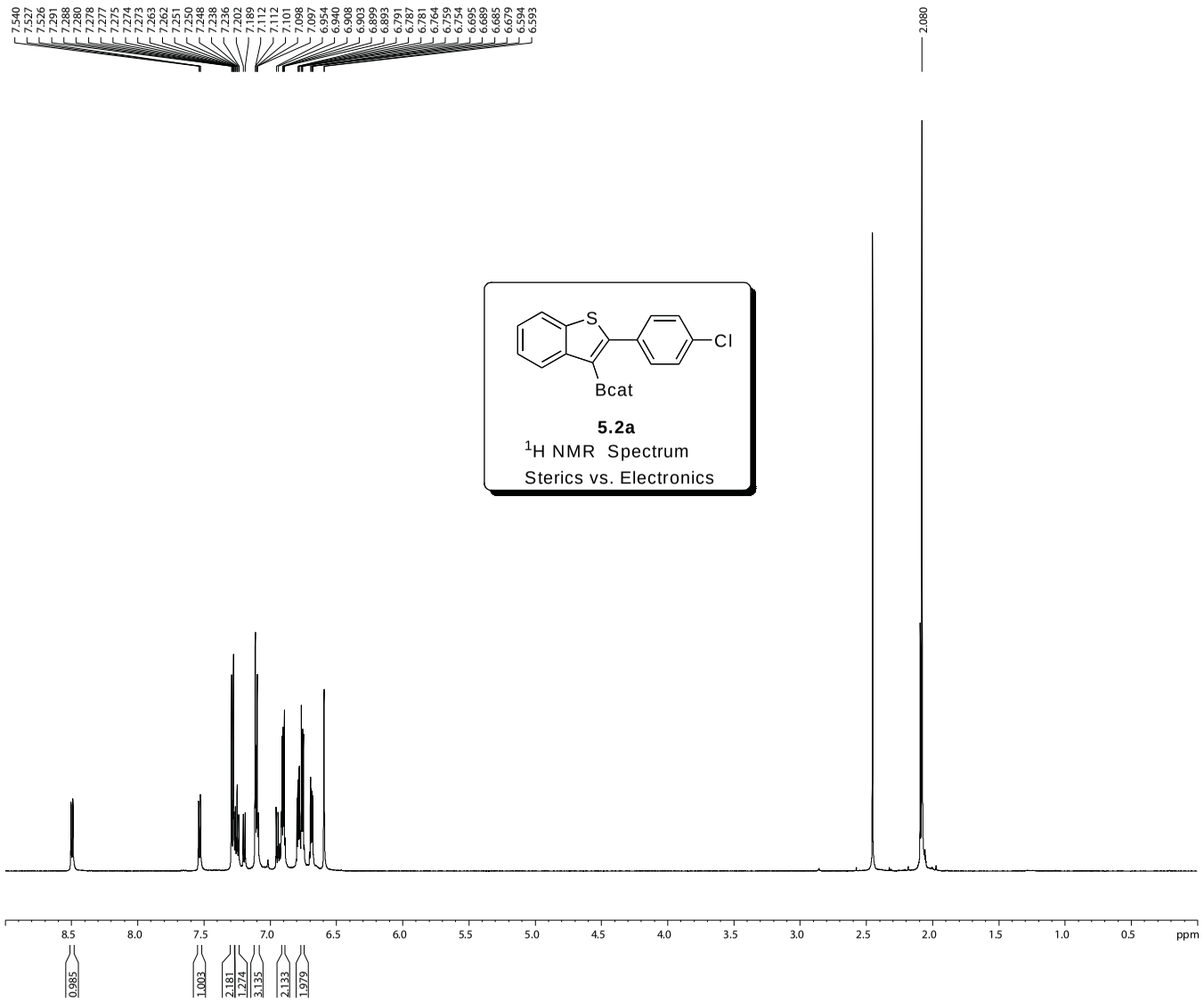
ppm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7.280
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7.277
7.275
7.274
7.273
7.263
7.262
7.251
7.250
7.248
7.238
7.236
7.202
7.189
7.112
7.112
7.101
7.098
7.097
6.954
6.940
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6.903
6.899
6.893
6.791
6.787
6.781
6.764
6.759
6.754
6.695
6.689
6.685
6.679
6.594
6.593
2.080
S
Cl
Bcat
5.2a
1H NMR Spectrum
Sterics vs. Electronics
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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1.0
0.5
ppm
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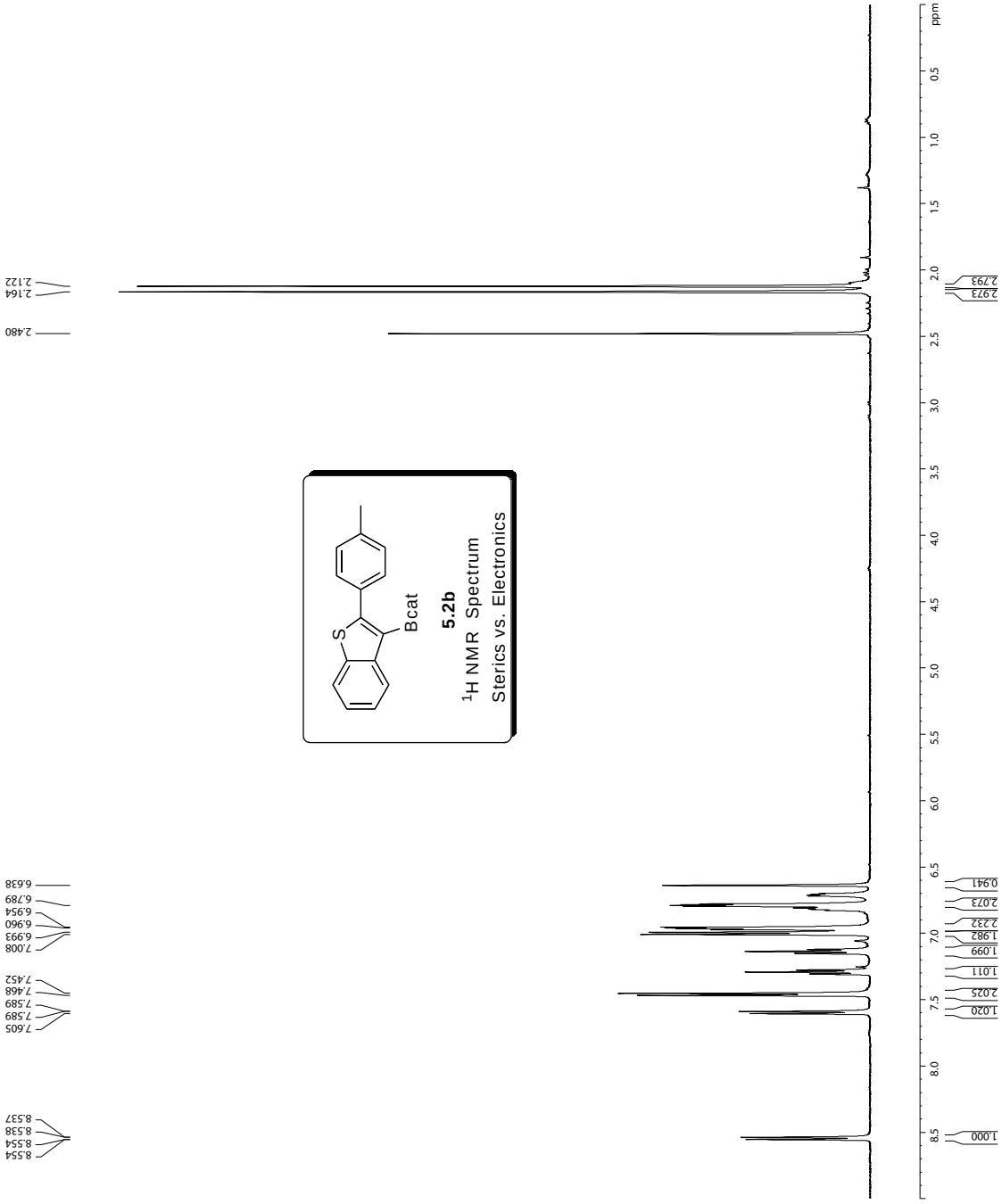
1.003
2.181
1.274
3.135
2.133
1.979


Bcat
S
5.2b
^{1}H NMR Spectrum
Sterics vs. Electronics
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2.122
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8.554
8.554
8.538
8.537
7.605
7.589
7.589
7.468
7.452
7.008
6.993
6.960
6.954
6.789
6.638
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1.020
2.025
1.011
1.099
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2.232
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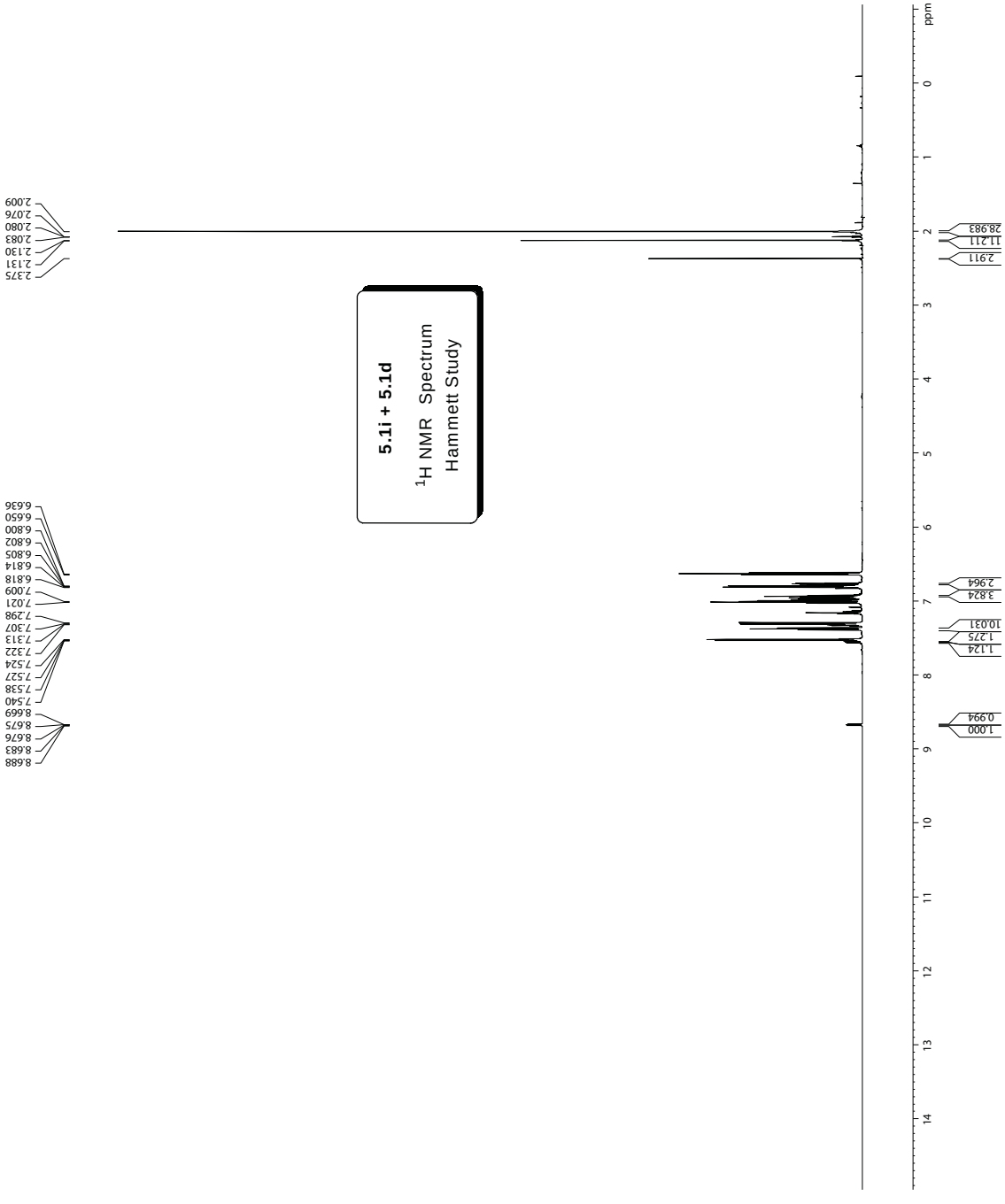
1.000
ppm


5.1i + 5.1d
1H NMR Spectrum
Hammett Study
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8.683
8.676
8.675
8.669
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7.527
7.524
7.322
7.313
7.307
7.298
7.021
7.009
6.818
6.814
6.805
6.802
6.800
6.650
6.636
2.375
2.131
2.130
2.083
2.080
2.076
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2.964
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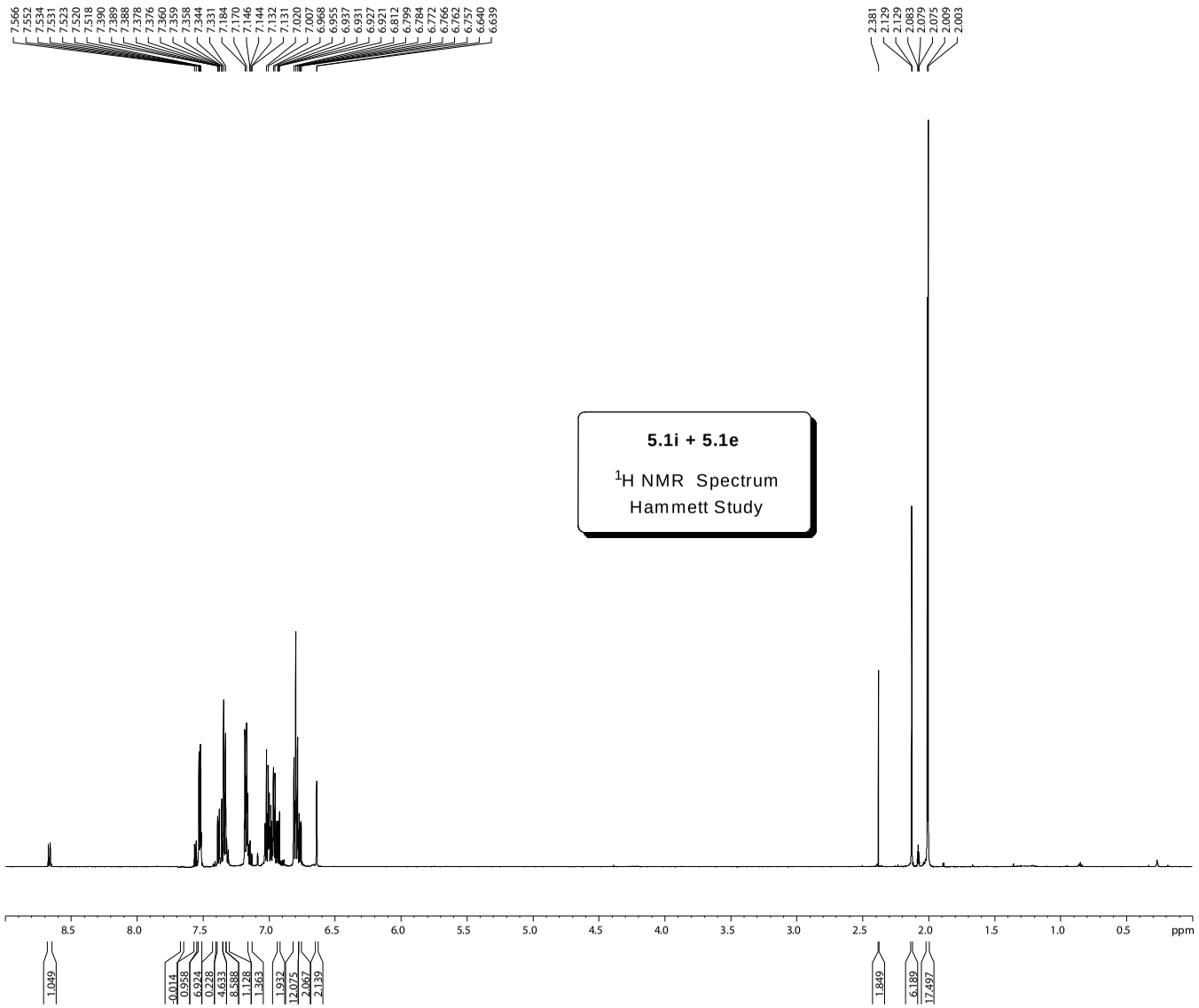
28.983
ppm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7.388
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7.360
7.359
7.358
7.344
7.331
7.184
7.170
7.146
7.144
7.132
7.131
7.020
7.007
6.968
6.955
6.937
6.931
6.927
6.921
6.812
6.799
6.784
6.772
6.766
6.762
6.757
6.640
6.639
2.381
2.129
2.129
2.083
2.079
2.075
2.009
2.003
5.1i + 5.1e
1H NMR Spectrum
Hammett Study
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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1.0
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ppm
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0.958
6.924
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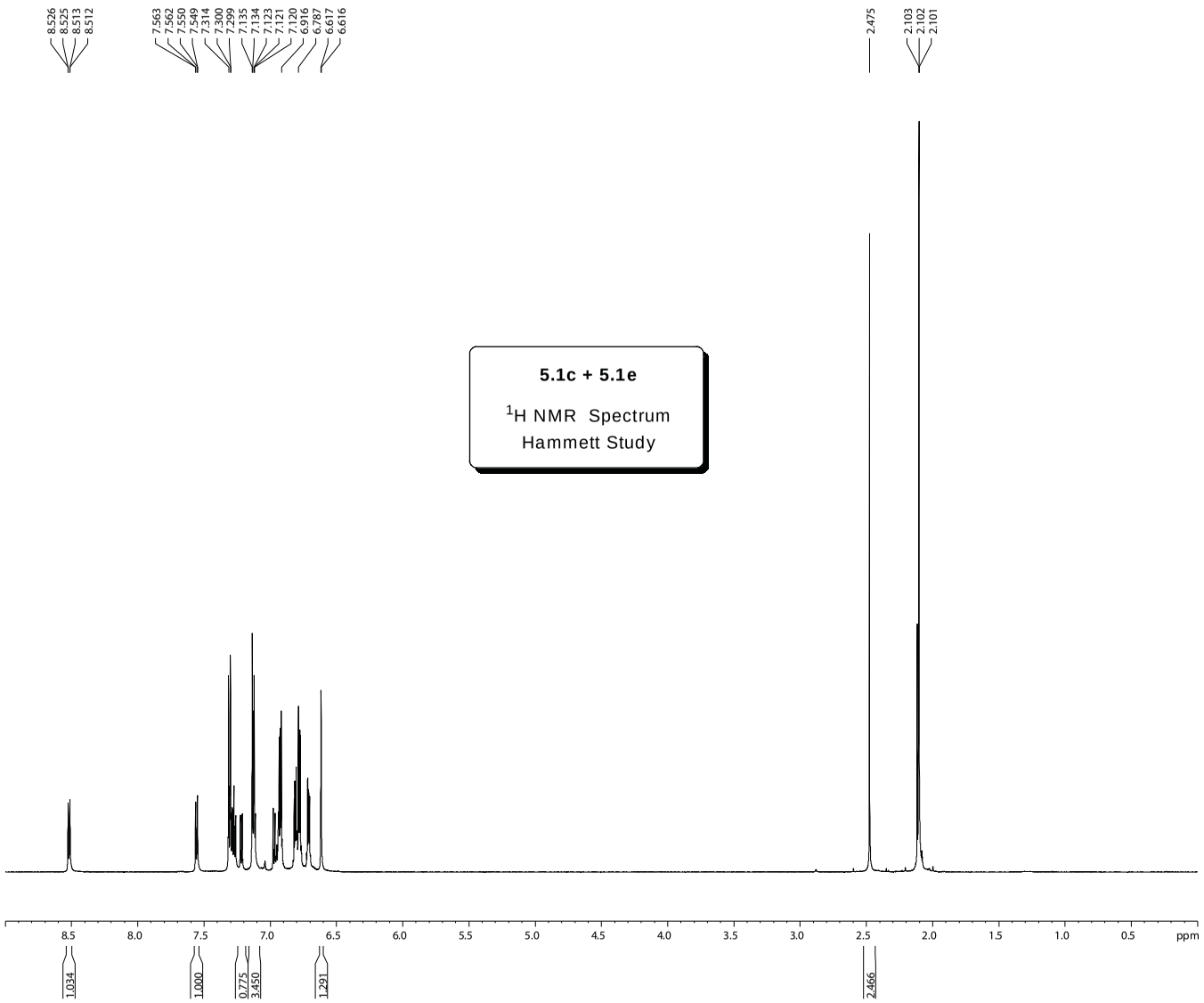
17.497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7.562
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7.549
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7.299
7.135
7.134
7.123
7.121
7.120
6.916
6.787
6.617
6.616
2.475
2.103
2.102
2.101
5.1c + 5.1e
1H NMR Spectrum
Hammett Study
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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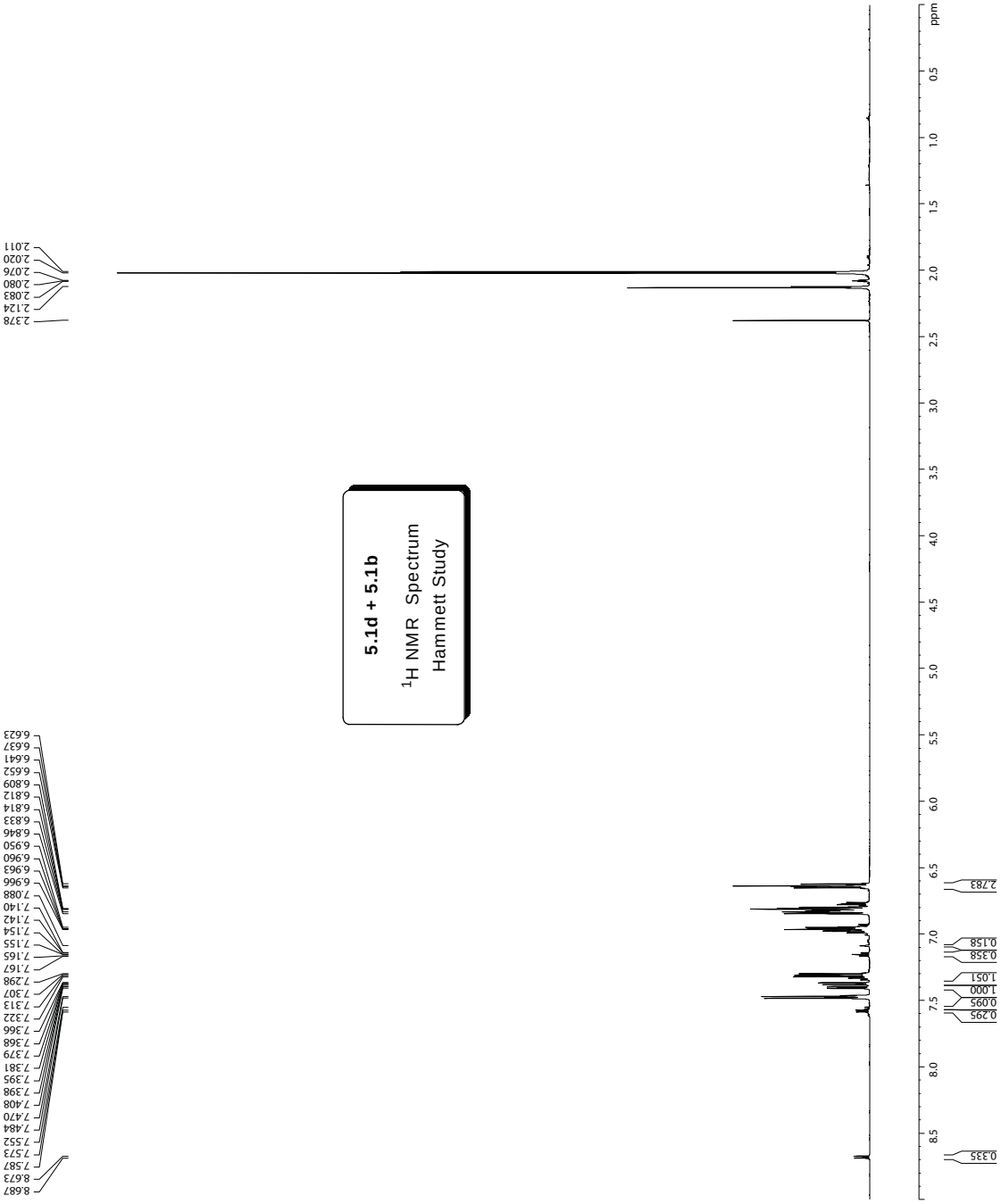
2.466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1H NMR Spectrum
Hammett Study
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0.095
0.295
2.378
2.124
2.083
2.080
2.076
2.020
2.011
8.687
8.673
7.587
7.573
7.552
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7.470
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7.395
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7.322
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7.307
7.298
7.167
7.165
7.155
7.154
7.142
7.140
7.088
6.966
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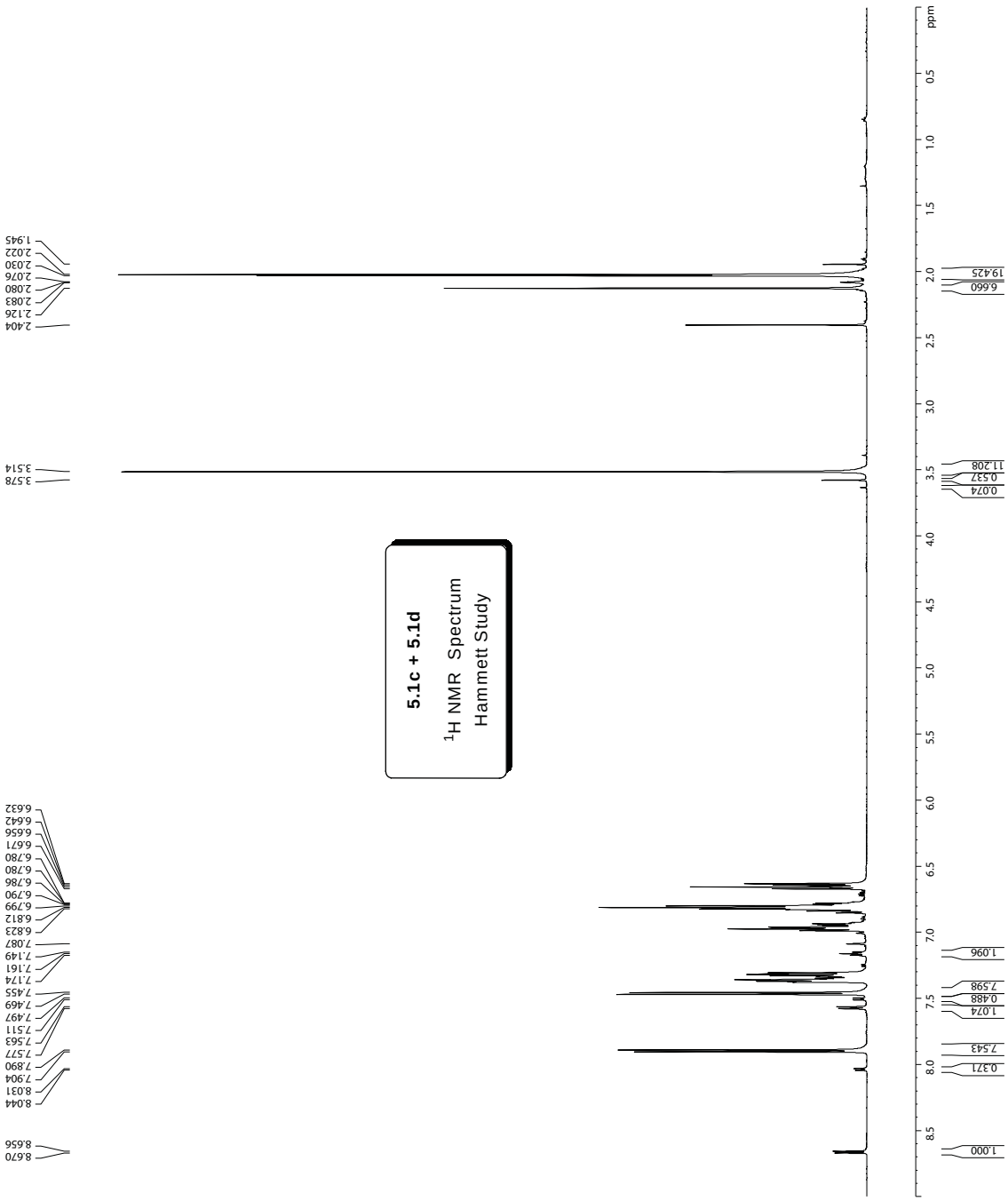
6.637
6.623


5.1c + 5.1d
1H NMR Spectrum
Hammett Study
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7.511
7.497
7.469
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7.174
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7.149
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6.823
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6.799
6.790
6.786
6.780
6.780
6.671
6.656
6.642
6.632
3.578
3.514
2.404
2.126
2.083
2.080
2.076
2.030
2.022
1.945
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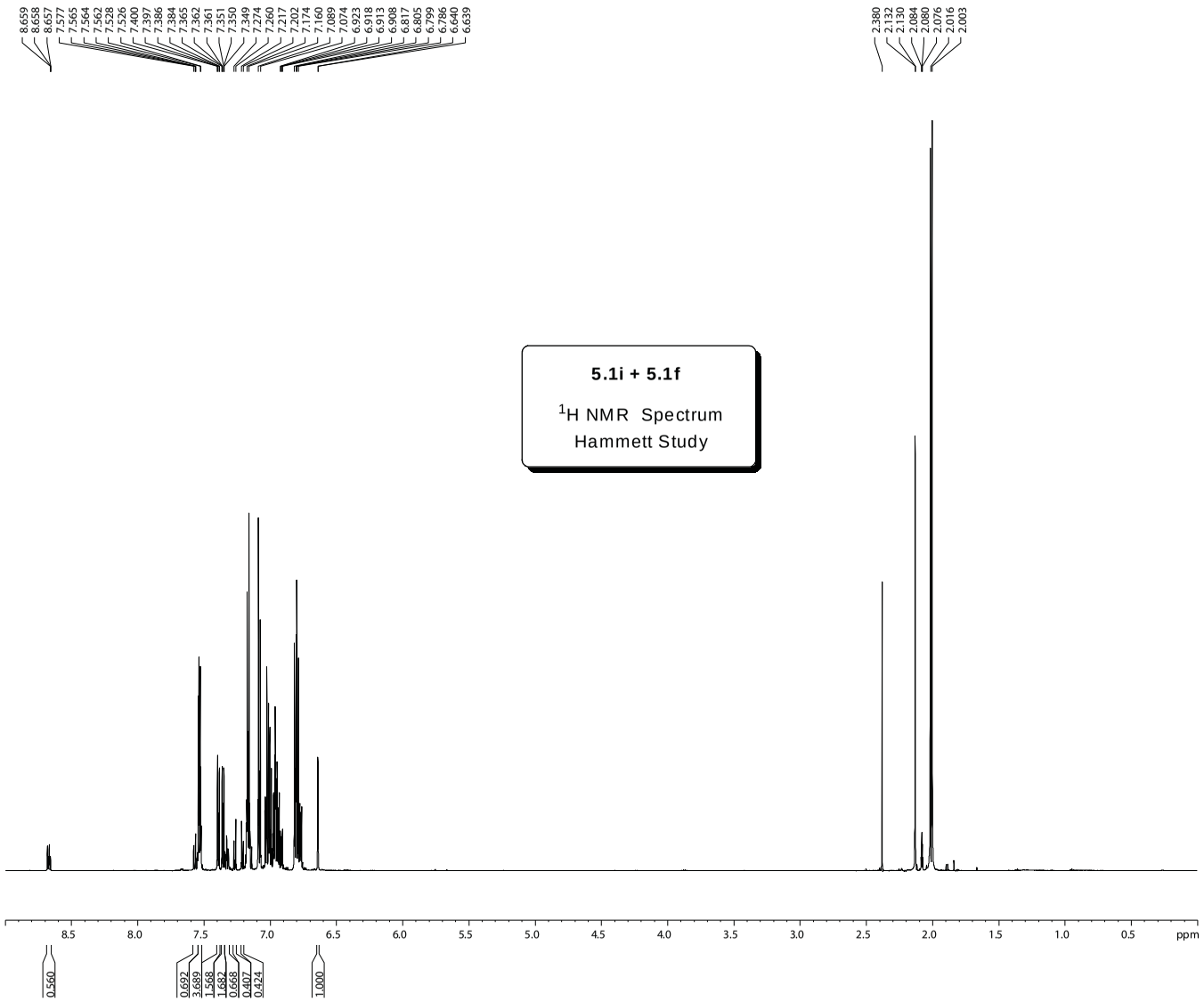
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7.564
7.562
7.528
7.526
7.400
7.397
7.386
7.384
7.365
7.362
7.361
7.351
7.350
7.349
7.274
7.260
7.217
7.202
7.174
7.160
7.089
7.074
6.923
6.918
6.913
6.908
6.817
6.805
6.799
6.786
6.640
6.639
2.380
2.132
2.130
2.084
2.080
2.076
2.016
2.003
5.1i + 5.1f
1H NMR Spectrum
Hammett Study
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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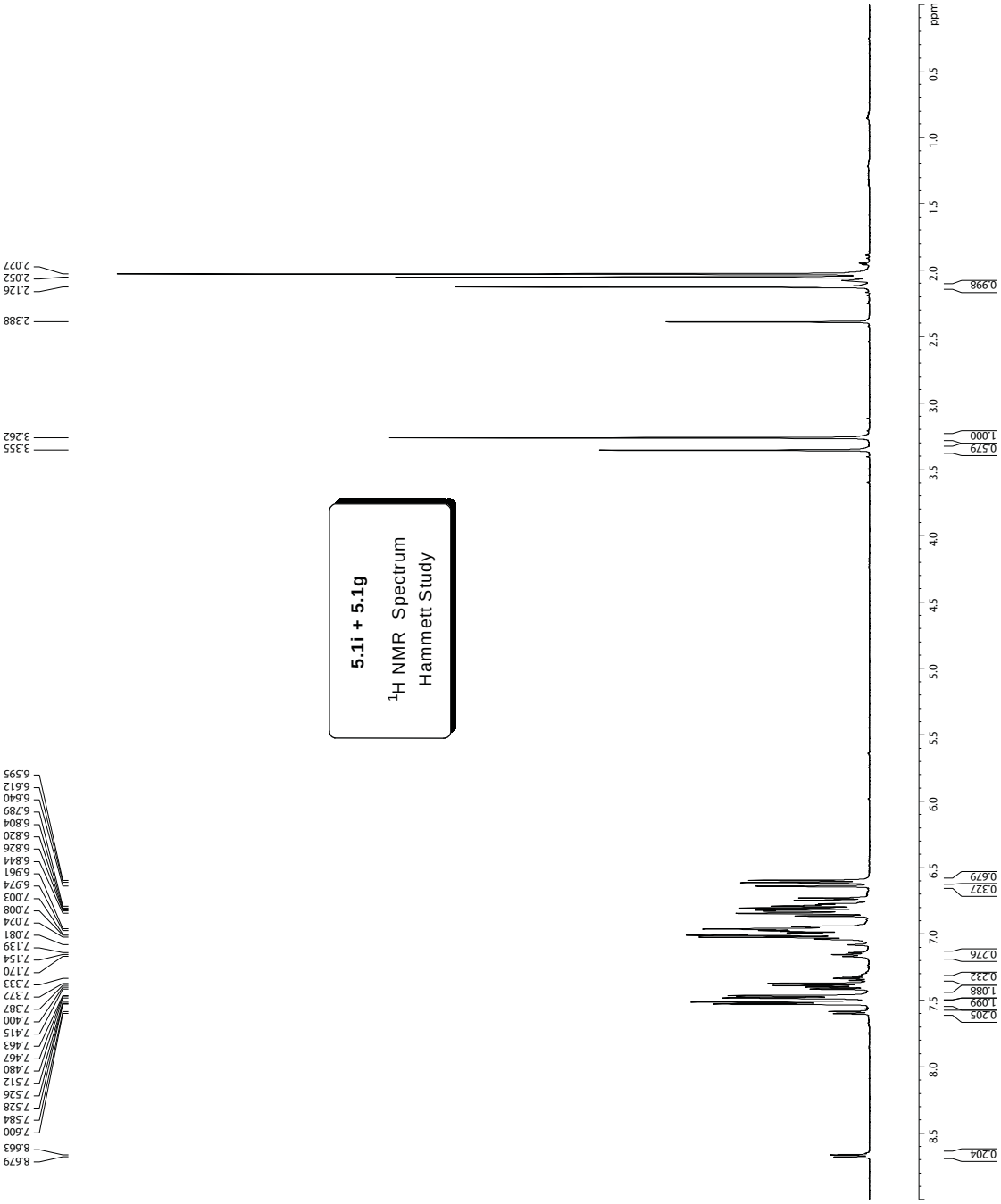
5.1i + 5.1g
^{1}H NMR Spectrum
Hammett Study
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3.262
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6.826
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7.139
7.154
7.170
7.333
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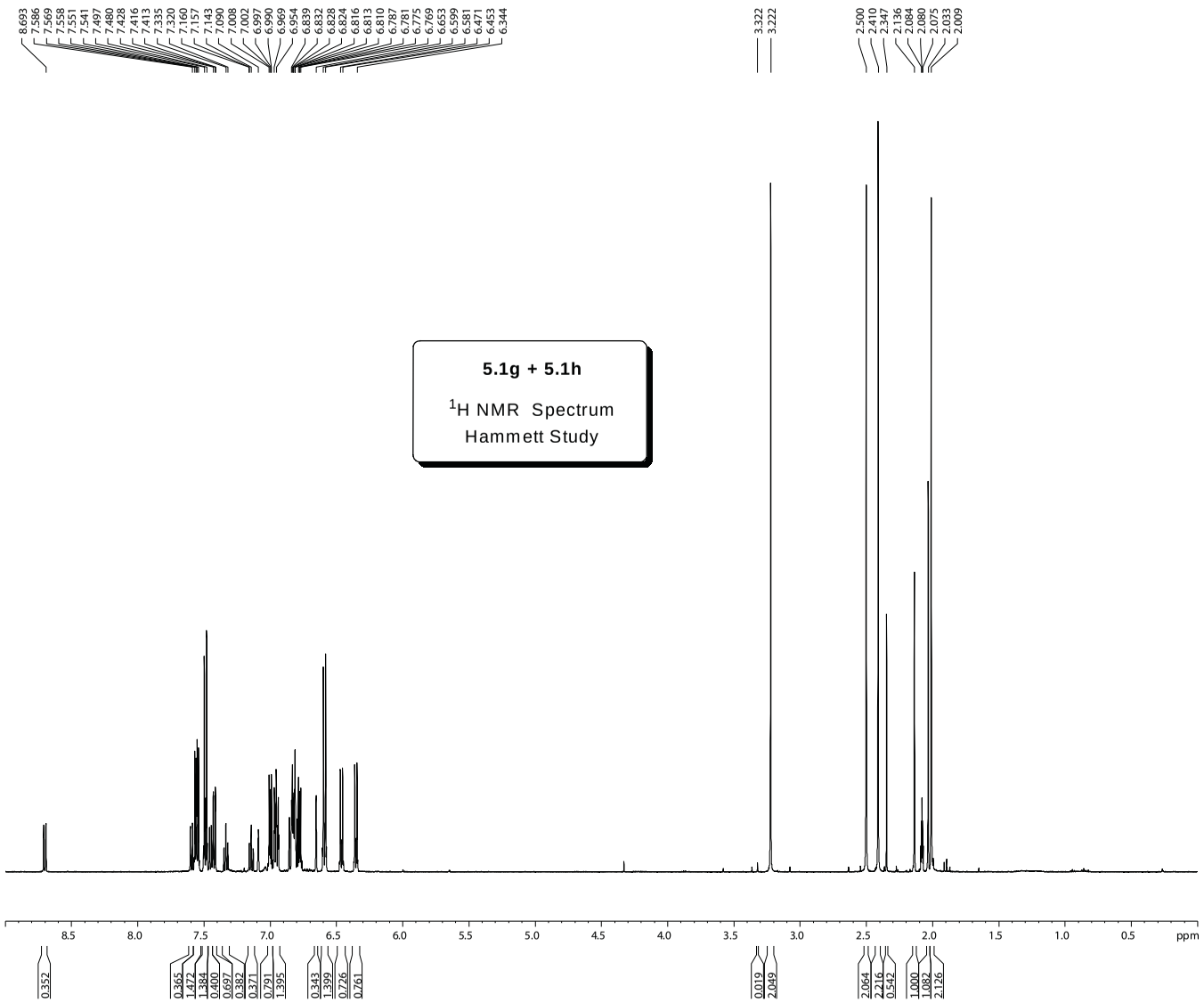
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7.320
7.160
7.157
7.143
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7.008
7.002
6.997
6.990
6.969
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6.839
6.832
6.828
6.824
6.816
6.813
6.810
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6.781
6.775
6.769
6.653
6.599
6.581
6.471
6.453
6.344
3.322
3.222
2.500
2.410
2.347
2.136
2.084
2.080
2.075
2.033
2.009
5.1g + 5.1h
1H NMR Spectrum
Hammett Study
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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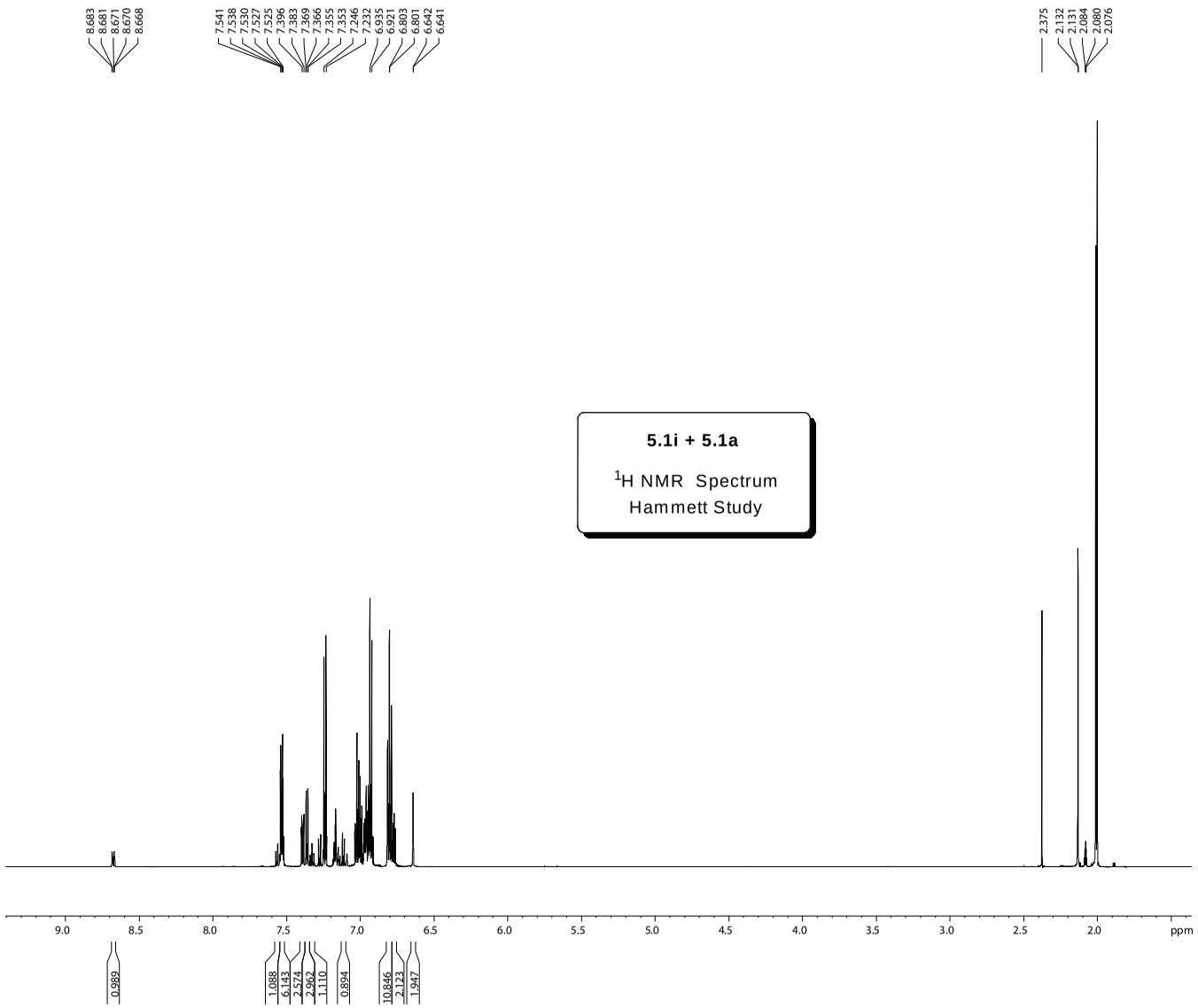
2.126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7.366
7.355
7.353
7.246
7.232
6.935
6.921
6.803
6.801
6.642
6.641
2.375
2.132
2.131
2.084
2.080
2.076
5.1i + 5.1a
1H NMR Spectrum
Hammett Study
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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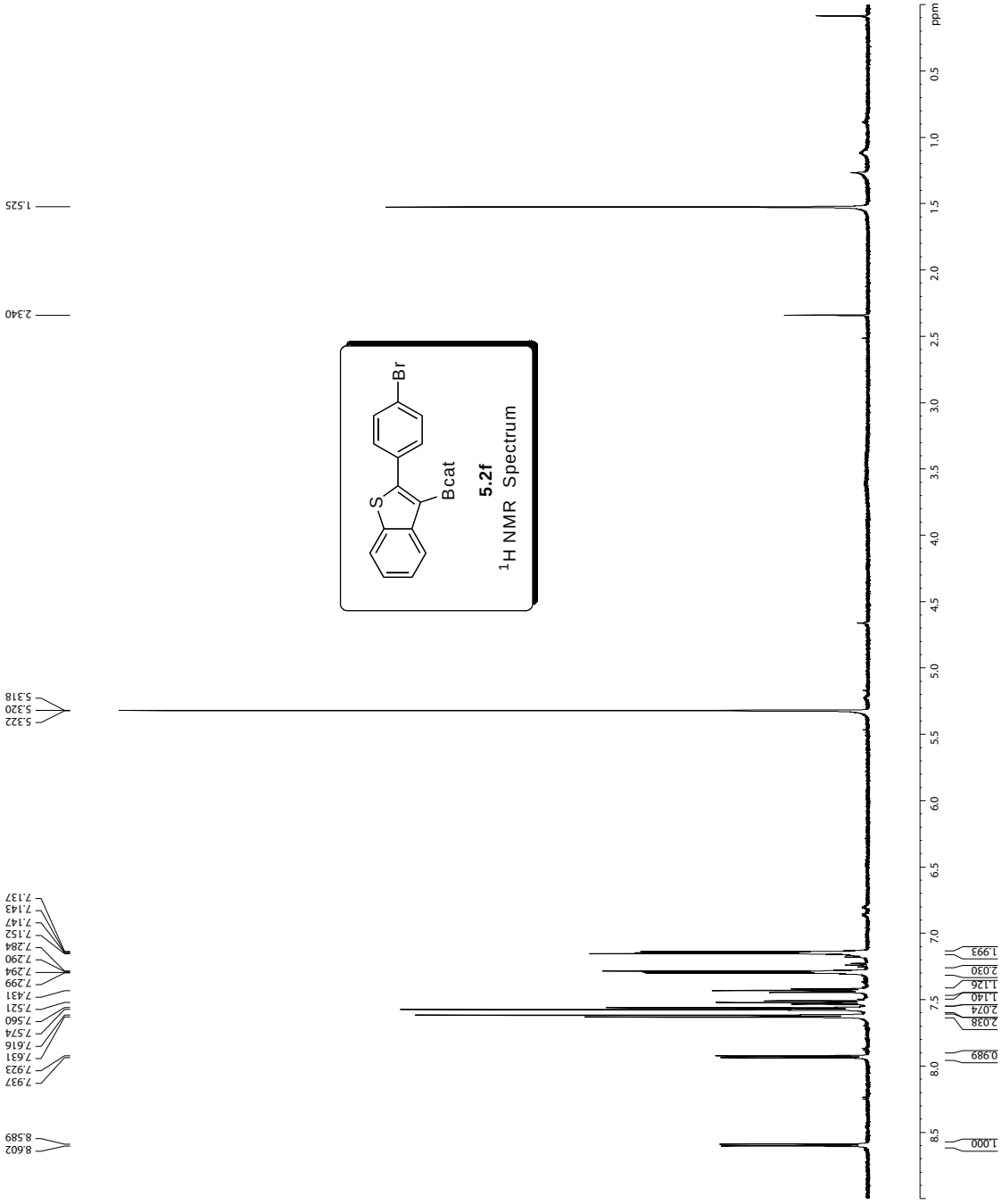
1.947


Br
S
Bcat
5.2f
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7.521
7.431
7.299
7.294
7.290
7.284
7.152
7.147
7.143
7.137
5.322
5.320
5.318
2.340
1.525
1.000
0.989
2.038
2.074
1.140
1.126
2.030
1.993
ppm

Br
S
Bcat
5.2f
^{11}B NMR Spectrum
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ppm
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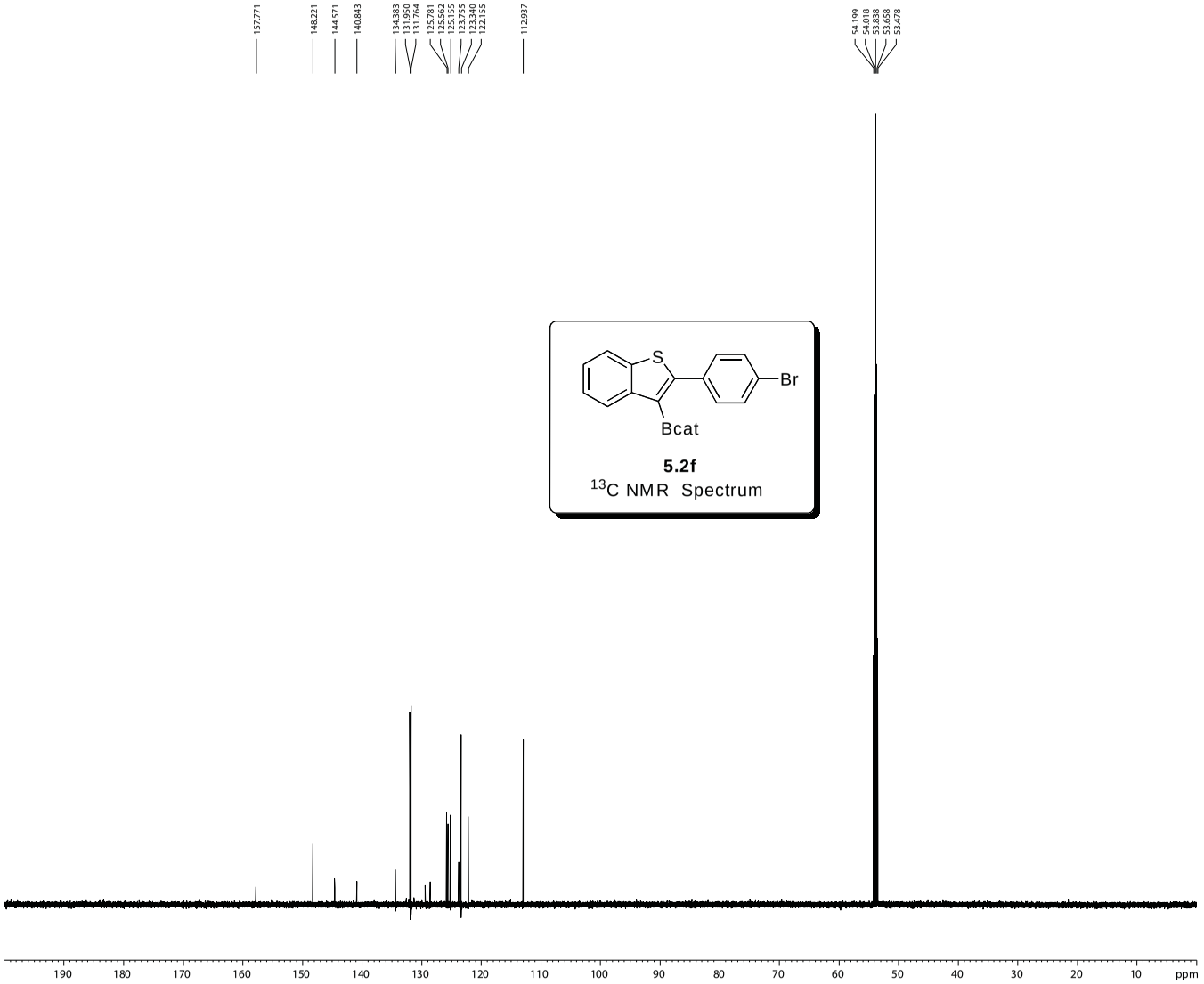
10
15
20
25
30
35
40
45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112.937
54.199
54.018
53.838
53.658
53.478
S
Br
Bcat
5.2f
13C NMR Spectrum
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm