# Short Syntheses of 1-Substituted Dibenzothiophenes and 3-Substituted Naphthothiophenes

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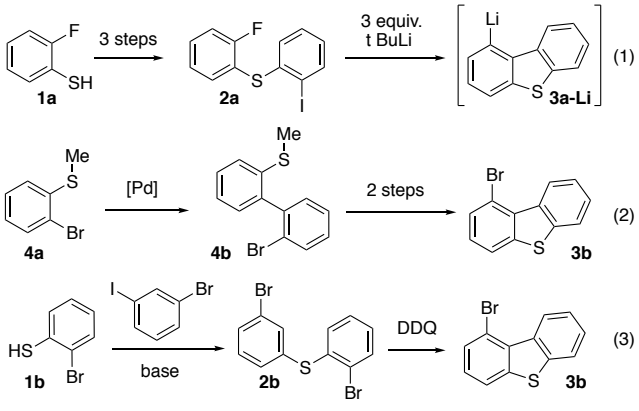
**ABSTRACT:** The 1-substituted dibenzothiophene motif is an unusual substitution pattern. We demonstrate a simple one-pot preparation of 1-lithiodibenzothiophene via a cascade of two benzyne additions and conversion to the aldehyde, boronic ester, and iodide. This work avoids the use of precious metals or tert-butyllithium and is shorter than existing routes to these compounds. We also report an improved route to the isomeric 3-substituted naphthothiophene scaffold. These protocols will allow rapid access to families of these two related heteroacenes.

Substituted polycyclic aromatic hydrocarbons have myriad uses in chemistry, however some substitution patterns are more common than others. Different sites on the rings vary in reactivity, meaning substituents on less reactive sites are difficult to selectively introduce on the parent heterocycle. Isomeric arenes can confer dramatically different properties on molecules that contain them.[1,2] Introduction of heteroatoms such as sulfur into polycyclic aromatic hydrocarbons further changes their properties relative to the parent hydrocarbons, and chemistry to access sulfur-containing polycyclic aromatic hydrocarbons has been an area of substantial study.[3]

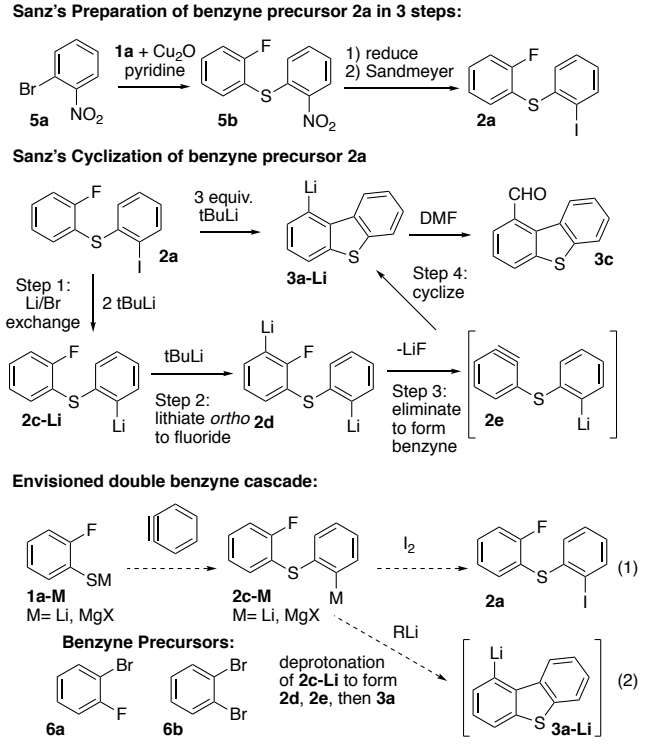
**Scheme 1. Representative syntheses of 1-substituted dibenzothiophenes**




This work concentrates on the chemistry of dibenzothiophene and naphthothiophene, which are isomeric $C_{12}H_8S$ compounds that are both considered sulfur-containing cousins of anthracene. Dibenzothiophenes have been used as components in organic light emitting diodes,[4] and as bulky aryl groups in chiral thiourea based catalysts.[5]Despite interest in accessing 1-functionalized dibenzothiophenes, no reactions exist that are capable of directly functionalizing dibenzothiophene at this position.[6] Dibenzothiophenes functionalized in the 1 position were initially accessed through lengthy introduction, then removal of directing groups on the dibenzothene scaffold.[7] Because of the lengths of these syntheses, subsequent investigations focused on preparation of functionalized dibenzothiophene derivatives via de novo approaches shown in Scheme 1. The most commonly used route to 1-functionalized dibenzothiophenes is based on an elegant intramolecular anionic cyclization developed by Sanz and co-workers (Equation 1, Scheme 1).[8] Thiophenol **1a** is converted to benzyne precursor **2a** which undergoes an intramolecular anionic cyclization to 1-lithiodibenzothiophene **3a-Li**, which can be quenched with electrophiles. Pummerer-based approaches beginning with cross-coupling of **4a** to form biaryl **4b**, which can undergo oxidative conversion to 1-functionalized dibenzothiophene **3b** (Equation 2, Scheme 1).[9] Similar strategies using C-H activation,[10] also require palladium catalysis. The synthesis of **3b** was also reported in patent literature through a two-step procedure involving oxidative cyclization of dibrominated diphenylthioether **2b** with DDQ (Equation 3, Scheme 1).[11]

In the course of our group's research, we required 1-formyldibenzothiophene **3c** (Scheme 2). Preparing this compound from 1-lithiodibenzothiophene **3a-Li** according to the Sanz procedure appeared to be the most efficient route, however we wished to improve the established three-step synthetic route to precursor **2a** for reasons of both time/step economy, and safety.[12]

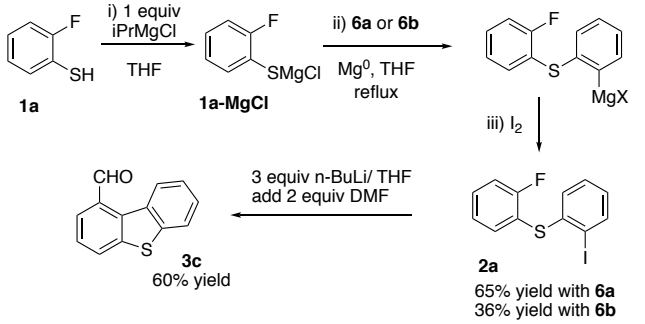
**Scheme 2. Existing and proposed anionic cyclizations**




In the Sanz procedure, compound **2a** was prepared in three steps from 2-fluorothiophenol; a copper-mediated Ullman coupling in pyridine with nitroarene **5a** was followed by reduction of the nitro group in product **5b** to an aniline, then a Sandmeyer reaction to convert the aniline to iodide **2a**. Exposure of **2a** to three equivalents of t-BuLi results in a cascade that ultimately produces 1-lithiodibenzothiophene. Two equivalents of t-BuLi effect a lithium-iodine exchange to produce **2c-Li**. The third equivalent ortho-lithiates the fluorine-bearing aromatic ring on **2c-Li**, producing **2d**. Warming the reaction results in the elimination of lithium fluoride from **2d** to generate benzyne **2e**, which is rapidly trapped by an intramolecular addition of the aryllithium that arose from the aryl iodide. Sanz and co-workers showed that the resulting 1-lithiodibenzothiophene could be trapped by a variety of electrophiles, including DMF (to give **3c**), yielding diverse 1-substituted dibenzothiophenes.

We hypothesized that the carbon sulfur bond in compound **2a** could be prepared by addition of a metal thiolate to benzyne, as shown in the lower part of Scheme 2. Thiolates are one of the best nucleophiles for addition to benzyne,[13] and Knochel and co-workers have reported procedures to generate complex arylthioethers through thiolate addition to benzyne followed by trapping with an electrophile.[14] Applied to target **2a**, addition of the 2-fluorothiophenolate anion **1a-M** to benzyne, followed by quenching the resulting organometallic **2c-M** with iodine would afford **2a** in a one-step procedure. This avoids the C–S coupling on a halo-nitroarene and subsequent reduction and Sandmeyer reactions (Equation 1, Scheme 2). Alternatively, for M=Li, more butyllithium could be added to **2c-Li** to intercept the Sanz cascade, terminating in 1-lithiodibenzothiophene **3a-Li** (equation 2, Scheme 2). In our initial reaction attempt, we chose the insertion of magnesium into 1,2-bromofluorobenzene **6a** to generate benzyne (Scheme 3), rather than using the relatively expensive iodophenol-derived benzyne precursors used by Knochel. Benzyne precursor dihalobenzenes have been used on a large scale to prepare hindered phosphine ligands,[15] and the pharmaceutical Chantix.[16]

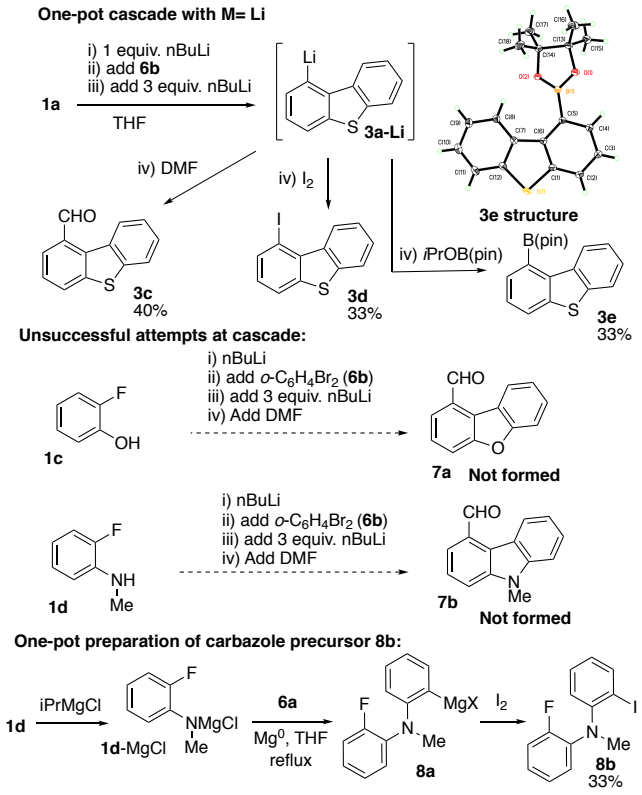
**Scheme 3. Magnesium thiolate/benzyne route to 2a**




Compound **1a** in THF was deprotonated with isopropylmagnesium chloride, with magnesium turnings already in the vessel. The resulting mixture was heated to reflux, and benzyne precursor **6a** was added. Upon disappearance of the magnesium, the reaction was allowed to cool and solid iodine was added. Quenching and work-up, followed by crystallization afforded dihalothioether **2a** in 65% yield. Dibromobenzene **6b** could be used instead of **6a**, however a reduction in yield to 36% was observed.

We explored the cyclization of **2a** without the use of tert-butyllithium. N-butyllithium would be able to effect lithium-halogen exchange on **2a**, and deprotonation ortho to the aryl fluoride. We added three equivalents of *n*-butyllithium at –78 °C, followed by aging at that temperature for 30 minutes, then holding at °0 C for 30 minutes. The reaction mixture was re-cooled to –78 °C and DMF was added. After work-up, 1-dibenzothiophene carbaldehyde **3c** was obtained in 60% yield. Gratified that the *tert*-butyllithium could be replaced with *n*-butyllithium, we investigated the use of *n*-butyllithium for both thiolate and initial benzyne formation (Scheme 4), to directly intercept intermediate **2c-Li** (shown in Scheme 2) and allow access to **3a-Li** and subsequent derivatives in one pot from thiol **1a**. This would avoid the use of iodine and magnesium, further increasing the efficiency of this cascade reaction.

**Scheme 4. Exploration of one-pot lithium thiolate route to 1-dibenzothiophene derivatives and related compounds**

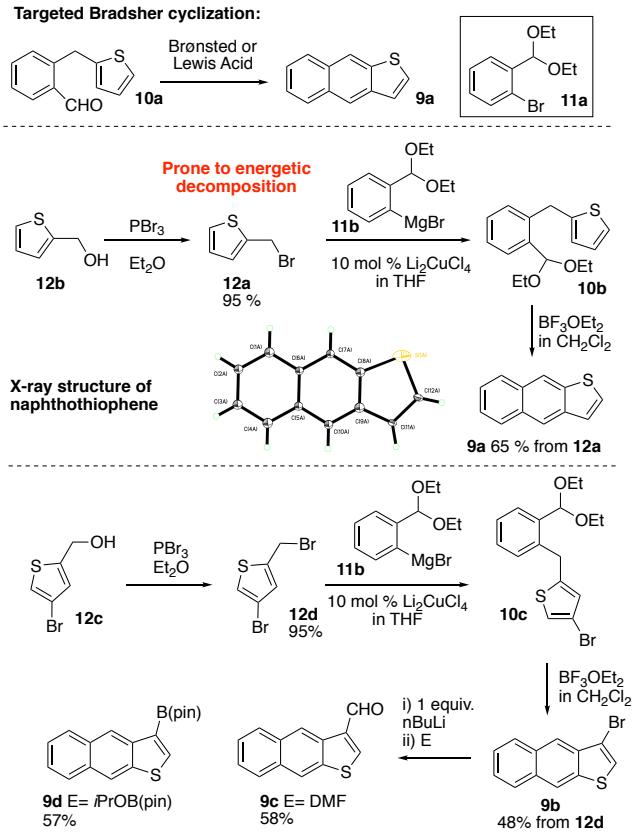



Thiol **1a** was deprotonated with *n*-butyllithium at –78 °C, followed by addition of either benzyne precursor **6a** or **6b**. Subsequent addition of 3 equivalents of *n*-butyllithium was followed by aging at –78 °C for 30 minutes.[17] The reaction mixture was then warmed to 0 °C for 30 minutes, recooled, and quenched with DMF. Benzyne precursor **6a** gave a complex mixture, and while **3a** was present, it was a minor component. Gratifyingly, **3b** allowed production of aldehyde **3c** in 40 % isolated yield after purification by column chromatography. We attribute this difference to the fact that benzyne formation from **6b** and butyllithium is known to be complete at –78 °C, whereas **6a** does not produce benzyne at that temperature, and requires warming meaning competing reactions could occur in the interim.[16b,17] The success of this reaction also depends on the thiolate preferentially adding to the benzyne rather than butyllithium. Use of THF as the solvent was critical. Substitution of diethyl ether or toluene for THF using the same procedure provided more complicated mixtures than the THF reaction, with only traces of **3c**. Bailey has reported heptane/THF mixtures can provide cleaner lithium halogen exchanges than pure THF.[18] Replacing THF with a 10:1 mixture of heptane and THF in the cascade resulted in a complex mixture of products. The deprotonation of thiophenol **1a** in the 10:1 mixture of heptane/THF at either –78 °C or 0 °C resulted in the formation of a white precipitate. Reaction inhomogeneity in this solvent system presumably prevented rapid addition of the thiophenoxide anion to benzyne, allowing side reactions. We explored the use of other quenching agents to produce potential cross-coupling partners. Quenching with iodine afforded iodide **3d** in 33% yield. Quenching with isopropoxyB(pin) allowed isolation of pinacolborate **3e** in 33% yield. This compound was crystallized, and single crystal X-ray diffraction allowed confirmation of the regioslectivity.

The high nucleophilicity of the thiophenoxide appeared crucial to the reaction's success. Attempts to prepare the dibenzofuran analogue with the optimized cascade starting with 2-fluorophenol **1c** yielded complex mixtures of products with nothing we could attribute to **7a**. Sanz and co-workers reported the preparation of 1-substituted N-methylcarbazoles such as **7b** by a comparable route to that used with the dibenzothiophenes. Attempted use of **1d** in the one-pot sequence resulted in an intractable mixture. We surmised that the addition of the lithiated aniline to benzyne was slower than the corresponding thiophenoxide, allowing undesirable side reactions to predominate. Fortunately, the magnesium route was successful applied to conversion of 2-fluoro-N-methylaniline **1d** to organomagnesium **8a**, and subsequently to fluoro-iodoaniline **8b**. Compound **8b** had been previously prepared in a 3-step sequence starting with palladium mediated Buchwald-Hartwig coupling between 2-fluoro-N-methylaniline **1d** and 2-bromonitrobenzene. While the yield for the sequence to prepare **8b** shown in Scheme 4 was only 33%, this is comparable to the Sanz route over three steps. Compound **8a** can now be accessed in one step, rather than three, without the use of palladium salts, nitroarene reduction, or the Sandmeyer reaction.

We subsequently explored derivatives of naphthothiophene **9a** (Scheme 5), which is an isomer of the dibenzothiophene scaffold. Naphthothiophene is not currently commercially available. Existing syntheses of naphthothiophene and derivatives involve a multi-step synthesis consisting of a Friedel-Crafts reaction, followed by Clemmsen reduction or HI/ red phosphorus reduction, redox transformation of a carboxylate to an aldehyde, and Bradsher cyclization on a substrate such as **10a**.[19,20] Bradsher cyclizations to prepare thiophene-containing acenes are particularly effective, because of the electron-rich nature of thiophenes so we wished to keep this as a key step.[21,22]A related strategy to access thiophene analogs of anthrone was used by MacDowell and co-worker. [23] We sought to prepare the Bradsher cyclization substrate by alkylation of a Grignard reagent derived from commercially available bromoacetal **11a** with thienylmethyl bromide **12a**.[24] Bromide **12a** is accessible in 1 step from commercial flavoring ingredient thienylmethanol **12b**.

**Scheme 5. Bradsher route to 3-naphthothiophene derivatives**




Addition of an excess of the Grignard reagent **11b**, formed from **11a** and magnesium turnings to a mixture of thienylmethyl bromide **12a** and 10 mol% lithium tetrachlorocuprate in THF at 0 °C afforded coupling product **10b**.[25] Addition of $BF_3$-$OEt_2$ to a dichloromethane solution of unpurified **10b** effected Bradsher cyclization to naphthothiophene **9a**, which was readily purified by column chromatography. This sequence afforded naphthothiophene **9a** on gram scale in 65% yield over three steps from abundant 2-thienylmethanol **12b** with one purification. Crystals of 9a were grown by evaporation from an ethereal solution that while disordered allowed satisfactory X-ray analysis, providing the first crystal structure of **9a.** Unfortunately during scale-up we observed that intermediate **12a** was not a stable compound. A five-gram sample of **12a** underwent vigorous decomposition at room temperature. The unobserved decomposition ejected the stopper and charred material from the flask. The remaining black solid was not soluble in any common laboratory solvents, precluding further analysis. Many electron-rich alkoxybenzyl halides are unstable or are only stable in solution.[26] We assume the decomposition noted in our sample of **12a** was a consequence of an exothermic ring-alkylation polymerization with release of HBr.

We turned to a synthesis of derivative **9b** via an analogous route to that employed for **9a**, but where the bromine was pre-installed on the desired position of the thienylmethyl group with the anticipation this would stabilize the corresponding intermediate. Compound **9b** has been previously prepared using traditional approaches to naphthothiophene synthesis that requires HI/red phosphorus, which can be difficult to obtain in some jurisdictions.[20] Alcohol **12c**, prepared by sodium borohydride reduction of the commercially available aldehyde, was brominated with $PBr_3$. Thienyl bromide **12d** solidified upon cooling, and we never observed decomposition of this compound in the solid state. Lithium tetrachlorocuprate-mediated coupling with Grignard reagent **11b** gave **10c**. Attempts to purify **10c** by column chromatography before the Bradsher cyclization did not result in improved purity and only detracted from the yield in the subsequent step. Unpurified **10c** underwent Bradsher cyclization mediated by boron trifluoride etherate to form **9b** in 48% yield from **12d**, indicating minimal perturbation from the bromide to the cyclization reaction. Use of an excess of Grignard reagent in the previous step is important to ensure complete consumption of **12d** since **12d** is challenging to separate from naphthothiophene **9b** by column chromatography, and can release HBr, which decomposes **9b**. Only one positional isomer of bromide **9b** was observed in the Bradsher cyclization. Bromonaphthothiophene **9b** was prepared on a 2.5 gram scale over 3 steps from **12d** by this route, with only one purification required. This compares favourably in terms of yield, step-count, and reagent availability to the existing route to **9b**.[20]

A family of derivatives of naphthothiophene were prepared in analogy to those we prepared with dibenzothiophene. We had some trepidation about the stability of 3-lithionaphthothiophene.[27] Bromide **9b** underwent lithium halogen exchange at –78 C in THF, however addition of the bromide to an excess of nBuLi was essential to obtain a clean reaction. Addition of nBuLi to a solution of the bromide gave isomeric product mixtures, which is also known for the lithiation of 3-bromothiophenes.[28] Quenching with DMF afforded aldehyde **9c** in 58% yield. Quenching the aryllithium with isopropoxy pinacolboronate afforded arylpinacolboronate **9d** in 57% yield.

In conclusion, we demonstrate the synthesis of polycyclic thiophenes with functionalization at specific positions. These convenient methods do not use precious metal catalysts or tert-butyllithium and are shorter and of comparable or higher yield than existing approaches to these families of heterocycles. Study of applications of these heterocycles is underway in our laboratory and will be reported in due course.

**Experimental:**

General experimental: All reactions were conducted under nitrogen in oven dried glassware unless otherwise stated. Solvents were purchased as anhydrous grades and were not further purified before use, with the exception of dichloromethane, which was not anhydrous, and was dried by distillation from calcium hydride.

**2-fluorophenyl-2-iodophenyl thioether (2a):** Magnesium turnings (0.683 g, 28.1 mmmol, 1 equiv) were placed in a 100 mL three neck flask equipped with a condenser under a nitrogen atmosphere. THF (28 mL) was added. Thiophenol **1a** (3.0 mL, 28.1 mmol, 1 equiv) was added. Isopropylmagnesium chloride (1.67 M in THF, 16.8 mL, 28.1 mmol, 1 equiv) was carefully added, which resulted in heating of the reaction to reflux. After bubbling subsided, the reaction was placed in an oil bath at 80 °C. When reflux resumed, halide **6x** (3.07 mL, 28.1 mmol, 1 equiv) was cautiously added in 5 portions with 10 minutes between each portion. The reaction was heated for a further hour, at which time negligible magnesium remained and the solution was clear and light brown. The reaction was removed from heat, allowed to cool to ambient temperature, and solid iodine was cautiously added with stirring. The reaction self-heated to a gentle reflux, which abated as the reaction was stirred for a further hour. The resulting cloudy brown mixture was poured into 50 mL of saturated aqueous $Na_2S_2O_3$ and stirred for 10 minutes. The mixture was extracted with 2x 100 mL portions of diethyl ether, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil, which slowly solidified. This was dissolved in 100 mL hexanes with heating and placed in a –15 °C freezer. Colourless crystals formed, which were collected by filtration to afford 3.34 g of **2a**. The mother liquor was purified by column chromatography (1% ethyl acetate in hexanes) to afford a further 2.70 g of **2a** (6.04 g total, 18.2 mmol, 65% yield from **1a**). Spectral data agreed with literature values.[8]

$^1$H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, *J*= 7.9, 1.4 Hz, 1H), 7.40–7.36 (m, 2H), 7.23–7.20 (m, 1H), 7.18–7.14 (m, 2H), 6.96 (ap. d, *J*= 7.9 Hz, 1H), 6.89 (td, *J*= 7.6, 1.6 Hz, 1H). $^{13}$C{$^1$H} NMR (125 MHz, $CDCl_3$): δ 162.0 (d, *J*= 248.4 Hz), 140.5, 139.9, 135.2, 130.9 (d, *J*= 8.1 Hz), 129.3, 128.9, 127.9, 125.2 (ap. d, *J*= 3.44 Hz), 121.2 (d, *J*= 18.3 Hz), 116.5 (d, *J*= 22.3 Hz), 99.3. $^{19}$F NMR (470 MHz, $CDCl_3$): δ -107.0–-107.1 (m).

**1-lithiodibenzothiophene (3a-Li):** Compound **1a** (0.84 mL, 7.86 mmol, 1 equiv) was dissolved in 10 mL THF in a 100 mL Schlenk flask. The mixture was cooled to –78 °C in dry ice/acetone. *N*-Butyllithium (2.6 M in hexanes, 3.12 mL, 8.1 mmol, 1 equiv) was added dropwise over 1 minute. The reaction was stirred for 30 minutes, then dibromobenzene **6b** (0.96 mL, 7.95 mmol, 1 equiv) was added. *N*-butyllithium (2.6 M in hexanes, 9.36 mL, 24 mmol, 3 equiv) was added dropwise over 5 minutes, and the reaction was stirred for 30 minutes. The reaction was moved from the dry ice/acetone bath to an ice bath and stirred for 45 minutes. The reaction was then returned to the dry ice/actone bath, allowed to cool for 5 minutes, the appropriate quenching agents was added:

**1-dibenzothiophenecarboxaldehyde (3c):** To the above prepared solution of 1-lithiodibenzothiophene was added DMF (1.81 mL, 23.2 mmol, 3 equiv). A thick precipitate immediately formed. The reaction was removed from the dry ice/acetone bath, stirred for 1 hour, and then quenched by the addition of 25 mL 1 N HCl. The mixture was extracted with 2x 100 mL portions of diethyl ether, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated The residue was purified by column chromatography (7.5 % ethyl acetate in hexanes) to afford **3c** (667 mg, 3.14 mmol, 40% yield) as a yellow solid. Spectral data were in accordance with literature values.[9a]

$^1$H NMR (500 MHz, $CDCl_3$): δ 10.72 (s, 1H), 8.98 (ap. d, *J*= 7.6 Hz, 1H), 8.12–8.10 (m, 1H), 7.99–7.98 (m, 1H), 7.92–7.91 (m, 1H), 7.61 (t, *J*= 7.7, 1H), 7.56–7.51 (m, 2H). $^{13}$C NMR{$^1$H} (125 MHz, $CDCl_3$): δ 192.0, 141.5, 140.4, 134.7, 134.6, 134.1, 130.5, 128.6, 127.7, 127.3, 125.9, 124.9, 122.9. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{13}H_8NaOS$ 235.0188 found 235.0184. Mp (95–98 °C)

**1-iododibenzothiophene (3d):** To the above prepared solution of 1-lithiodibenzothiophene was added solid iodine (3.96 g, 15.6 mmol, 2 equiv) was added through the top of the flask with a strong countercurrent of nitrogen. The reaction was then moved from the dry ice/actone bath to the ice bath, stirred for 30 minutes, and then quenched by the addition of 25 mL saturated $Na_2S_2O_3$. The mixture was extracted with 2x 100 mL portions of diethyl ether, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The waxy residue was purified by chromatography with pure hexanes, to give an inseparable mixture of 1-iododibenzothiophene and dibenzothiophene. This mixture was placed in a sublimation chamber with a dry-ice finger and evacuated to approximately 5 torr. The residue was heated with a heat gun until it became liquid, and a white sublimate was observed on the cold finger. The chamber was disassembled, the finger cleaned, and the process was repeated twice more, until a negligible amount of sublimation was observed. The remaining material in the bottom of the sublimation chamber (803 mg, 2.59 mmol, 33% yield), was found to be approximately 95% 1-iododibenzothiophene with the balance being dibenzothiophene. No 1-iododibenzothiophene sublimed under these conditions.

$^1$H NMR (500 MHz, $CDCl_3$): δ 9.41–9.39 (m, 1H), 8.03 (d, *J*= 7.6 Hz, 1H), 7.88–7.86 (m, 2H), 7.57–7.52 (m, 2H), 7.10 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.7, 140.4, 137.7, 135.7, 134.9, 127.4, 127.1, 124.8, 123.4, 122.8, 122.7, 88.9. HRMS (APCI) *m/z* [M radical cation]$^+$ calcd for $C_{12}H_7IS$ 309.9308 found 309.9298. MP 65–70 °C.

**1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan2-yl)-dibenzothiophene (3e):** To the above prepared solution of 1-lithiodibenzothiophene was added *i*PrOB(pin) (3.2 mL, 15.7 mmol, 2 equiv) was added. The cooling bath was removed, and the reaction was stirred for 1 hour, and then quenched by the addition of 15 mL 1 N HCl. The mixture was extracted with 2x 100 mL portions of diethyl ether, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The grey waxy residue was purified by column chromatography with 2.5% ethylacetate/hexanes, then further recrystallized by cooling a solution in hexanes with a few drops of ethyl acetate to give boronate **3e** (804 mg, 2.59 mmol, 33% yield) as white colourless crystals, which were suitable for X-ray analysis.

$^1$H NMR (500 MHz, $CDCl_3$): δ 9.03–9.02 (m, 1H), 7.96–7.94 (m, 1H), 7.89–7.84 (m, 2H), 7.45–7.43 (m, 3H), 7.92–7.91 (m, 1H), 1.50 (s, 12H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.8, 139.7, 138.8, 136.8, 132.7, 126.5, 125.5, 125.4, 125.2, 123.9, 122.7, 122.6, 84.5, 25.1. $^{11}$B NMR (160 MHz, $CDCl_3$): δ 32.1 (br. s). HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{18}H_{19}BNaO_2S$ 333.1091 found 333.1100.

***N*-(2-fluorophenyl)-*N*-(2-iodophenyl)-methylamine (8b):** Magnesium turnings (0.683 g, 28.1 mmmol, 1 equiv) were placed in a 100 mL three neck flask equipped with a condenser under a nitrogen atmosphere. THF (28 mL) was added. Aniline **1d** (3.52 g, 28.1 mmol, 1 equiv) was added. Isopropylmagnesium chloride (1.67 M in THF, 16.8 mL, 28.1 mmol, 1 equiv) was carefully added, which resulted in heating of the reaction to reflux. After bubbling subsided, the reaction was placed in an oil bath at 80 °C. When reflux resumed, halide **6a** (3.07 mL, 28.1 mmol, 1 equiv) was cautiously added in 5 portions with 10 minutes between each portion. The reaction was heated for a further hour, at which time negligible magnesium remained and the mixture was clear and dark yellow. The reaction was removed from heat, allowed to cool to ambient temperature, and solid iodine (7.13 g, 28.1 mmol, 1 equiv) was cautiously added with stirring. The reaction self-heated to a gentle reflux, which abated as the reaction was stirred for a further hour. The resulting black solution was poured into 50 mL of saturated aqueous $Na_2S_2O_3$ and stirred for 10 minutes. The mixture was extracted with 2x 100 mL portions of diethyl ether, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated to give a black oil. This was purified by column chromatography to afford **8b** as a clear colourless oil (3.05 g, 9.32 mmol, 33% yield). Spectral data agreed with literature values.[8]

$^1$H NMR (500 MHz, $CDCl_3$): δ 7.90 (dd, *J*= 7.9, 1.4 Hz, 1H), 7.34–7.31 (m, 1H), 7.13 (dd, *J*= 7.9, 1.5, 1H), 7.06–6.98 (m, 2H), 6.93–6.84 (m, 3H), 3.24 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 155.0 (d, *J*= 247.2 Hz), 140.4, 138.0 (d, *J*= 8.5 Hz), 135.2, 130.9 (d, *J*= 8.1 Hz), 129.4, 126.7, 125.7, 124.4 (ap. d, *J*= 3.86 Hz), 122.0 (d, *J*= 7.2 Hz), 120.3 (d, *J*= 3.0 Hz), 116.5 (d, *J*= 20.3 Hz), 98.2, 41.4. $^{19}$F NMR (470 MHz, $CDCl_3$): δ -121.7.

**2-bromomethylthiophene (12a):** The following reaction was not conducted under nitrogen to avoid contamination of the manifold with HBr. Alcohol **12b** (1.66 mL, 17.5 mmol, 1 equiv) was dissolved in 15 mL of diethyl ether, cooled to 0 °C, and $PBr_3$ (1.66 mL, 17.5 mmol, 1 equiv) was added. The cooling bath was allowed to decay, and the reaction was stirred for 16 hours. The reaction was recooled and quenched by the dropwise addition of 30 mL of water. When HBr evolution ceased, the layers were separated, and the aqueous layer was extracted with a further 45 mL of ether. The combined organic layers were cautiously washed with saturated $NaHCO_3$, then brine, then dried over $Na_2SO_4$. Concentration gave **12a** as a yellow oil (2.94 g, 16.6 mmol, 95% yield), which was prone to decomposition as mentioned in the text and was used without further purification.

**Lithium tetrachlorocuprate (0.5 M)**: Solid LiCl (1.26 g, 29.7 mmol, 2 equiv) and $CuCl_2$ (2.00 g, 14.9 mmol, 1 equiv) were placed in a 50 mL Schlenk storage tube under nitrogen. THF (30 mL) was added, and the dark red/brown reaction was stirred until all solids were dissolved. The dark red solution was stored under nitrogen at room temperature. A 0.1 M of $Li_2CuCl_4$ in THF was also made in the same fashion.

**Naphthothiophene (9a):** Magnesium turnings (0.315 g, 13.0 mmol, 1.65 equiv) were placed in a 3-neck flask equipped with a reflux condenser under nitrogen. Syringes with halide **11a** (2.38 mL, 11.8 mmol, 1.5 equiv) and THF (15 mL) were placed in the other septa. THF (5 mL) and halide **11a** (2.38 mL) were added, and the reaction was heated in an oil bath at 80 °C. A crystal of iodine, and 0.1 mL of dibromoethane were added. After several minutes, the color of the iodine disappeared, and THF and halide **11a** were gradually added at a rate to maintain reflux. When the addition was complete, the light brown solution of Grignard reagent **11b** was stirred for a further

hour, until only very small pieces of magnesium remained. It was then allowed to cool. Separately, lithium tetrachlorocuprate (0.1 M in THF, 7.85 mL, 0.785 mmol, 0.1 equiv) was added to a solution of bromide **12a** (1.39 g, 7.85 mmol, 1 equiv) in 8 mL THF. This bright orange mixture was cooled to 0 C. The Grignard solution **11b** was transferred into this solution with a syringe and stainless needle. The red solution darkened during the addition, then suddenly turned very pale yellow. After completion of the addition, the solution remained yellow, but gradually became cloudy. The solution was stirred for 16 hours. The reaction was quenched with saturated $NH_4Cl$, and 10 mL aqueous ammonia was added. Diethyl ether 100 mL was added, and the mixture was vigorously shaken in a separatory funnel until it turned bright blue. The layers were separated, and the aqueous layer was extracted with another 100 mL of diethyl ether. The combined organic layers were washed with brine, and dried over $Na_2SO_4$, then concentrated. The resulting orange oil was used directly in the next step without further purification.

The orange oil was dissolved in 20 mL DCM and cooled to 0 °C. Boron trifluoride etherate (3.37 mL, 27.3 mmol, 3.5 equiv) was added, and the reaction immediately turned deep black. The cooling bath was allowed to decay, and the reaction was stirred for 16 hours. The reaction was quenched by the addition of saturated $NaHCO_3$. When bubbling ceased, layers were separated, and the aqueous layer was extracted with a further 50 mL DCM. The combined organic layers were dried over $Na_2SO_4$, and concentrated. The brown residue purified by flash chromatography on silica gel (1% ethyl acetate/ hexanes). Combination of the product containing fractions yielded compound x as a white solid (0.936g, 5.08 mmol, 65% yield over 2 steps).

$^1$H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.33 (s, 1H), 7.99–7.97 (m, 1H), 7.93–7.92 (m, 1H), 7.52–7.47 (m, 3H), 7.43 (ap. d, *J*= 5.64 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.0, 138.4, 131.1, 131.0, 128.4, 128.3, 127.4, 125.4, 125.1, 123.6, 122.0, 120.8.

**2-(4-bromothiophene)methanol (12c):** The following reaction was conducted under air in an open flask. Commercially available 4-bromo-2-thiophenecarboxaldehyde (10.0 g, 52 mmol, 1 equiv) was dissolved in 100 mL ethanol and cooled to 0 °C. Sodium borohydride (2.0 g, 53 mmol, 1 equiv) was cautiously added. The reaction was stirred for 2 hours, at which time an NMR aliquot showed complete consumption of the aldehyde. The reaction was cautiously quenched with 1.0 M aqueous HCl. When gas evolution ceased, volatiles were removed in vacuo. The residue was diluted with 100 mL water, and extracted with 100 mL diethyl ether, and a further 50 mL diethyl ether. The combined organic layers were dried with $Na_2SO_4$, and concentrated to yield alcohol **12c** (10.1 g, 52 mmol, quant) as a light brown liquid, which was used in the next step without further purification.

**2-bromomethyl-4-bromothiophene (12d):** The following reaction conducted under air, in a flask equipped with a septum, and 22 gauge needle for pressure release to avoid contamination of the manifold with HBr. Alcohol **12c** (3.80 g, 19.6 mmol, 1 equiv) was dissolved in 20 mL of diethyl ether, cooled to 0 °C, and $PBr_3$ (2.00 mL, 21.6 mmol, 1.1 equiv) was added. The cooling bath was allowed to decay, and the reaction was stirred for 16 hours. The reaction was recooled, and quenched by the dropwise addition of 30 mL of water. When HBr evolution ceased, the layers were separated, and the aqueous layer was extracted with a further 40 mL of ether. The combined organic layers were cautiously washed with saturated $NaHCO_3$, then brine, then dried over $Na_2SO_4$. Concentration with a non-heated rotavap bath gave **12d** as a yellow oil, which was dried under vacuum in a flask placed in an ice bath, which caused the compound solidify (4.8 g, 18.8 mmol, 95% yield). Decomposition was not observed with this compound in the solid state at this scale. An attempt to filter a highly concentrated ethereal solution of bromide **12d** through basic alumina did result in darkening and exothermic decomposition, indicating this compound should be treated cautiously.

$^1$H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.03 (s, 1H), 4.65 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.8, 130.5, 124.2, 109.7, 25.5. HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_5H_5Br^{79}Br^{81}S$ 256.8453 found 256.8455.

**3-bromonaphthothiophene (9b):** Magnesium turnings (0.729 g, 30.0 mmol, 1.6 equiv) were placed in a 3-neck flask equipped with a reflux condenser under nitrogen. Syringes with halide **11a** (6.05 mL, 30.0 mmol, 1.6 equiv) and THF (30 mL) were placed in the other septa. THF (5 mL) and halide **11a** (0.5 mL) were added, and the reaction was heated in an oil bath at 70 °C. A crystal of iodine, and 0.1 mL of dibromoethane were added. After several minutes, the color of the iodine disappeared, and THF and halide **11a** were gradually added at a rate to maintain reflux. When the addition was complete, the light brown solution of Grignard reagent **11b** was stirred for a further hour, until only very small pieces of magnesium remained. It was then allowed to cool. Separately, lithium tetrachlorocuprate (0.5 M in THF, 6 mL, 3.0 mmol, 0.16 equiv) was added to a solution of bromide **12d** (4.8 g, 18.8 mmol, 1 equiv) in 15 mL THF. This bright orange mixture was cooled to 0 °C. The Grignard solution **11b** was transferred into this solution with a syringe and stainless needle. The red solution darkened during the addition, then suddenly turned very pale yellow. After completion of the addition, the solution remained yellow, but gradually became cloudy. The solution was stirred for 16 hours. The reaction was quenched with saturated

$NH_4Cl_{(aq)}$, and 10 mL aqueous ammonia was added. Diethyl ether 100 mL was added, and the mixture was vigorously shaken in a separatory funnel until it turned bright blue. The layers were separated, and the aqueous layer was extracted with another 100 mL of diethyl ether. The combined organic layers were washed with brine, and dried over $Na_2SO_4$, then concentrated. The resulting orange oil was used directly in the next step without further purification.

The orange oil (18.8 mmol maximum theoretical amount) was dissolved in 60 mL DCM and cooled to 0 °C. Boron trifluoride etherate (3.70 mL, 30.1 mmol, 1.6 equiv) was added, and the reaction immediately turned deep black. The cooling bath was allowed to decay, and the reaction was stirred for 16 hours. The reaction was quenched by the addition of saturated $NaHCO_3$. When bubbling ceased, layers were separated, and the aqueous layer was extracted with a further 50 mL DCM. The combined organic layers were dried over $Na_2SO_4$, and concentrated. The brown residue was redissolved in DCM, and several scoops of celite were added, and solvent was removed in vacuo. This was added on top of a pre-wetted silica-gel column, and elution was carried out with 1% ethyl acetate/ hexanes. Combination of the product containing fractions yielded compound **9b** as a white solid (2.40 g, 9.12 mmol, 48% yield over 2 steps). Spectral data were in accordance with literature values.[20]

$^1$H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.30 (s, 1H), 8.05–8.03 (m, 1H), 7.92–7.90 (m, 1H), 7.53–7.50 (m, 2H), 7.52 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.5, 136.2, 131.5, 131.2, 128.6, 127.3, 126.1, 125.6, 125.3, 121.9, 121.3, 107.4. HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{12}H_8Br^{79}S$ 262.9525 found 262.9516.

**3-naphthothiophenecarboxaldehyde (9c):** In a recovery flask, 3-bromoaphthothiophene (1.60 g, 6.08 mmol, 1 equiv) was dissolved in 4 mL THF. Separately 6 mL of THF was placed in a Schlenk flask and cooled to –84 °C (liquid nitrogen/ethyl acetate). N-butyllithium 2.5 M in hexanes (3.89 mL, 9.72 mmol, 1.6 equiv) was added to the Schlenk, and the solution was allowed to stir at –84 °C for another 10 minutes. The solution of 3-naphthothiophene was added over 1 minute, running the solution down the inside of the flask to facilitate pre-cooling, with a further 2 mL THF used to quantitiate the transfer. The solution became inky blue in colour, and occasionally a greyish precipitate formed. The reaction was stirred at –84 °C for 10 minutes, then DMF (0.94 mL, 12 mmol, 2 equiv) was added. The dark greenish reaction was stirred for 10 minutes, warmed to 0 °C for 5 minutes, then quenched with 10 mL $NH_4Cl_{(aq)}$ and 10 mL 2 M HCl. To the solution was added 25 mL of dichloromethane, and the mixture was vigorously stirred for 5 minutes. The layers were separated. The aqueous layer washed with an additional 25 mL dichloromethane, and the combined residues were dried over $Na_2SO_4$ and concentrated. The brown residue was purified by flash chromatography (5%–10% ethyl acetate/hexanes) to afford aldehyde **9c** as a orange/yellow solid (749 mg, 3.52 mmol, 58% yield)

$^1$H NMR (500 MHz, $CDCl_3$): 10.15 (s, 1H), 9.21 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 8.08–8.03 (m, 1H), 7.92–7.88 (m, 1H), 7.57–7.50 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): 185.1, 146.3, 138.2, 136.1, 133.2, 131.7, 131.6, 128.9, 127.2, 126.3, 125.7, 123.9, 120.8. HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{13}H_8NaOS$ 235.0188 found 235.0197.

**3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan2-yl)-naphthothiophene (9d):** In a recovery flask, 3-bromoaphthothiophene (500 mg, 1.9 mmol, 1 equiv) was dissolved in 3 mL THF. Separately 6 mL of THF was placed in a Schlenk flask and cooled to –84 °C (liquid nitrogen/ethyl acetate). N-butyllithium 2.5 M in hexanes (0.87 mL, 2.2 mmol, 1.1 equiv) was added to the Schlenk flask, and the solution was allowed to stir at –84 °C for another 10 minutes. The solution of 3-naphthothiophene was added over 1 minute, running the solution down the inside of the flask to facilitate pre-cooling. The solution became inky blue in colour, and occasionally a greyish precipitate formed. The reaction was stirred at –84 °C for 5 minutes, then *i*PrOB(pin) (0.47 mL, 2.3 mmol, 1.2 equiv) was added. The dark greenish reaction was stirred for 10 minutes, warmed to 0 °C for 5 minutes, then quenched with 10 mL of 2 M HCl. To the solution was added 25 mL of dichloromethane, and the mixture was vigorously stirred for 5 minutes. The layers were separated. The aqueous layer washed with an additional 25 mL dichloromethane, and the combined residues were dried over $Na_2SO_4$ and concentrated. The brown residue was purified by flash chromatography (1% ethyl acetate/hexanes) to afford boronic ester **9d** as a white solid (338 mg, 1.09 mmol, 57% yield)

$^1$H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.39 (s, 1H), 8.18 (s, 1H), 8.09–8.07 (m, 1H), 7.92–7.90 (m, 1H), 7.50–7.46 (m, 2H), 1.44 (s, 12H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.8, 141.5, 139.6, 131.2, 130.9, 128.9, 127.3, 125.3, 124.8, 123.9, 120.4, 83.9, 25.1. $^{11}$B NMR (160 MHz, $CDCl_3$): δ 29.1 (br. s). HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{19}BNaO_2S$ 333.1091 found 333.1082.

## ASSOCIATED CONTENT

**Supporting Information**.
NMR Spectra of intermediates and products, ORTEPS, and other X-ray crystallography data as a PDF.

CIF files for compounds **3e** and **9a**.

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