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Regiocontrolled Halogen Dance of Bromothiophenes and Bromofurans

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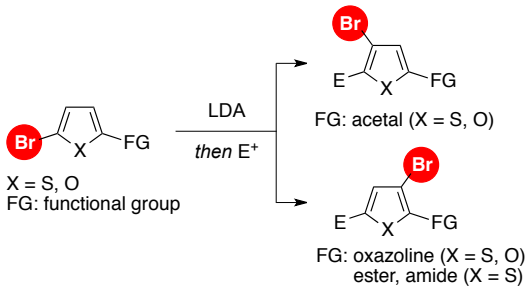
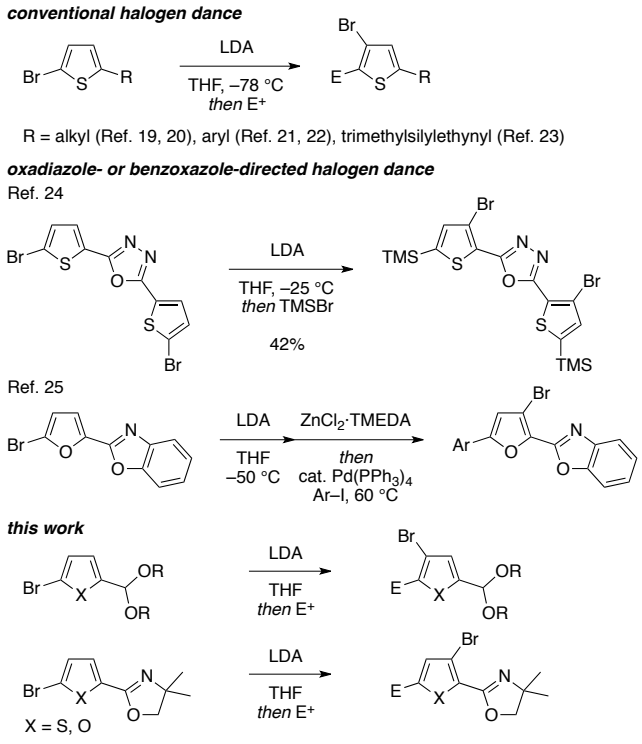
Supporting Information Placeholder



ABSTRACT: The LDA (lithium diisopropylamide)-promoted regiocontrolled halogen dance of α-bromothiophenes and α-bromofurans is described. Bromothiophenes bearing a diethyl acetal moiety undergo selective deprotonation at the β-position adjacent to the bromo group. In contrast, oxazoline, ester, and amide groups act as directing groups in the initial lithiation step to generate a carbanion at the β-position neighboring the directing group to exclusively give the other regioisomer. These results can be applied to the regiocontrolled halogen dance of bromofuran derivatives.

Multiply substituted thiophenes and furans are found in a variety of functional material,[1–3] bioactive compounds,[4–6] and pharmaceutically important compounds.[7–9] Classical methods such as Paal–Knorr synthesis,[10] Gewald thiophene synthesis,[11] and Feist–Benary synthesis[12] are powerful methods for the regiocontrolled synthesis of such heteroaromatic compounds. However, they require preparation of functionalized acyclic dicarbonyl compounds before cyclization under heating conditions in the presence of a strong acid, which therefore limits the scope for substrates. Substantial efforts have been made to achieve stepwise regioselective introduction of functional groups after the formation of these heterocyclic skeletons by employing different reactivity of the α-/β-positions and different acidity of α-/β-proton.[13] However, control of the unsymmetrical substrates using two β-positions' reactivity is still difficult except for the special examples, and it also depends on the nature of the substituents.[14] Recently, the development of catalyst-controlled Pd-catalyzed C–H arylation and amide-directed Rh-catalyzed C–H halogenation has reached a practical level.[15] A base-mediated halogen dance of bromothiophenes involves the migration of an α-bromo group to a β-position through intermolecular halogen–lithium exchange.[16–18] The resulting thienyl lithium species react with an electrophile to form two chemical bonds in one pot. The halogen dance of thiophenes and other heteroaromatic compounds has been utilized as a synthetic tool for introducing functional groups; however, effects of substituents on regioselectivity in the halogen dance have not been investigated. Examples of regioselective halogen dance are shown in

Scheme 1. Regiochemistry in the halogen dance

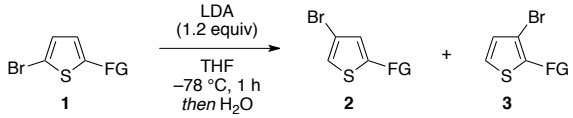


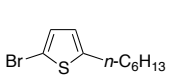
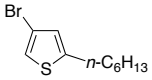
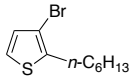
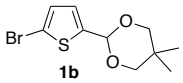
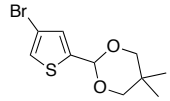
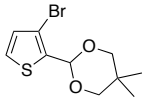
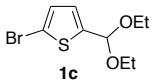
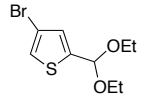
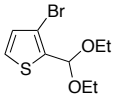
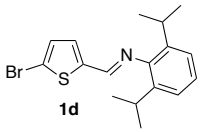
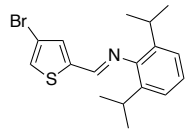
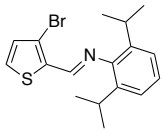
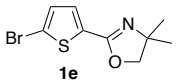
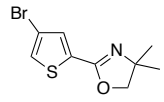
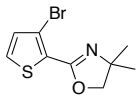
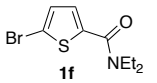
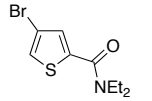
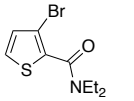
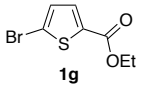
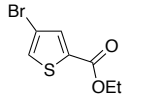
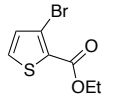
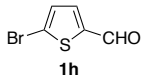
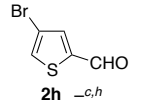
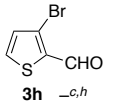
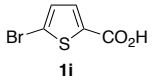
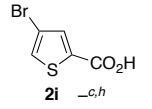
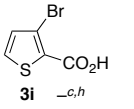
Scheme 1. The 2-bromothiophenes bearing alkyl,[19,20] aryl,[21,22] and trimethylsilylethynyl[23] groups on position 5 undergo 1,2-migration-type halogen dance. To the best of the authors' knowledge, 1,3-halogen dance was induced only by oxadiazole,[24] benzoxazole,[25] or ester moieties.[18c] However, they require harsh conditions to get converted to other functional groups, making its synthetic application difficult. The current study reports on a halogen dance of 2-bromothiophenes and 2-bromofurans using LDA as a base for developing reliable and direct access to functionalized thiophenes and furans in a regioselective manner.

A suitable functional group for the regiocontrolled halogen dance of 2-bromothiophene derivatives was first explored (Table 1). These substrates were typically treated with LDA (1.2 equiv) in THF at –78 °C for 1 h, and the reaction was quenched with water. Regioselectivity was evaluated by ^{1}H NMR yields of the crude products using 1,1,2,2-tetrachloroethane as an internal standard. We chose 2-bromo-5-hexylthiophene (**1a**) because 2-bromo-5-alkylthiophenes have been reported to give only 2-alkyl-4-bromothiophenes.[19,20] Careful inspection of the ^{1}H NMR spectrum of the crude material showed that 4-bromo-2-hexylthiophene (**2a**) formed exclusively without the generation of 3-bromo-2-hexylthiophene (**3a**). Bromothiophene **1b,** having a six-membered cyclic acetal, was converted to a ca. 2:1 mixture of regioisomers **2b** and **3b** with a 68% combined yield and recovery of the starting bromothiophene **1b** (5%). Switching the cyclic acetal **1b** to diethyl acetal **1c** led to the exclusive formation of compound **2c**, probably, because of the steric hindrance of the acyclic acetal in the initial deprotonation. A directing group for the synthesis of another regioisomer was then investigated. Imine moiety was effective for obtaining the desired isomer **3d** as a major product, but the product ratio was unsatisfactory. Based on the evidence that the sterically demanding acetal **1c** prohibited the deprotonation of the proton neighboring the acetal, the reaction was then performed with oxazoline **1e**. As expected, the halogen dance took place smoothly to provide regioisomer **3e** in 87% ^{1}H NMR yield without the detection of other regioisomer **2e**. The reaction could be performed at –40 °C or 0 °C to provide the desired product **3e** in almost the same yields. Amide and ester also worked as directing groups to provide compounds **3f** and **3g** in 78% and 75% yields, respectively, with concomitant generation of the minor regioisomer.[26] The use of 2-bromo-5-formylthiophene (**1h**) and 2-bromo-5-thiophenecarboxylic acid (**1i**) did not provide the corresponding products even with three equivalents of LDA, with recovery of the starting thiophenes.

Having found that diethyl acetal and oxazoline were suitable functional groups for the regiocontrolled halogen dance of bromothiophenes, we then trapped the resulting anion species with electrophiles. Upon treatment of bromothiophene bearing a diethyl acetal **1c** with LDA at –78 °C for 1 h, 1,2-migration of the bromo group took place smoothly, and the generated thienyl lithium species was trapped with several electrophiles. Treatment with benzaldehyde provided the corresponding alcohol **4a** in 78% yield (Table 2, entry 1). Trapping of the resultant anion species with ethyl chloroformate yielded the corresponding product **4b** in 61% yield (entry 2). Similarly, allyliodide and cyclohexanone reacted with the thienyl anion species to provide **4c** and **4d** in 68% and 52% yields, respectively (entries 3 and 4). The same reaction was

Table 1. Effects of functional groups on the regioselectivity of the halogen dance[a]

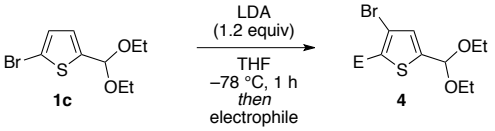


substrate	products		
 **1a**	 **2a** 99%[b,g]	 **3a** –[c,g]
 **1b**	 **2b** 46%[b,g]	 **3b** 22%[b,g]
 **1c**	 **2c** 93%[b] (83%[d])	 **3c** –[c]
 **1d**	 **2d** 35%[b,i]	 **3d** 54%[b,i]
 **1e**	 **2e** –[c,j] <1%[b,e,j] <1%[f,j]	 **3e** 87%[b,j] 92%[b,e,j] 93%[d,f,j] (79%[d,j])
 **1f**	 **2f** 4%[b]	 **3f** 78%[b]
 **1g**	 **2g** 2%[b]	 **3g** 75%[b]
 **1h**	 **2h** –[c,h]	 **3h** –[c,h]
 **1i**	 **2i** –[c,h]	 **3i** –[c,h]

[a]Reaction conditions: bromothiophene **1** (1.0 equiv), LDA (1.2 equiv), THF, –78 °C, 1 h. [b]The yield was determined by ^{1}H-NMR of the crude material using 1,1,2,2-tetrachloroethane as an internal standard. [c]Not observed. [d]Isolated yield. [e]Reaction temperature: –40 °C. [f]Reaction temperature: 0 °C. [g]LDA (2 equiv). [h]LDA (3 equiv). [i]Reaction time: 3 h. [j]Reaction time: 30 min.

performed using bromothiophene **1e** bearing an oxazoline moiety, which resulted in 1,3-migration of the bromo group. The thienyl anion species were trapped with these electrophiles to give **5a–5d** (Table 3, entries 1–4).

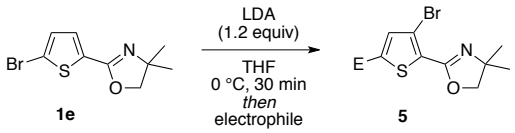
Table 2 Halogen dance of bromothiophene bearing an acetal moiety and trapping with electrophiles[a]



entry	electrophile	E	product	yield[b] (%)
1	PhCHO		**4a**	78
2	$ClCO_2Et$		**4b**	61
3	allyl iodide		**4c**	68[c]
4	cyclohexanone		**4d**	52

[a]Reaction conditions: bromothiophene (**1c**) (1.0 equiv), LDA (1.2 equiv), THF, –78 °C, 1 h; electrophile. [b]Isolated yield. [c]Reaction conditions: bromothiophene (**1c**) (1.0 equiv), LDA (1.2 equiv), THF, –78 °C, 1 h; CuI (1.4 equiv), –78 °C to 0 °C, 1 h; allyl iodide, –78 °C.

Table 3 Oxazoline-directed halogen dance of bromothiophene and trapping with electrophiles[a]

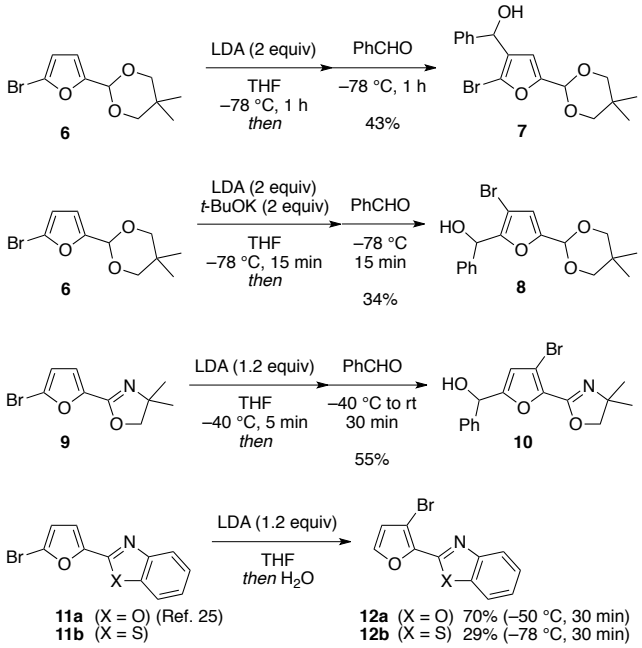


entry	electrophile	E	product	yield[b] (%)
1	PhCHO		**5a**	65
2[c]	$ClCO_2Et$		**5b**	41
3	allyl iodide		**5c**	49
4[c]	cyclohexanone		**5d**	83

[a]Reaction conditions: bromothiophene (**1e**) (1.0 equiv), LDA (1.2 equiv), THF, 0 °C, 30 min; electrophile. [b]Isolated yield. [c]Reaction temperature: –78 °C.

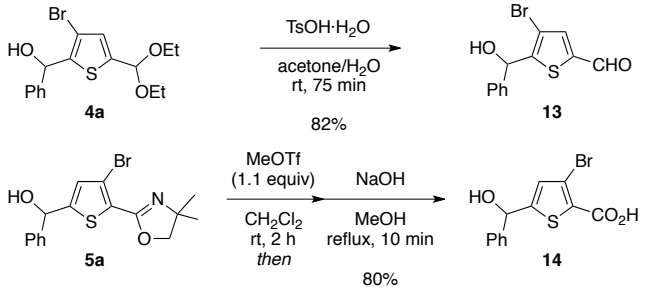
The regiocontrolled halogen dance of bromofurans was also investigated (Scheme 2). In contrast to bromothiophene **1b**, treatment of bromofuran **6** bearing a six-membered acetal with LDA resulted in only deprotonation. Subsequent trapping of the resulting anion species with benzaldehyde provided compound **7** exclusively.[27] According to a related work,[28] the desired regioselective halogen dance proceeded in the presence of potassium *tert*-butoxide. Prolonged reaction time led to a significant reduction of the yield of the product **8**, indicating that the generated furyl anion was a short-lived reactive species.[29] Potassium *tert*-butoxide should promote the requisite halogen–lithium exchange because of coordination to the initially formed furyl lithium species. Similar to the authors' previous report,[25] the halogen dance of bromofuran **9** bearing an oxazoline took place smoothly in the absence of potassium *tert*-butoxide, and the subsequent treatment of benzaldehyde provided the desired product **10** in 55% yield. These results suggested that the oxazoline moiety acted as a directing group in the initial deprotonation, and the following halogen–lithium exchange was promoted by coordination of the oxazoline nitrogen to the furyl lithium and led to the generation of a reactive, lower aggregation state.[30] We also performed the reaction with 2-bromofurans bearing an ethyl ester and an *N*,*N*-diethylamide that promote 1,3-migration of the bromo group in the case of thiophenes; however, we did not observe clean transformation despite of further optimization of reaction conditions. In addition of our successful example of 1,3-halogen dance of benzoxazole-conjugated bromofuran **11a**,[25] its benzothiazole derivative **11b** also underwent selective 1,3-halogen dance to provide the corresponding product **12b** in 29% isolated yield with 19% recovery of the starting material **11b**. These results indicated that the oxazoline and benzoxazole proved to be effective directing groups for the smooth 1,3-halogen dance of both 2-bromothiophenes and 2-bromofurans.

Scheme 2 Scope and limitation of bromofurans.



The diethyl acetal and oxazoline moieties were converted to formyl and carboxyl groups, respectively (Scheme 3).[31] Diethyl acetal **4a** was hydrolyzed under acidic conditions to give the corresponding aldehyde **13** in 82% yield. Conversion of oxazoline to a carboxyl group was achieved by N-methylation with MeOTf, and the resultant oxazolium salt was treated with NaOH/MeOH by refluxing for 10 min, which smoothly provided the desired carboxylic acid **14** in 80% yield.

Scheme 3 Conversion of acetal and oxazoline moieties to formyl and carboxyl groups.



In summary we have demonstrated the regiocontrolled halogen dance of α-bromothiophenes and α-bromofurans using LDA as a base. The 2-bromothiophene and 2-bromofuran derivatives bearing the acetal moieties in position 5 underwent regioselective 1,2-migration of the bromo group, whereas oxazoline, ester, and amide groups worked as directing groups to facilitate 1,3-migration of the bromo group. The established method provides reliable access to functionalized thiophenes and furans in a regioselective manner.

EXPERIMENTAL SECTION

General Experimental Details

Analytical thin layer chromatography (TLC) was performed on Merck 60 F_{254} aluminum sheets precoated with a 0.25 mm thickness of silica gel. Melting points (m.p.) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wave numbers (cm^{-1}). ^1H NMR (400 MHz) and $^{13}C\{^1H\}$ NMR (100 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^1H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, tetramethylsilane: δ 0 ppm) and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, and br = broad. Chemical shifts for $^{13}C\{^1H\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). High-resolution mass spectra (HRMS) were performed on a JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with a JEOL MS-5414DART attachment. Unless otherwise stated, all reactions were conducted in flame-dried glassware under an inert atmosphere of nitrogen. All work-up and purification procedures were carried out with reagent solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel® C-300 (45–75 μm, Wako Pure Chemical Industries, Ltd.). Recycling preparative SEC-HPLC was performed with LC-9201 (Japan Analytical Industry Co., Ltd.) equipped with preparative SEC columns (JAI-GEL-1H and JAI-GEL-2H). Anhydrous THF was purchased from Wako Pure Chemical Industries, Ltd. LDA (ca. 1.5 M in THF/ethylbenzene/
heptane) was purchased from Tokyo Chemical Industry Co., Ltd (Product number: L0171). Molecular sieves 4A were "activated" in the following manner: a round-bottomed flask containing molecular sieves was heated in a regular microwave (730 W) for 1.5 minute and the flask was immediately evacuated. The above procedure was repeated three times.

General Procedure for Halogen Dance (Table 1)

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2-bromo-5-hexylthiophene (**1a**) (75.4 mg, 0.31 mmol, 1.0 equiv) and anhydrous THF (2.0 mL). The solution was cooled to −78 °C. LDA (1.5 M, 0.40 mL, 0.60 mmol, 1.9 equiv) was added dropwise to the Schlenk tube and the resulting mixture was stirred at −78 °C for 1 h, at which time the brown reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material. The yield of compound **2a** (0.302 mmol, 99%) was determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane (24.1 mg, 0.144 mmol) as an internal standard by comparing relative values of integration for the peak observed at 7.00 ppm (one proton) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. Purification was carried out by silica gel column chromatography and/or SEC-HPLC.

Synthesis of Starting Materials (Table 1)

2-(5-Bromothiophen-2-yl)-5,5-dimethyl-1,3-dioxane (1b). To a 20-mL round bottomed flask equipped with a Teflon-coated magnetic stirring bar were added 5-bromothiophene-2-carbaldehyde (216.8 mg, 1.13 mmol, 1.0 equiv), neopentyl glycol (224.4 mg, 2.15 mmol, 1.9 equiv), *p*-toluenesulfonic acid monohydrate (9.1 mg, 0.045 mmol, 4 mol%) and toluene (2.4 mL). The resulting mixture was heated to reflux for 19 h, at which time the reaction was quenched with saturated aqueous sodium hydrogen carbonate (2 mL). After partitioned, the aqueous layer was extracted with diethyl ether (5 mL x 1, 2 mL x 2) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the corresponding product as an orange oil (288.2 mg, 1.04 mmol, 92%). R_f = 0.28 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 2956, 1469, 1447, 1376, 1366, 1209, 1190, 1096, 1021, 986, 971, 923, 795, 777, 641; ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, 1H, J = 3.6 Hz), 6.87 (d, 1H, J = 3.6 Hz), 5.54 (s, 1H), 3.73 (d, 2H, J = 11.4 Hz), 3.60 (d, 2H, J = 11.4 Hz), 1.25 (s, 3H), 0.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.1, 129.4, 125.4, 113.1, 97.9, 77.5, 30.3, 23.0, 21.9; HRMS (DART$^+$) m/z: calcd. for $C_{10}H_{14}O_2{}^{79}BrS$, 276.9898 $[M+H]^+$; found, 276.9885.

5-Bromo-2-(diethoxymethyl)thiophene (1c).
To a 20-mL test tube equipped with a Teflon-coated magnetic stirring bar were added 5-bromothiophene-2-carbaldehyde (958.2 mg, 5.02 mmol, 1.0 equiv), ammonium chloride (133.7 mg, 2.50 mmol, 0.50 equiv), ethanol (0.88 mL) and triethyl orthoformate (1.66 mL, 10.0 mmol, 2.0 equiv). The resulting mixture was heated to reflux for 43 h. To the reaction mixture were further added triethyl orthoformate (0.84 mL, 5.0 mmol, 1.0 equiv) and ethanol (0.29 mL). After stirring for 9 h, additional ammonium chloride (135.1 mg, 2.52 mmol, 0.50 equiv) was added and the reaction mixture was then stirred for 15 h, at which time the solvent was removed under reduced pressure. The residue was washed with saturated aqueous sodium hydrogen carbonate (8 mL), and the aqueous layer was extracted with diethyl ether (3 mL) four times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the corresponding product as a brown oil (1.24 g, 4.69 mmol, 94%). R_f = 0.35 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 1740, 1735, 1374, 1364, 1354, 1229, 1217, 668, 575, 550, 538, 516; ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, 1H, *J* = 4.0 Hz), 6.82 (dd, 1H, *J* = 4.0, 0.8 Hz), 5.64 (s, 1H), 3.66 (dq, 2H, *J* = 9.6, 7.2 Hz), 3.56 (dq, 2H, *J* = 9.6, 7.2 Hz), 1.23 (t, 6H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.6, 129.6, 125.5, 112.5, 98.1, 61.1, 15.2; HRMS ($DART^+$) *m*/*z*: calcd. for $C_7H_8O^{81}BrS$, 220.9459 $[M–OEt]^+$; found, 220.9467.

(*E*)-1-(5-Bromothiophen-2-yl)-*N*-(2,6-diisopropylphenyl)methanimine (1d).
To a 20-mL test tube equipped with a Teflon-coated magnetic stirring bar were added 5-bromothiophene-2-carbaldehyde (416.6 mg, 3.71 mmol, 1.3 equiv), 2,6-diisopropylaniline (524.0 mg, 2.96 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (32.0 mg, 0.17 mmol, 6 mol%) and dichloromethane (6.0 mL). The resulting mixture was heated to reflux for 1 h, after which time additional 5-bromothiophene-2-carbaldehyde (236.7 mg, 2.11 mmol, 0.7 equiv) was added to the test tube. The reaction mixture was heated to reflux for 3 h, at which time the reaction was quenched with saturated aqueous sodium hydrogen carbonate (3 mL). After partitioned, the aqueous layer was extracted with dichloromethane (2 mL x 2). The combined organic extracts were washed with brine (8 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 30:1) followed by recrystallization from hexane/ethanol to afford the corresponding product as an orange crystals (696.4 mg, 1.99 mmol, 67%). R_f = 0.38 (hexane/diethyl ether = 50:1); M.p. 80–83 °C; IR (ATR, cm^{-1}): 2962, 2870, 1626, 1456, 1418, 1260, 1220, 1163, 1095, 1018, 874, 847, 799, 766, 757; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.18–7.07 (m, 5H), 2.95 (sept, 2H, *J* = 6.8 Hz), 1.16 (d, 12H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.2, 148.4, 144.3, 137.9, 131.8, 130.8, 124.6, 123.2, 118.9, 28.2, 23.6; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{17}H_{21}N^{79}BrS$, 350.0578 $[M+H]^+$; found, 350.0592.

2-(5-Bromothiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (1e).
To a 100-mL round bottomed flask equipped with a Teflon-coated magnetic stirring bar were added 5-bromothiophene-2-carbaldehyde (1.91 g, 10.0 mmol, 1.0 equiv), 28% ammonium hydroxide (16 mL), and THF (1.0 mL). After stirring at room temperature for 5 min, iodine (2.79 g, 11.0 mmol, 1.1 equiv) and THF (2.3 mL) were added and the resulting mixture was stirred for 1 h. The reaction mixture was treated with saturated aqueous sodium thiosulfate. After partitioned, the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with water, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude 5-bromo-2-cyanothiophene (1.82 g, 9.67 mmol, 97%), which was used to the next reaction without any purification. ^1H NMR spectra of this product were identical to those reported in the literature.[32] ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 1H, *J* = 3.8 Hz), 7.10 (d, 1H, *J* = 3.8 Hz).
A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with potassium carbonate (89.0 mg, 0.64 mmol, 0.09 equiv), glycerol (6.4 mL), 5-bromo-2-cyanothiophene (1.35 g, 7.17 mmol, 1.0 equiv), 2-amino-2-methyl-1-propanol (1.00 g, 11.2 mmol, 1.6 equiv) and ethylene glycol (8.6 mL). The resulting mixture was heated to 110 °C for 27 h, at which time the reaction mixture was treated with saturated aqueous ammonium chloride (10 mL). After partitioned, the aqueous layer was extracted with diethyl ether (20 mL x 1, 10 mL x 3, 5 mL x 1). The combined organic extracts were washed with water (20 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1) to provide the corresponding product as a colorless solid (1.61 g, 6.17 mmol, 86%). R_f = 0.33 (hexane/diethyl ether = 3:1); M.p. 74.6–75.3 °C; IR (ATR, cm^{-1}): 2968, 2928, 1648, 1432, 1353, 1305, 1273, 1263, 1210, 1063, 1024, 947,803, 702, 567; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (br s, 1H), 7.03 (d, 1H, *J* = 3.6 Hz), 4.08 (s, 2H), 1.37 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.9, 132.2, 130.6, 130.4, 117.1, 79.5, 68.1, 28.3; HRMS ($DART^+$) *m*/*z*: calcd. for $C_9H_{11}ON^{79}BrS$, 259.9745 $[M+H]^+$; found, 259.9733.

5-Bromo-*N*,*N*-diethylthiophene-2-carboxamide (1f).
To a 100-mL round bottomed flask equipped with a Teflon-coated magnetic stirring bar were added 5-bromothiophene-2-carboxylic acid (989.6 mg, 4.78 mmol, 1.0 equiv), dichloromethane (20 mL), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.92 g, 10.0 mmol, 2.1 equiv), 1-hydroxybenzotriazole (1.53 g, 10.0 mmol, 2.1 equiv), diethyl amine (1.06 g, 14.6 mmol, 3.1 equiv) and *N*,*N*-diisopropylethylamine (1.92 g, 14.9 mmol, 3.1 equiv). The resulting mixture was stirred at room temperature for 23 h, at which time TLC indicated complete consumption of the starting carboxylic acid. The reaction mixture was washed with 1 M hydrochloric acid (20 mL), saturated aqueous sodium hydrogen carbonate (20 mL), and brine (20 mL). The organic layer was dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:2) to provide the corresponding product as a light green oil (984.8 mg, 3.76 mmol, 79%). R_f = 0.25 (hexane/diethyl ether = 2:1); IR (ATR, cm^{-1}): 2974, 1607, 1530, 1479, 1433, 1381, 1362, 1317, 1280, 1220, 1083, 1049, 968, 840, 803, 734, 693; ^1H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, 1H, *J* = 3.6 Hz), 7.00 (d, 1H, *J* = 3.6 Hz), 3.53 (q, 4H, *J* = 7.2 Hz), 1.25 (t, 6H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100

MHz, $CDCl_3$): δ 162.5, 140.1, 129.8, 128.6, 116.4, 42.2, 13.7; HRMS (DART$^+$) *m/z*: calcd. for $C_9H_{13}ON^{81}BrS$, 263.9881 $[M+H]^+$; found, 263.9876.

Ethyl 5-bromothiophene-2-carboxylate (1g).
To a 20-mL test tube equipped with a Teflon-coated magnetic stirring bar were added 5-bromothiophene-2-carboxylic acid (470.4 mg, 2.28 mmol, 1.0 equiv), ethanol (2.3 mL), and concentrated sulfuric acid (4 drops). The resulting mixture was heated to reflux for 24 h, at which time ethanol (1.0 mL) was added to the test tube and the reaction mixture was stirred for 69 h. The reaction mixture was treated with saturated aqueous sodium hydrogen carbonate (5 mL). After partitioned, the aqueous layer was extracted with diethyl ether (3 mL x 2, 2 mL x 1) three times. The combined organic extracts were washed with brine (3 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/dichloromethane = 3:1) to provide the corresponding product as a colorless oil (325.2 mg, 1.38 mmol, 61%). R_f = 0.29 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 1711, 1533, 1417, 1367, 1327, 1280, 1250, 1210, 1088, 1049, 1014, 973, 810, 745; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, 1H, *J* = 3.8 Hz), 7.07 (d, 1H, *J* = 3.8 Hz), 4.33 (q, 2H, *J* = 7.2 Hz), 1.36 (t, 3H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.0, 135.1, 133.4, 130.8, 120.0, 61.3, 14.3; HRMS (DART$^+$) *m/z*: calcd. for $C_7H_8O_2{}^{79}BrS$, 234.9428 $[M+H]^+$; found, 234.9429.

Synthesis of Authentic Samples (Table 1)
^1H NMR spectra of 3-bromo-*N*,*N*-diethylthiophene-2-carboxamide (**3f**)[15b], Ethyl 4-bromothiophene-2-carboxylate (**2g**)[33], and ethyl 3-bromothiophene-2-carboxylate (**3g**)[34] were reported.

2-(4-Bromothiophen-2-yl)-5,5-dimethyl-1,3-dioxane (2b).
A 20-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar with Dean-Stark apparatus was charged with 4-bromo-2-formylthiophene (95.2 mg, 0.50 mmol, 1.0 equiv), neopentyl glycol (57.4 mg, 0.55 mmol, 1.1 equiv), *p*-TsOH·H_2O (4.8 mg, 0.025 mmol, 5 mol%) and toluene (2.0 mL). The resulting mixture was heated to reflux for 50 h, at which time additional neopentyl glycol (45.4 mg, 0.44 mmol, 0.9 equiv) was added to the flask and the resulting mixture was stirred for another 20 h. The reaction mixture was treated with saturated aqueous sodium bicarbonate (2 mL). After partitioned, the aqueous layer was extracted with diethyl ether (6 mL x 1, 2 mL x 2) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the corresponding product **2b** (105.4 mg, 0.380 mmol, 76%. R_f = 0.30 (hexane/diethyl ether = 50:1); M.p. 71–74 °C; IR (ATR, cm^{-1}): 3098, 2956, 2865, 1464, 1441, 1378, 1225, 1209, 1180, 1092, 1026, 1013, 986, 966, 923, 874, 852, 830, 792, 780, 738, 558, 544, 515; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, 1H, *J* = 1.2 Hz), 7.06 (d, 1H, *J* = 1.2 Hz), 5.56 (s, 1H), 3.74 (d, 2H, *J* = 10.6 Hz), 3.61 (d, 2H, *J* = 10.6 Hz), 1.25 (s, 3H), 0.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 142.7, 127.8, 123.0, 109.2, 97.4, 77.5, 30.3, 23.0, 21.8; HRMS (DART$^+$) *m/z*: calcd. for $C_{10}H_{14}O_2{}^{79}BrS$, 276.9898 $[M+H]^+$; found, 276.9884.

2-(3-Bromothiophen-2-yl)-5,5-dimethyl-1,3-dioxane (3b).
The title compound was obtained as a light yellow oil in 70% yield (97.9 mg, 0.353 mmol) from 3-bromo-2-formylthiophene (96.2 mg, 0.51 mmol) according to the above procedure. R_f = 0.30 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 2854, 1537, 1470, 1446, 1396, 1363, 1342, 1307, 1201, 1189, 1156, 1091, 1028, 1013, 984, 969, 929, 876, 755, 716, 620; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, 1H, *J* = 5.4 Hz), 6.94 (d, 1H, *J* = 5.4 Hz), 5.70 (s, 1H), 3.76 (d, 2H, *J* = 11.0 Hz), 3.67 (d, 2H, *J* = 11.0 Hz), 1.30 (s, 3H), 0.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 136.0, 129.8, 126.4, 109.3, 97.6, 77.8, 30.2, 23.0, 21.8; HRMS (DART$^+$) *m/z*: calcd. for $C_{10}H_{14}O_2{}^{79}BrS$, 276.9898 $[M+H]^+$; found, 276.9886.

4-Bromo-2-(diethoxymethyl)thiophene (2c).
A 20-mL test tube equipped with a Teflon-coated magnetic stirring bar and a reflux condenser was charged with 4-bromo-2-formylthiophene (96.8 mg, 0.51 mmol, 1.0 equiv), ammonium chloride (13.3 mg, 0.25 mmol, 0.49 equiv), and EtOH (0.50 mL). To the resulting mixture was added triethyl orthoformate (0.10 mL, 0.60 mmol, 1.2 equiv), and the mixture was heated to 100 °C for 16 h. Another triethyl orthoformate (0.10 mL, 0.60 mmol, 1.2 equiv) was added and the mixture was further stirred at 100 °C for 28 h. Another triethyl orthoformate (0.10 mL, 0.60 mmol, 1.2 equiv) and ethanol (0.30 mL) were added and the mixture was stirred at 100 °C for 44 h, at which time the organic solvents were removed under reduced pressure. The residue was treated with saturated sodium bicarbonate (3 mL), and the mixture was extracted with diethyl ether (3 mL x 1 then 2 mL x 2) three times. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. Purification was performed by silica gel column chromatography (hexane/diethyl ether = 50:1) to afford the desired acetal **2c** (112.3 mg, 0.424 mmol, 84%) as a colorless oil. R_f = 0.50 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 1771, 1738, 1717, 643, 611, 590, 572, 556, 543, 535, 515; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, 1H, *J* = 1.6 Hz), 7.01–6.99 (m, 1H), 5.68 (s, 1H), 3.70–3.66 (dq, 2H, *J* = 9.6, 7.0 Hz), 3.58 (dq, 2H, *J* = 9.6, 7.0 Hz), 1.24 (t, 6H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.3, 127.9, 123.1, 109.2, 97.7, 61.2, 15.2; HRMS (DART$^+$) *m/z*: calcd. for $C_7H_8O^{81}BrS$, 220.9459 $[M–OEt]^+$; found, 220.9456.

3-Bromo-2-(diethoxymethyl)thiophene (3c).
The title compound was obtained as a colorless oil in 92% yield (125.7 mg, 0.474 mmol) from 3-bromo-2-formylthiophene (98.9 mg, 0.52 mmol) according to the above procedure. R_f = 0.33 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 2976, 2880, 1739, 1520, 1440, 1368, 1350, 1319, 1190, 1158, 1090, 1054, 1004, 867, 708; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, 1H, *J* = 5.4 Hz), 6.94 (d, 1H, *J* = 5.4 Hz), 5.71 (s, 1H), 3.67 (dq, 2H, *J* = 9.6, 6.8 Hz), 3.60 (dq, 2H, *J* = 9.6, 6.8 Hz), 1.24 (t, 6H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 137.3, 130.0, 126.0, 108.9, 97.9, 61.9, 15.2; HRMS (DART$^+$) *m/z*: calcd. for $C_7H_8O^{79}BrS$, 218.9479 $[M–OEt]^+$; found, 218.9488.

(*E*)-1-(4-Bromothiophen-2-yl)-*N*-(2,6-diisopropylphenyl)methanimine (2d).
A 10-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with 4-bromo-2-formylthiophene (104.3 mg, 0.55 mmol, 1.1 equiv), 2,6-diisopropylaniline (85.2 mg, 0.48 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (15.0 mg, 0.079 mmol, 16 mol%), and dichloromethane (1.0 mL). The resulting mixture was heated to reflux for 18 h,

at which time the reaction mixture was treated with saturated aqueous sodium hydrogen carbonate (2 mL). After partitioned, the aqueous layer was extracted with dichloromethane (2 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) to provide the corresponding product as a yellow solid (149.0 mg, 0.425 mmol, 88%). R_f = 0.38 (hexane/diethyl ether = 50:1); M.p. 71–74 °C; IR (ATR, cm^{-1}): 3088, 2961, 2921, 2869, 1626, 1455, 1418, 1219, 1163, 1097, 847, 766; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.42 (d, 1H, *J* = 1.4 Hz), 7.36 (d, 1H, *J* = 1.4 Hz), 7.16–7.08 (m, 3H), 2.94 (sept, 2H, *J* = 6.8 Hz), 1.16 (d, 12H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.8, 148.2, 143.3, 137.9, 133.7, 127.5, 124.7, 123.2, 110.6, 28.2, 23.6; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{17}H_{21}N^{79}BrS$, 350.0578 $[M+H]^+$; found, 350.0589.

(*E*)-1-(3-Bromothiophen-2-yl)-*N*-(2,6-diisopropylphenyl)methanimine (3d).

The title compound was obtained as a yellow solid in 93% yield (153.8 mg, 0.439 mmol) from 3-bromo-2-formylthiophene (108.2 mg, 0.57 mmol) and 2,6-diisopropylaniline (83.8 mg, 0.47 mmol, 1.0 equiv) according to the above procedure. R_f = 0.26 (hexane/diethyl ether = 100:1); M.p. 99–103 °C; IR (ATR, cm^{-1}): 2959, 1750, 1741, 1734, 1717, 1684, 1654, 1636, 1623, 1617, 1559, 1507, 1457; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, 1H, *J* = 1.2 Hz), 7.50 (dd, 1H, *J* = 5.0, 1.2 Hz), 7.18–7.09 (m, 4H), 2.97 (sept, 2H, *J* = 6.8 Hz), 1.19 (d, 12H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.6, 148.6, 138.0, 136.5, 131.2, 130.3, 124.7, 123.2, 115.8, 28.1, 23.7; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{17}H_{21}N^{79}BrS$, 350.0578 $[M+H]^+$; found, 350.0561.

2-(4-Bromothiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (2e).

To a 25-mL round bottomed flask equipped with a Teflon-coated magnetic stirring bar were added 4-bromo-2-formylthiophene (96.4 mg, 0.50 mmol, 1.0 equiv), 28% ammonium hydroxide (1.3 mL) and THF (1.4 mL). After stirring at room temperature for 10 min, iodine (151.8 mg, 0.60 mmol, 1.1 equiv) was added to the flask and the resulting mixture was stirred at room temperature for 3 h. Iodine (105.2 mg, 0.41 mmol, 0.83 equiv) was added to the flask, and the reaction mixture was stirred for 1.5 h, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate (2 mL). After partitioned, the aqueous layer was extracted with diethyl ether (5 mL x 1, 2 mL x 2) three times. The combined organic extracts were washed with water (2 mL), brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material (91.9 mg, 0.489 mmol, 97%), which was used to the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, 1H, *J* = 1.4 Hz), 7.50 (d, 1H, *J* = 1.4 Hz).

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 4-bromo-2-cyanothiophene (55.5 mg, 0.30 mmol, 1.0 equiv), potassium carbonate (3.2 mg, 0.023 mmol, 0.08 equiv), glycerol (0.36 mL), 2-amino-2-methyl-1-propanol (43.4 mg, 0.49 mmol, 1.6 equiv) and ethylene glycol (0.30 mL). The resulting mixture was heated at 110 °C for 19 h, at which time the reaction mixture was quenched with saturated aqueous ammonium chloride (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 5:1) to provide the title compound as a colorless oil (38.5 mg, 0.148 mmol, 50%). R_f = 0.31 (hexane/diethyl ether = 5:1); IR (ATR, cm^{-1}): 2967, 1649, 1517, 1422, 1353, 1306, 1271, 1202, 1179, 1205, 985, 954, 876, 846, 814, 751, 701, 678, 616, 583, 526; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, 1H, *J* = 1.8 Hz), 7.30 (d, 1H, *J* = 1.8 Hz), 4.08 (s, 2H), 1.35 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.8, 132.5, 131.9, 126.8, 110.3, 79.7, 68.2, 28.3; HRMS ($DART^+$) *m*/*z*: calcd. for $C_9H_{11}ON^{79}BrS$, 259.9745 $[M+H]^+$; found, 259.9743.

2-(3-Bromothiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (3e).

To a 30-mL round bottomed flask equipped with a Teflon-coated magnetic stirring bar were added 3-bromo-2-formylthiophene (184.7 mg, 0.97 mmol, 1.0 equiv), 28% aqueous ammonium hydroxide (2.6 mL), and THF (2.8 mL). After stirring at room temperature for 10 min, the reaction mixture was treated with iodine (154.4 mg, 0.61 mmol, 0.63 equiv) and the resulting mixture was stirred at room temperature for 6 h. Iodine (125.8 mg, 0.50 mmol, 0.51 equiv) was added to the flask, and the reaction mixture was stirred for 3 h, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate (3 mL). After partitioned, the organic layer was washed with water (10 mL), brine (10 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material (157.0 mg, 0.835 mmol, 86%), which was used to the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 1H, *J* = 5.2 Hz), 7.11 (d, 1H, *J* = 5.2 Hz).

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with potassium carbonate (6.0 mg, 0.043 mmol, 0.15 equiv), glycerol (0.36 mL), 3-bromo-2-cyanothiophene (53.4 mg, 0.28 mmol, 1.0 equiv), 2-amino-2-methyl-1-propanol (50.5 mg, 0.57 mmol, 2.0 equiv) and ethylene glycol (0.30 mL). The resulting mixture was heated at 110 °C for 49 h, at which time 2-amino-2-methyl-1-propanol (90.3 mg, 1.01 mmol, 3.6 equiv) was added to the Schlenk tube. After stirring for 45 h, the reaction mixture was treated with saturated aqueous ammonium chloride (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (2 mL x 1, 1 mL x 3) four times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a rude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1) followed by preparative SEC-HPLC to provide the title compound as a yellow oil (24.8 mg, 0.0954 mmol, 34%). R_f = 0.29 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 3111, 2966, 2929, 2895, 1646, 1573, 1494, 1291, 1183, 1050, 999, 984, 955, 886, 790; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 1H, *J* = 5.4 Hz), 7.04 (d, 1H, *J* = 5.4 Hz), 4.12 (s, 2H), 1.39 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.8, 132.6, 129.1, 126.1, 113.2, 79.6, 68.0, 28.4; HRMS ($DART^+$) *m*/*z*: calcd. for $C_9H_{11}ON^{79}BrS$, 259.9745 $[M+H]^+$; found, 259.9733.

4-Bromo-*N*,*N*-diethylthiophene-2-carboxamide (2f).

To a 30-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar were added 4-bromothiophene-2-carboxylic acid (104.9 mg, 0.51 mmol, 1.0 equiv), dichloromethane (2.0 mL), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (194.0 mg, 1.0 mmol, 2.0 equiv), 1-hydroxybenzotriazole (154.8 mg, 1.0 mmol, 2.0 equiv), diethylamine (106.3 mg, 1.5 mmol, 2.9 equiv) and *N*,*N*-diisopropylethylamine (195.5 mg, 1.5 mmol, 2.9 equiv). The resulting mixture stirred at room temperature for 22 h, at which time the reaction mixture was treated with 1 M aqueous hydrochloric acid (3 mL). After partitioned, the organic layer was washed with saturated aqueous sodium hydrogen carbonate (3 mL) and brine (3 mL). The organic solvents were removed under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:2) followed by (hexane/diethyl ether = 5:1 to 4:1, gradient) to provide the title compound as a yellow oil (85.5 mg, 0.326 mmol, 64%). R_f = 0.21 (hexane/diethyl ether = 4:1); IR (ATR, cm^{-1}): 2974, 1750, 1620, 1612, 1546, 1516, 1455, 1432, 1379, 1363, 1338, 1278, 1217, 1175, 838; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, 1H, *J* = 1.2 Hz), 7.15 (d, 1H, *J* = 1.2 Hz), 3.48 (q, 4H, *J* = 6.8 Hz), 1.21 (t, 6H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.2, 139.7, 130.0, 125.9, 109.2, 42.3, 13.6; HRMS ($DART^+$) *m*/*z*: calcd. for $C_9H_{13}ON^{79}BrS$, 261.9901 $[M+H]^+$; found, 261.9897.

Halogen Dance/Trapping of the Anion Species (Tables 2 and 3)

(3-Bromo-5-(diethoxymethyl)thiophen-2-yl)(phenyl)methanol (4a).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 5-bromo-2-(diethoxymethyl)thiophene (**1c**) (81.1 mg, 0.31 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to −78 °C for 30 min, LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added to the Schlenk tube dropwise. The reaction mixture was stirred at −78 °C for 1 h, at which time benzaldehyde (62 μL, 0.60 mmol, 1.9 equiv) was added to the Schlenk tube. After stirring at −78 °C for 1 h, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1 to 5:1, gradient) to provide the title compound as a yellow solid (88.7 mg, 0.239 mmol, 78%). R_f = 0.32 (hexane/diethyl ether = 5:1); M.p. 56–57 °C; IR (ATR, cm^{-1}): 3381, 2978, 1342, 1200, 1153, 1126, 1087, 1041, 1029, 986, 855, 838, 716, 698, 572, 561, 554, 537, 521, 511; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51–7.46 (m, 2H), 7.40–7.27 (m, 3H), 6.92 (d, 1H, *J* = 1.0 Hz), 6.12 (d, 1H, *J* = 3.2 Hz), 5.62 (d, 1H, *J* = 1.0 Hz), 3.66 (dq, 2H, *J* = 9.6, 6.8 Hz), 3.55 (dq, 2H, *J* = 9.6, 6.8 Hz), 2.44 (d, 1H, *J* = 3.2 Hz), 1.224 (t, 3H, *J* = 7.4 Hz), 1.218 (t, 3H, *J* = 7.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 142.7, 142.6, 141.9, 128.7, 128.2, 127.8, 126.5, 107.5, 97.9, 71.7, 61.3, 61.2, 15.2; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{14}H_{14}O_2{}^{81}BrS$, 326.9877 $[M–OEt]^+$; found, 326.9885.

Ethyl 3-bromo-5-(diethoxymethyl)thiophene-2-carboxylate (4b).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 5-bromo-2-(diethoxymethyl)thiophene (**1c**) (101.1 mg, 0.38 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to −78 °C for 30 min, LDA (0.31 mL, 0.46 mmol, 1.2 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at −78 °C for 1 h, at which time ethyl chloroformate (73 μL, 0.76 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at −78 °C for 1 h, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 20:1) to provide the title compound as a yellow oil (78.1 mg, 0.232 mmol, 61%). R_f = 0.30 (hexane/diethyl ether = 20:1); IR (ATR, cm^{-1}): 2978, 1724, 1700, 1527, 1456, 1368, 1338, 1314, 1277, 1237, 1190, 1170, 1133, 1077, 1054, 844, 759, 604; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, 1H, *J* = 0.8 Hz), 5.65 (s, 1H), 4.32 (q, 2H, *J* = 7.2 Hz), 3.62 (dq, 2H, *J* = 9.6, 7.4 Hz), 3.56 (dq, 2H, *J* = 9.6, 7.4 Hz), 1.35 (t, 3H, *J* = 6.8 Hz), 1.22 (t, 6H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.9, 148.7, 130.6, 127.5, 116.2, 97.4, 61.4, 61.3, 15.2, 14.3; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{10}H_{12}O_3{}^{81}BrS$, 292.9670 $[M–OEt]^+$; found, 292.9655.

2-Allyl-3-bromo-5-(diethoxymethyl)thiophene (4c).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 5-bromo-2-(diethoxymethyl)thiophene (**1c**) (78.1 mg, 0.30 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to −78 °C for 30 min, LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at −78 °C for 1 h, at which time CuI (82.3 mg, 0.43 mmol, 1.4 equiv) was added to the Schlenk tube. After warming to 0 °C for 1 h, the reaction mixture was cooled to −78 °C and allyl iodide (53 μL, 0.58 mmol, 1.9 equiv) was added to the Schlenk tube. The resulting mixture stirred at −78 °C for 3 h, at which time the reaction mixture was treated with water (1 mL) and 28% aqueous ammonia (2 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed twice with 28% aqueous ammonia (2 mL), brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 50:1) followed by preparative SEC-HPLC to provide the title compound as a yellow oil (60.7 mg, 0.199 mmol, 68%). R_f = 0.30 (hexane/diethyl ether = 50:1); IR (ATR, cm^{-1}): 2977, 2886, 1640, 1541, 1481, 1443, 1427, 1370, 1337, 1195, 1168, 1123, 1052, 1003, 919, 845, 805, 706; ^1H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, 1H, *J* = 1.2 Hz), 5.92 (ddt, 1H, *J* = 17.2, 10.4, 6.4 Hz), 5.63 (s, 1H), 5.18–5.09 (m, 2H), 3.65 (dd, 2H, *J* = 9.6, 6.8 Hz), 3.56 (dd, 2H, *J* = 9.6, 6.8 Hz), 3.48 (ddd, 2H, *J* = 6.4, 1.2, 1.2 Hz), 1.23 (t, 6H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 140.8, 137.5, 134.8, 127.9, 117.2, 108.0, 98.0, 61.2, 33.7, 15.2; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{10}H_{12}O^{79}BrS$, 258.9792 $[M–OEt]^+$; found, 258.9784.

1-(3-Bromo-5-(diethoxymethyl)thiophen-2-yl)cyclohexan-1-ol (4d).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 5-bromo-2-(diethoxymethyl)thiophene (**1c**) (76.2 mg,

0.29 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to −78 °C for 30 min, LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at −78 °C for 1 h, at which time cyclohexanone (59.4 mg, 0.61 mmol, 2.1 equiv) was added to the Schlenk tube. After stirring at −78 °C for 1 h, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 10:1) followed by preparative SEC-HPLC to provide the title compound as a colorless solid (55.4 mg, 0.150 mmol, 52%). R_f = 0.32 (hexane/diethyl ether = 4:1); M.p. 85–86 °C; IR (ATR, cm^{-1}): 2976, 2932, 2861, 1446, 1336, 1309, 1258, 1165, 1125, 1083, 1052, 1001, 972, 904, 847, 827; ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, 1H, *J* = 1.2 Hz), 5.60 (s, 1H), 3.65 (dq, 2H, *J* = 9.6, 7.0 Hz), 3.56 (dq, 2H, *J* = 9.6, 7.0 Hz), 2.45 (br s, 1H), 2.16 (dt, 2H, *J* = 13.2, 4.0 Hz), 1.89 (d, 2H, *J* = 12.8 Hz), 1.78–1.57 (m, 6H), 1.23 (t, 6H, *J* = 6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.5, 139.6, 130.1, 103.0, 98.0, 73.5, 61.3, 36.6, 25.2, 21.8, 15.2; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{13}H_{16}O_2{}^{79}BrS$, 317.0211 $[M–OEt]^+$; found, 317.0214.

(4-Bromo-5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)thiophen-2-yl)(phenyl)methanol (5a).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 2-(5-bromothiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**1e**) (76.9 mg, 0.30 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to 0 °C for 30 min, LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at 0 °C for 30 min, at which time benzaldehyde (62 µL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at 0 °C for 1 h, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1 to 1:1, gradient) followed by silica gel column chromatography (hexane/diethyl ether = 1:1) to provide the title compound as a yellow solid (70.3 mg, 0.192 mmol, 65%). R_f = 0.31 (hexane/diethyl ether = 1:1); M.p. 104–107 °C; IR (ATR, cm^{-1}): 1626, 1457, 1359, 1304, 1261, 1107, 1037, 949, 808, 717, 703; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.29 (m, 5H), 6.84 (s, 1H), 5.96 (s, 1H), 4.12 (s, 2H), 2.77 (br s, 1H), 1.37 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.6, 153.6, 142.4, 129.0, 128.7, 128.3, 126.5, 124.3, 112.5, 79.7, 71.6, 67.4, 28.1; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{16}H_{17}O_2N^{79}BrS$, 366.0163 $[M+H]^+$; found, 366.0159.

Ethyl 4-bromo-5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)thiophene-2-carboxylate (5b).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 2-(5-bromothiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**1e**) (78.0 mg, 0.30 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to -78 °C for 30 min, LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at −78 °C for 30 min, at which time ethyl chloroformate (57 µL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at −78 °C for 1 h, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with saturated aqueous ammonium chloride, water, brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/dichloromethane = 1:1 to 1:4, gradient) to provide the title compound as a yellow solid (40.8 mg, 0.123 mmol, 41%). R_f = 0.52 (hexane/diethyl ether = 3:2); M.p. 65–67 °C; IR (ATR, cm^{-1}): 2967, 2931, 1733, 1714, 1653, 1638, 1532, 1473, 1465, 1457, 1368, 1337, 1263, 1250, 1201, 1076, 1045, 1020, 966, 748; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 4.35 (q, 2H, *J* = 7.2 Hz), 4.13 (s, 2H), 1.39 (s, 6H), 1.36 (t, 3H, *J* = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.8, 156.2, 137.2, 135.7, 131.6, 112.8, 79.7, 68.4, 62.0, 28.3, 14.3; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{12}H_{15}O_3N^{79}BrS$, 331.9956 $[M+H]^+$; found, 331.9947.

2-(5-Allyl-3-bromothiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (5c).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 2-(5-bromothiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**1e**) (78.7 mg, 0.30 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to 0 °C for 30 min, LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at 0 °C for 30 min, at which time allyl iodide (56 µL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After warming to room temperature for 1 h, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1) followed by preparative SEC-HPLC to provide the title compound as a light green oil (49.1 mg, 0.149 mmol, 49%). R_f = 0.39 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 2968, 2928, 2895, 1635, 1535, 1477, 1428, 1352, 1304, 1275, 1202, 1186, 1026, 991, 951, 919, 846, 834, 810, 710, 604; ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (s, 1H), 5.97–5.86 (m, 1H), 5.22–5.13 (m, 2H), 4.11 (s, 2H), 3.51 (d, 2H, *J* = 6.4 Hz), 1.38 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.9, 147.1, 134.6, 130.1, 124.0, 117.9, 112.5, 79.5, 67.7, 34.3, 28.3; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{12}H_{15}ON^{79}BrS$, 300.0058 $[M+H]^+$; found, 300.0065.

1-(4-Bromo-5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)thiophen-2-yl)cyclohexan-1-ol (5d).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 2-(5-bromothiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**1e**) (78.0 mg, 0.30 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to −78 °C for 30 min, LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at −78 °C for 30 min, at which time cyclohexanone (56 µL, 0.54 mmol, 1.8 equiv) was added to the Schlenk tube. After stirring at −78 °C for 1 h, the reaction mixture was treated with

water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with saturated aqueous ammonium chloride, water, brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1 to 3:2, gradient) to provide the title compound as a yellow solid (89.5 mg, 0.250 mmol, 83%). R_f = 0.21 (hexane/diethyl ether = 3:2); IR (ATR, cm^{-1}): 2928, 1631, 1467, 1353, 1312, 1173, 1036, 977, 568, 519; ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (s, 1H), 4.11 (s, 2H), 1.93–1.59 (m, 11H), 1.37 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.4, 157.1, 127.4, 124.0, 112.2, 79.6, 72.5, 67.8, 39.7, 28.4, 25.3, 22.2; HRMS ($DART^+$) *m/z*: calcd. for $C_{15}H_{21}O_2N^{79}BrS$, 358.0476 $[M+H]^+$; found, 358.0467.

Scope and Limitations of Bromofurans (Scheme 2)

(2-Bromo-5-(5,5-dimethyl-1,3-dioxan-2-yl)furan-3-yl)(phenyl)methanol (7).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 2-(5-bromofuran-2-yl)-5,5-dimethyl-1,3-dioxane (**6**) (78.7 mg, 0.30 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to −78 °C, and LDA (0.40 mL, 0.60 mmol, 2.0 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at −78 °C for 1 h, at which time benzaldehyde (62 μL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at −78 °C for 1 h, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:3 to hexane/acetone = 3:1, gradient) followed by preparative SEC-HPLC to give a yellow oil (45.8 mg, 0.130 mmol, 43%). R_f = 0.27 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 2957, 2856, 1680, 1546, 1537, 1494, 1469, 1461, 1453, 1395, 1366, 1216, 1192, 1153, 1101, 1014, 982, 963, 948, 920, 823, 730, 700; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–7.22 (m, 5H), 6.46 (s, 1H), 5.74 (d, 1H, *J* = 2.6 Hz), 5.36 (s, 1H), 3.72 (d, 2H, *J* = 11.4 Hz), 3.57 (d, 2H, *J* = 11.4 Hz), 2.10 (d, 1H, *J* = 2.6 Hz), 1.23 (s, 3H), 0.77 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.9, 142.1, 128.6, 127.9, 127.7, 126.0, 120.7, 108.9, 95.7, 77.5, 68.7, 30.5, 23.0, 21.9; HRMS ($DART^+$) *m/z*: calcd. for $C_{17}H_{19}O_4{}^{79}Br$, 366.0467 $[M+H]^+$; found, 366.0460.

(3-Bromo-5-(5,5-dimethyl-1,3-dioxan-2-yl)furan-2-yl)(phenyl)methanol (8).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added potassium tertiary butoxide (66.9 mg, 0.60 mmol, 2.0 equiv) and THF (1.0 mL). The resulting solution was cooled to −78 °C, and LDA (0.40 mL, 0.60 mmol, 2.0 equiv) was added dropwise to the Schlenk tube. To the Schlenk tube was added the 2-(5-bromofuran-2-yl)-5,5-dimethyl-1,3-dioxane (**6**) (78.5 mg, 0.30 mmol, 1.0 equiv) in THF (1.0 mL) dropwise. The reaction mixture was stirred at −78 °C for 15 min, at which time benzaldehyde (62 μL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After stirring at −78 °C for 15 min, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography twice (hexane/acetone = 3:1, then hexane/CH_2Cl_2 = 1:3 to hexane/acetone = 3:1, gradient) followed by preparative SEC-HPLC and preparative TLC to provide the title product as a yellow oil (36.0 mg, 0.102 mmol, 34%). R_f = 0.32 (hexane/diethyl ether = 2:1); IR (ATR, cm^{-1}): 3423, 2956, 2861, 1470, 1453, 1395, 1365, 1340, 1309, 1217, 1189, 1124, 1097, 1038, 1008, 984, 963, 921, 831, 809, 728, 701, 503; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45-7.26 (m, 5H), 6.50 (s, 1H), 5.92 (s, 1H), 5.36 (s, 1H), 3.69 (d, 2H, *J* = 11.2 Hz), 3.54 (dd, 2H, *J* = 10.8, 2.8 Hz), 2.80 (br s, 1H), 1.21 (s, 3H), 0.75 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.4, 151.2, 140.2, 128.6, 128.0, 126.4, 111.5, 98.3, 95.7, 77.4, 68.1, 30.4, 23.0, 21.9; HRMS ($DART^+$) *m/z*: calcd. for $C_{17}H_{19}O_4{}^{79}Br$, 366.0467 $[M+H]^+$; found, 366.0466.

(4-Bromo-5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)furan-2-yl)(phenyl)methanol (10).

To a flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 2-(5-bromofuran-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**9**) (73.0 mg, 0.30 mmol, 1.0 equiv) and THF (2.0 mL). The resulting solution was cooled to −40 °C, and LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added dropwise to the Schlenk tube. The reaction mixture was stirred at −40 °C for 5 min, at which time benzaldehyde (62 μL, 0.60 mmol, 2.0 equiv) was added to the Schlenk tube. After the reaction mixture was let warm to room temperature and stirred for 30 min, the reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 1:1) to provide the title compound as a yellow solid (58.0 mg, 0.166 mmol, 55%). R_f = 0.37 (hexane/diethyl ether = 1:2); IR (ATR, cm^{-1}): 3224, 2966, 2349, 1658, 1187, 1140, 1045, 1010, 972, 954, 818, 725, 700; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.31 (m, 5H), 6.18 (s, 1H), 5.87 (d, 1H, *J* = 3.2 Hz), 4.11 (s, 2H), 3.02 (d, 1H, *J* = 3.2 Hz), 1.36 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 154.6, 140.4, 139.2, 128.6, 128.4, 126.8, 113.8, 105.3, 79.6, 69.3, 67.3, 28.1; HRMS ($DART^+$) *m/z*: calcd. for $C_{16}H_{17}O_3N^{79}Br$, 350.0392 $[M+H]^+$; found, 350.0386.

2-(3-Bromofuran-2-yl)benzo[*d*]thiazole (12b).

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2-(5-bromo-2-furanyl)-benzothiazole (**11b**) (84.8 mg, 0.30 mmol, 1.0 equiv) and anhydrous THF (2.0 mL). The solution was cooled to −78 °C. LDA (0.24 mL, 0.36 mmol, 1.2 equiv) was added dropwise to the Schlenk tube and the resulting mixture was stirred at −78 °C for 30 min, at which time the brown reaction mixture was treated with water (1 mL). After partitioned, the aqueous layer was extracted with diethyl ether (1 mL) three times. The combined organic extracts were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/methyl acetate = 20:1)

to provide the title compound as a yellow solid (24.4 mg, 0.0871 mmol, 29%). R_f = 0.17 (hexane/methyl acetate = 20:1); M.p. 81–83 °C; IR (ATR, cm^{-1}): 1573, 1501, 1450, 1428, 1384, 1315, 1064, 1027, 1012, 932, 922, 885, 752, 725, 691, 672; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, 1H, *J* = 8.4 Hz), 7.93 (d, 1H, *J* = 8.4 Hz), 7.60 (d, 1H, *J* = 2.0 Hz), 7.52 (m, 1H), 7.43 (m, 1H), 6.69 (d, 1H, *J* = 2.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.1, 153.0, 145.5, 144.7, 134.4, 126.7, 125.7, 123.6, 121.6, 116.7, 103.1; HRMS ($DART^+$) *m/z*: calcd. for $C_{11}H_5O^{81}BrNS$, 281.9411 $[M+H]^+$; found, 281.9398.

Synthesis of Starting Materials (Scheme 2)

2-(Furan-2-yl)-5,5-dimethyl-1,3-dioxane.

A 100-mL round bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with furfural (4.97 mL, 60 mmol, 1.0 equiv), toluene (72 mL), neopentyl glycol (6.25 g, 60 mmol, 1.0 equiv), and *p*-toluene sulfonic acid monohydrate (114.2 mg, 0.60 mmol, 1 mol%). The flask was fitted with a Dean-Stark apparatus, and the mixture was heated to reflux for 5 h, at which time the reaction mixture was treated with water. After partitioned, the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with water, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 5:1) on silica gel to provide the title product as a colorless oil (9.64 g, 52.9 mmol, 88%). R_f = 0.45 (hexane); IR (ATR, cm^{-1}): 1472, 1395, 1364, 1218, 1150, 1104, 1024, 987, 971, 953, 933, 917, 884, 813, 781, 740, 599; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.39 (m, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 6.36 (dd, *J* = 3.2, 2.0 Hz, 1H), 5.47 (s, 1H), 3.75 (d, *J* = 11.0 Hz, 2H), 3.61 (d, *J* = 11.0 Hz, 2H), 1.28 (s, 3H), 0.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.0, 142.6, 110.3, 107.5, 96.2, 77.6, 30.5, 23.0, 21.9; HRMS ($DART^+$) *m/z*: calcd. for $C_{10}H_{15}O_3$, 183.1021 $[M+H]^+$; found, 183.1018.

2-(5-Bromofuran-2-yl)-5,5-dimethyl-1,3-dioxane (6).

A flame-dried 200-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2-(furan-2-yl)-5,5-dimethyl-1,3-dioxane (9.64 g, 52.9 mmol, 1.0 equiv) and THF (150 mL). After cooling to 0 °C, the solution was treated with *N*-bromosuccinimide (14.1 g, 79.4 mmol, 1.5 equiv) and the resulting mixture was stirred at room temperature for 22 h, at which time the reaction mixture was treated with saturated aqueous sodium thiosulfate. After partitioned, the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with water and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 5:1) to provide the title compound as a pale yellow solid (8.67 g, 33.2 mmol, 63%). R_f = 0.66 (hexane/diethyl ether = 2:1); IR (ATR, cm^{-1}): 1504, 1210, 1104, 1039, 1022, 1014, 986, 978, 914, 809, 781, 511, 453; ^1H NMR (400 MHz, $CDCl_3$): δ 6.42 (d, *J* = 3.4 Hz, 1H), 6.28 (d, *J* = 3.4 Hz, 1H), 5.41 (s, 1H), 3.74 (d, *J* = 11.0 Hz, 2H), 3.59 (d, *J* = 11.0 Hz, 2H), 1.26 (s, 3H), 0.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.0, 122.3, 112.1, 110.2, 95.7, 77.5, 30.5, 23.0, 21.9; HRMS ($DART^+$) *m/z*: calcd. for $C_{10}H_{14}O_3{}^{79}Br$, 261.0126 $[M+H]^+$; found, 261.0118.

2-(5-Bromofuran-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (9).

A 500-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar was charged with 5-bromo-2-furaldehyde (8.75 g, 50.0 mmol, 1.0 equiv), 2-amino-2-methyl-1-propanol (9.04 g, 102 mmol, 2.0 equiv), and dichloromethane (300 mL). After the resulting solution was stirred at 40 °C for 30 min, activated MS 4Å (75.7 g) was added to the flask. The reaction mixture was stirred at 40 °C for 15 h, and *N*-bromosuccinimide (17.9 g, 101 mmol, 2.0 equiv) was added. The resulting mixture was stirred at 40 °C for 6 h, at which time the reaction mixture was filtered through a pad of Celite. The filtrate was washed with saturated aqueous sodium thiosulfate, water and brine. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 4:1 to 2:3, gradient) to provide the title compound as an ocher solid (6.71 g, 27.5 mmol, 55%). R_f = 0.36 (hexane/diethyl ether = 2:3); M.p. 71–72 °C; IR (ATR, cm^{-1}); 3073, 2965, 1677, 1479, 1367, 1217, 1094, 1024, 976, 922, 800; ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, 1H, *J* = 3.6 Hz), 6.41 (d, 1H, *J* = 3.6 Hz), 4.08 (s, 2H), 1.37 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.5, 144.8, 125.9, 116.3, 113.4, 79.2, 67.9, 28.3; HRMS ($DART^+$) *m/z*: calcd. for $C_9H_{11}O_2N^{79}Br$, 243.9973 $[M+H]^+$; found, 243.9985.

2-(5-Bromofuran-2-yl)benzo[*d*]thiazole (11b).

To a flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum were added 5-bromofuran-2-carbaldehyde (1.75 g, 9.97 mmol, 1.0 equiv), 2-aminothiophenol (1.36 g, 10.9 mmol, 1.1 equiv), and anhydrous xylene (30 mL). After stirring at 120 °C for 30 min, the resulting solution was treated with activated carbon (1.22 g). The resulting mixture was stirred at 120 °C for 13 h, then treated with water (10 mL). The mixture was filtered through Celite and the filter cake was washed with diethyl ether (40 mL). The filtrate was washed with water (20 mL) and brine (10 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was recrystallized from ethanol to provide the title compound as a brown solid (1.66 g, 5.93 mmol, 59%). ^1H NMR spectra of this product were identical to those reported in the literature.[35] R_f = 0.68 (hexane/methyl acetate = 3:1); M.p. 120–122 °C; IR (ATR, cm^{-1}): 3100, 1504, 1455, 1314, 1229, 1020, 1011, 925, 904, 786, 752, 723, 672, 664, 651, 632, 615; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, 1H, *J* = 8.2 Hz), 7.90 (d, 1H, *J* = 8.2 Hz), 7.50 (m, 1H), 7.40 (m, 1H), 7.14 (d, 1H, *J* = 3.4 Hz), 6.50 (d, 1H, *J* = 3.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.4, 153.7, 150.6, 134.3, 126.7, 125.5, 125.3, 123.3, 121.7, 114.6, 113.6; HRMS ($DART^+$) *m/z*: calcd. for $C_{11}H_5O^{79}BrNS$, 279.9432 $[M+H]^+$; found, 279.9445.

Conversion of Acetal and Oxazoline Moieties (Scheme 3)

4-Bromo-5-(hydroxy(phenyl)methyl)thiophene-2-carbaldehyde (13).

To a 20-mL round bottomed flask equipped with a Teflon-coated magnetic stirring bar were added (3-bromo-5-(diethoxymethyl)thiophen-2-yl)(phenyl)methanol (**4a**) (37.5 mg, 0.10 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (2.1 mg, 0.011 mmol, 11 mol%), water (1.0 mL), and acetone (1.0 mL). The resulting solution was stirred at room temperature for 75 min, at which time the reaction mixture was treated with saturated aqueous sodium hydrogen carbonate (1 mL). After partitioned, the aqueous layer was ex-

tracted with diethyl ether (6 mL x 1, 2 mL x 2). The combined organic extracts were washed with brine (2 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexane/diethyl ether = 3:1) followed by preparative SEC-HPLC to provide the title product as a colorless oil (24.5 mg, 0.0824 mmol, 82%). R_f = 0.25 (hexane/diethyl ether = 3:1); IR (ATR, cm^{-1}): 1667, 1452, 1223, 1140, 1038, 1024, 846, 722, 700, 667, 594, 575, 568, 544, 535, 522, 503; ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.60 (s, 1H), 7.50–7.45 (m, 2H), 7.42–7.32 (m, 3H), 6.12 (d, 1H, *J* = 3.2 Hz), 2.59 (d, 1H, *J* = 3.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 182.2, 153.5, 141.6, 140.6, 138.6, 129.0, 128.9, 126.9, 108.9, 72.4; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{12}H_{10}O_2{}^{79}BrS$, 296.9585 $[M+H]^+$; found, 296.9599.

3-Bromo-5-(hydroxy(phenyl)methyl)thiophene-2-carboxylic acid (14).

To an oven dried 20-mL test tube equipped with a Teflon-coated magnetic stirring bar were added (4-bromo-5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)thiophen-2-yl)(phenyl)methanol (**5a**) (36.6 mg, 0.10 mmol, 1.0 equiv), dichloromethane (1.0 mL), and methyl triflate (13 μL, 0.11 mmol, 1.1 equiv). The resulting solution was stirred at room temperature for 2 h, at which time the reaction mixture was concentrated under reduced pressure. The residue was treated with 6 M aqueous sodium hydroxide (0.65 mL) and methanol (0.65 mL). After stirring at 80 °C for 10 min, the reaction mixture was extracted once with diethyl ether. The aqueous layer was acidified with 3 M aqueous sulfuric acid and extracted twice with dichloromethane (3 mL). The combined organic extracts were washed with water (2 mL) three times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to provide the title compound as a light yellow solid (25.0 mg, 0.0798 mmol, 80%). R_f = 0.45 (dichloromethane/methanol = 4:1); M.p. 127–132 °C; IR (ATR, cm^{-1}): 1715, 1697, 1682, 1521, 1508, 1456, 1339, 1262, 1223, 1022, 864, 854, 844, 829, 818, 796, 781, 759, 742, 701, 683, 673, 664, 646, 612; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.33 (m, 5H), 6.88 (d, 1H, *J* = 0.8 Hz), 5.98 (d, 1H, *J* = 0.8 Hz), 2.13 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 155.7, 141.7, 130.3, 129.2, 129.1, 126.6, 125.8, 118.2, 72.7; HRMS ($DART^+$) *m*/*z*: calcd. for $C_{12}H_{10}O_3{}^{81}BrS$, 314.9514 $[M+H]^+$; found, 314.9514.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxxx. ^1H and ^{13}C NMR spectra for all new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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