HETEROCYCLES, Vol. 80, No. 2, 2010, pp. 1429 - 1448. © The Japan Institute of Heterocyclic Chemistry
Received, 20th November, 2009, Accepted, 21st December, 2009, Published online, 21st December, 2009
DOI: 10.3987/COM-09-S(S)135

DIVERGENT SYNTHESIS OF 2,3,5-SUBSTITUTED THIOPHENES BY C–H ACTIVATION/BORYLATION/SUZUKI COUPLING[a]

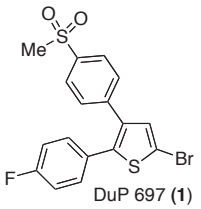
Venkata A. Kallepalli, Luis Sanchez, Hao Li, Nathan J. Gesmundo, Clarissa L. Turton, Robert E. Maleczka, Jr.,* and Milton R. Smith, III*

Department of Chemistry, Michigan State University, East Lansing, MI 48824-1322, USA E-mail: maleczka@chemistry.msu.edu, smithmil@msu.edu

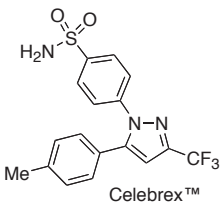
Abstract – C–H activation/borylation has been married with Suzuki coupling to prepare DuP 697 (**1**) and analogs that would be otherwise difficult to obtain via the traditional synthetic route to **1**.

INTRODUCTION

Iridium-catalyzed C-H activation/borylation is emerging as a versatile synthetic methodology for organic chemistry. Our group and others have demonstrated how C-H activation/borylation coupled with other transformations can be exploited in the synthesis of some previously inaccessible or hard to access compounds,[1-9] and we have recently described its application for the elaboration of thiophenes.[2] Thiophenes are an important class of heterocyclic compounds with applications in the design of advanced materials to the treatment of various diseases. In particular, 2,3-diarylthiophenes have been shown to selectively inhibit the cycloxygenase-2 (COX-2) enzyme,[10-13] which is induced during inflammatory conditions. DuP 697 (**1**) is one of the earliest members of this tricyclic class of inhibitors and it is moderately selective for COX-2. Although its unacceptably long half-life led to its withdrawal during phase I clinical trials, it was a forbearer to successful selective COX-2 inhibitors like Celebrex™. Thus, DuP 697 provides an intriguing backdrop for honing synthetic strategies for drug development.



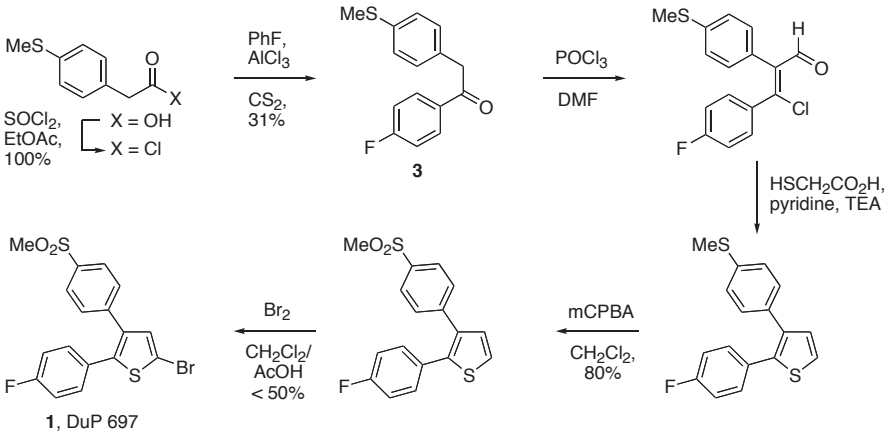
DuP 697 (**1**)



Celebrex™

[a]We dedicate this paper to Professor Suzuki on the occasion of his 80th birthday.

The first published synthesis of DuP 697 (Scheme 1)[11] was linear and involved construction of the thiophene ring from appropriate starting materials. It is interesting that a literature search of 2-bromothiophenes that bear cyclic substituents at the 4 and 5-positions yields only 56 compounds, 28 of which have been the subject of biological studies. The route in Scheme 1 likely contributes to this dearth of structural diversity for the following reasons. First, a linear sequence where the critical 4- and 5-substituents of the thiophene nucleus are installed in the first steps is not attractive for QSAR studies. Second, Friedel-Crafts acylation and oxidation steps employed in the synthesis are relatively harsh and limit the scope of substituents that can be accommodated.

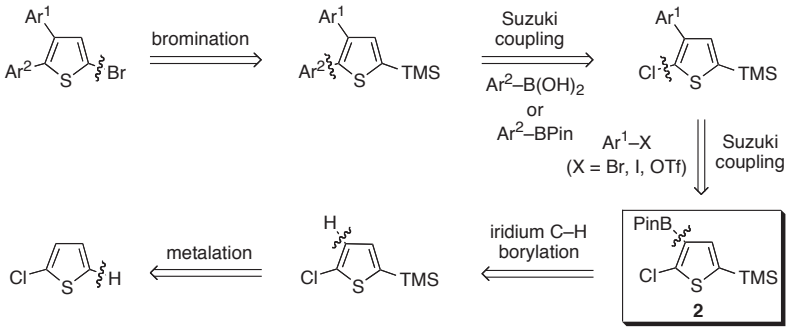


Scheme 1. Original synthesis of DuP 697

To overcome some of these limitations, a second approach to diarylthiophenes related to **1** was devised, which entailed a series of alternating brominations and Suzuki couplings.[13] This route was an improvement, but an even more attractive strategy would utilize a building block possessing all of functionality required for the couplings that introduce the 4 and 5-subsitutents. Herein, we show how the combination of the Suzuki cross-coupling[14,15] and C-H activation/borylation makes such an approach to **1** and its analogs possible.

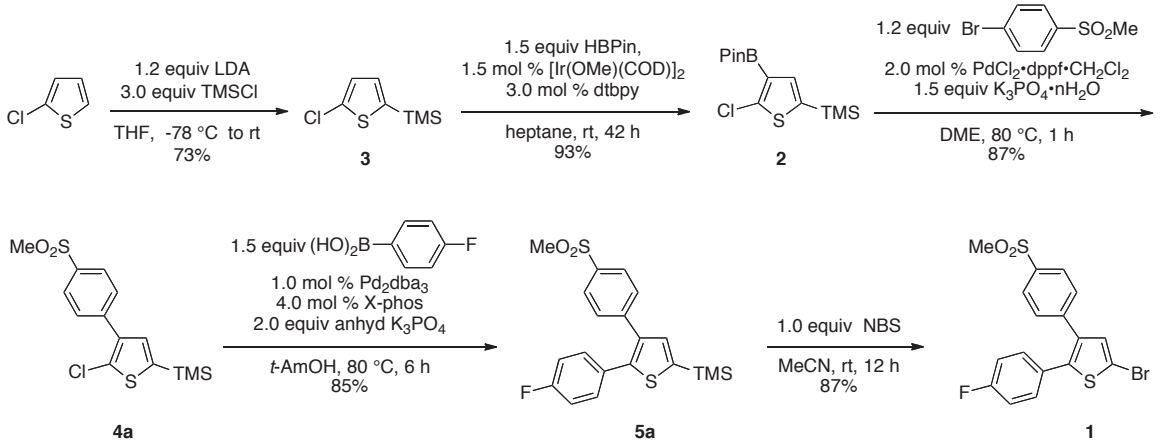
RESULTS AND DISCUSSION

Aryl boronate esters are versatile synthetic intermediates that are widely used in the construction of carbon–carbon and carbon heteroatom bonds, and Ir-catalyzed borylation of C-H bonds provides a convenient way to access them. The key player in our approach to **1** and its analogs (Scheme 2) is compound **2**, which is obtained from Ir-catalyzed C–H borylation of 2-chloro-5-trimethylsilylthiophene. Because C–H borylations are sensitive to steric effects, the selectivity for the C–H at the 3-position is excellent. The BPin and Cl groups serve as Suzuki coupling sites for elaborating the thiophene core, and the trimethylsilyl substituent is transformed to Br in the final step.



Scheme 2. Retrosynthesis of DuP 697and its analogs

Synthesis of **1** provided the first test for this route. As illustrated in Scheme 3, deprotonation at 5-position of 2-chlorothiophene, followed by trapping with TMSCl generated **3**.[16] Isolated **3** was then subjected to Ir C–H borylation conditions to afford compound **2** in excellent yield. Compound **4** was obtained from the Suzuki cross-coupling of **2** with 1-bromo-4-(methylsulfonyl)benzene. There was no evidence for Suzuki coupling polymerization, indicating that the chloride position in **2** does not compete with the aryl bromide partner. Using a catalyst and conditions developed by Buchwald,[17] the second aryl ring was introduced by cross-coupling between chloride **4** and 4-fluorophenylboronic acid. Finally, the trimethylsilyl group is transformed to bromide with NBS to yield DuP 697 in five steps and 42% overall yield.



Scheme 3. Synthesis of DuP 697 (**1**) via C–H activation/borylation

Having validated the strategy in Scheme 2, we next assessed its utility for preparing analogs of DuP 697. Table 1 shows the results obtained for the trimethylsilyl compounds (**5b-j**) that are potential precursors to corresponding DuP 697 analogs upon desilylative bromination. The choices for Ar^1 and Ar^2 were not based on particular pharmaceutical relevance, even though many of the substituents appear in bioactive molecules. Rather, Ar^1 and Ar^2 were chosen to illustrate how the strategy in Scheme 2 enables synthesis of analogs that would be difficult to obtain via the linear (Scheme 1) or bromination/Suzuki coupling

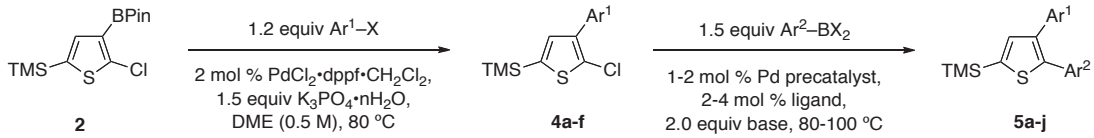
routes. Suzuki cross-couplings of compound **2** were straightforward, and gave good yields of compounds **4a-f** after reaction times of ~ 3 h.

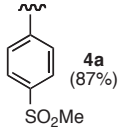
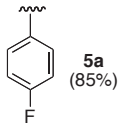
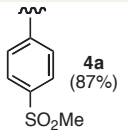
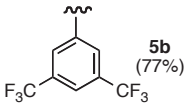
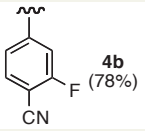
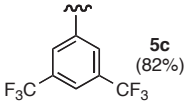
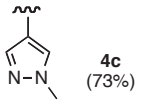
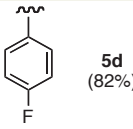
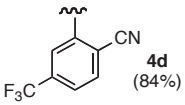
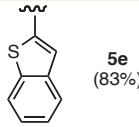
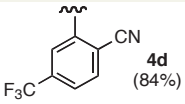
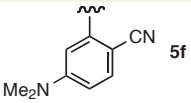
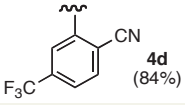
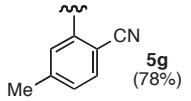
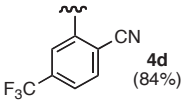
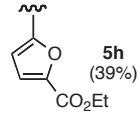
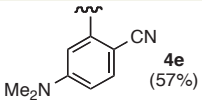
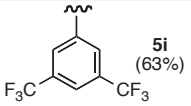
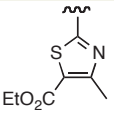
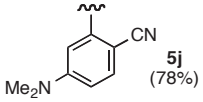
For the second set of Suzuki cross-couplings, three different conditions were used. Entries 2 and 3 were carried out in toluene/H_2O at 100 °C with S-phos. Reactions under these conditions were typically faster, although Ar^2–BPin was prone to deborylation. The remaining couplings were carried in tertiary alcohol solvents (usually *t*-BuOH) at 80 °C, using a Pd_2dba_3/X-phos precatalyst/ligand combination. Both anhydrous and hydrated K_3PO_4 were used. Variation in base had little effect on the reactions. With the exception of entries 6 and 8, the isolation of compounds **5a-j** was uneventful. Product **5f** could not be separated from 4-(*N*,*N*-dimethylamino)benzonitrile, which arose from deborylation of Ar^2–BPin. While analytically pure **5h** could be obtained, a similar quantity of unreacted **4d** was also recovered. While it was not confirmed, a similar deborylation of Ar^2–BPin would be consistent with the diminished yield.

The primary advantage of the approach in Scheme 3 over that in Scheme 1 pertains to the Ar^2 group. In Scheme 1, Ar^2 is installed via Friedel-Crafts acylation. This imposes several problems. First, the arene, Ar^2H, must be sufficiently electron rich to be a viable substrate. Consequently, introduction of the bis(trifluoromethyl)phenyl group (entries 2, 3, and 9) would be virtually impossible using the original synthetic route. Second, the regiochemistry present in the Ar^2 rings of **5** must be consistent with the established regioselectivities for Friedel-Crafts reactions. This clearly is not the case for entry 5, where substitution would be expected at the 3-position of benzothiophene, or entries 6 and 10, where acylation would occur ortho to NMe_2. The route in Scheme 2 also offers advantages over an iterative bromination/Suzuki coupling approach, where installation of Ar^1 requires the availability of $Ar^1B(OH)_2$ or $Ar^1B(OR)_2$ coupling partners. Since the BPin group is present in compound **2**, the roles of the electrophile and nucleophile are swapped. Consequently, Ar^1 can be introduced using Ar^1–X (X = Br, OTf), which expands the structural diversity that can be accessed for Ar^1 substituents. This is highlighted by entry 10. The thiazole bromide is commercially available, whereas corresponding boron compounds are unknown.

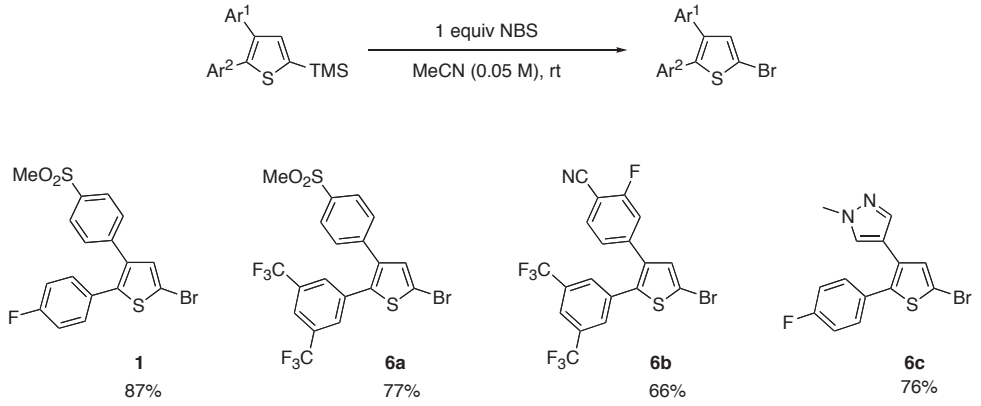
With compounds **5a**–**j** in hand, the desilylative bromination that successfully affords **1** could be examined. As shown in Scheme 4, compounds **5b**–**d** were smoothly converted into compounds **6a**–**c**, providing three new analogs of **1**. Under similar conditions compounds **5e**, **5f**, and **5j** gave products **7a–c**, where bromination occurred at the Ar^2 ring, leaving the TMS group in place (Scheme 5). Since we envisioned similar outcomes for substrates **5h** and **5i**, bromination of these substrates was not examined.

Table 1. Trimethylsilyl precursors to Dup 697 analogs.[a]

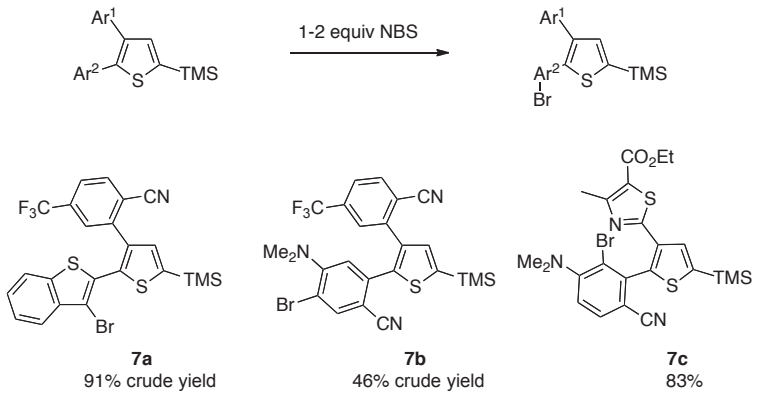


Entry	Ar^1 (% yield)	Ar^2 (% yield)
1[b]	 **4a** (87%)	 **5a** (85%)
2[c-e]	 **4a** (87%)	 **5b** (77%)
3[c-e]	 **4b** (78%)	 **5c** (82%)
4[c,f,g]	 **4c** (73%)	 **5d** (82%)
5[d,h,i]	 **4d** (84%)	 **5e** (83%)
6[d,h-j]	 **4d** (84%)	 **5f**
7[d,h,i]	 **4d** (84%)	 **5g** (78%)
8[d,h,k]	 **4d** (84%)	 **5h** (39%)
9[d,h,i]	 **4e** (57%)	 **5i** (63%)
10[c,d,g]	 **4f** (84%)	 **5j** (78%)

[a]Yields are for isolated compounds. [b]See Scheme 3 for conditions. [c]Ar^1–X = Ar^1–Br. [d]BX_2 = BPin. [e]Precatalyst = $Pd(OAc)_2$ (1 mol %), ligand = S-phos (2 mol %), base = K_3PO_4•nH_2O, toluene/H_2O (10:1), 100 °C. [f]BX_2 = $B(OH)_2$. [g]Precatalyst = Pd_2dba_3 (1 mol %), ligand =X-phos (4 mol %), base = K_3PO_4, DME, 80 °C. [h]Ar^1–X = Ar^1–OTf. [i]Precatalyst = Pd_2dba_3 (5 mol %), ligand =X-phos (20 mol %), base = K_3PO_4•nH_2O, *t*-BuOH, 80 °C. [j]Contaminated with ~30% Ar^2–H. [k]Precatalyst = Pd_2dba_3 (2 mol %), ligand =X-phos (8 mol %), base = K_3PO_4•nH_2O, *t*-BuOH, 70 °C, 40% recovery of **4d**.

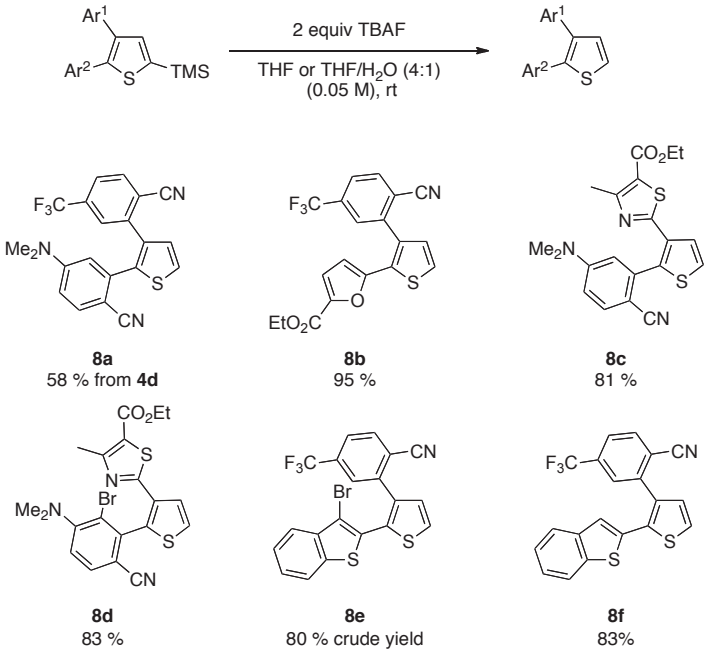


Scheme 4. Synthesis of DuP 697 analogs via desilylative bromination

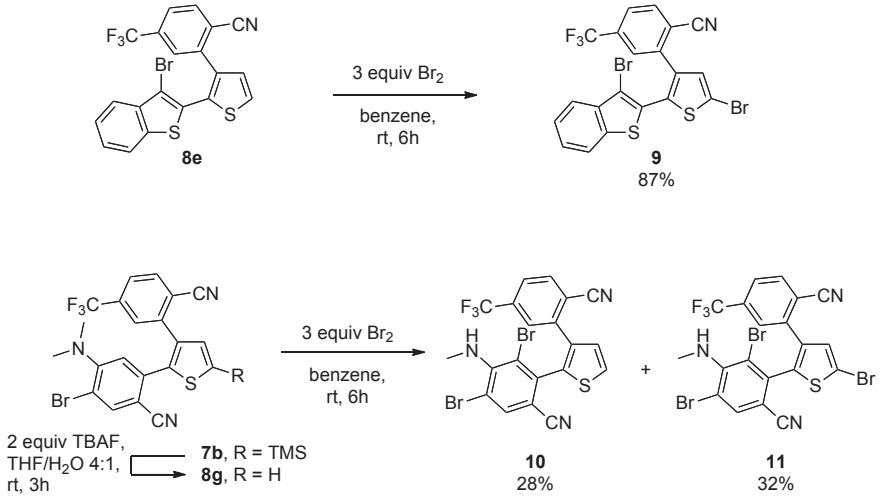


Scheme 5. Alternate outcomes from attempted desilylative bromination

Because derivatives of **1** where Br is substituted by H are known to be COX-2 selective,[12,13] it was of interest to determine whether the TMS groups in compounds **5** could be deprotected. As shown in Scheme 6, this indeed proved to be the case as compounds **8a**–**f** were obtained in excellent yield. Rather than exhaustively surveying all compounds in Table 1, we chose examples where desilylative brominations were either demonstrated, or likely, to be complicated. It is noteworthy that even though we could not isolate compound **5f**, pure **8a** could be obtained by desilylating reaction mixtures that contained **5f**. In addition, bromination products **7a** and **7c** could be deprotected without incident. In two cases, we showed that desilylated products **8e** and **8g** (generated in situ from **7b**) could be brominated at the 5-position of the thiophene ring to afford compounds **9** and **11** (Scheme 7). While the yield for **9** was quite good, NMe_2 demethylation and nearly exhaustive arene bromination accompanied formation of **11**.



Scheme 6. 2,3-Disubstituted thiophenes from TMS deprotection



Scheme 7. Bromination of 2,3-disubstituted thiophenes after TMS deprotection

CONCLUSIONS

In conclusion, the DuP 697 family of COX-2 inhibitors serves as a backdrop for demonstrating the synthetic flexibility that can result when Ir-catalyzed C–H borylation is married to Suzuki cross-couplings. The halogen tolerance that is a hallmark of Ir C–H borylation[1] makes it trivial to construct compound **2**, a building block possessing halogen and boronate ester functionality. This plays directly to one of the strengths of the Suzuki cross–coupling—its exquisite chemoselectivity for halogen functional groups.[14,15] This feature makes **2** a versatile core for efficiently preparing a range 2,3-diaryl thiophenes.

EXPERIMENTALS

Unless otherwise stated, starting materials were subjected to purification before use, yields refer to chromatographically and spectroscopically pure compounds, and reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere. All solvents were reagent grade. 1,2-Dimethoxyethane (DME) and tetrahydrofuran (THF) were distilled from sodium/benzophenone and acetonitrile and toluene were distilled from calcium hydride under nitrogen atmosphere before use. Freeze-pump-thaw method was preferred for solvent degassing. $Pd_2(dba)_3$ (dba = dibenzylideneacetone), $PdCl_2$•dppf•CH_2Cl_2 (dppf = 1,1'-bis(diphenylphosphino) ferrocene), $Pd(OAc)_2$, S-phos (2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl), and X-phos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) were purchased and used as received. Bromide coupling partners: 1-bromo-4-(methylsulfonyl)benzene, 4-bromo-2-fluorobenzonitrile, 4-bromo-1-methyl-1*H*-pyrazole, and 2-bromo-4-methylthiazole-5-carboxylate were purchased and used as received. Triflate partners were prepared from the corresponding precursors 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzonitrile and 4-(dimethylamino)-2-hydroxybenzonitrile; these compounds were purchased and used without purification. Borylated partners: 4-fluorophenylboronic acid, 2-(3,5-bis(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 2-(benzo[b]thiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 4-(dimethylamino)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile, 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile, and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxylate were purchased and used as received. *N*-bromosuccinimide was crystallized from water and dried in vacuo. Reactions were monitored by thin layer chromatography using pre-coated silica gel plates. Column chromatography was performed on 60 Å silica gel (230–400 Mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-300 (300.11 and 75.47 MHz respectively), Varian VXR-500 or Varian Unity-500-Plus spectrometer (499.74 and 125.67 MHz respectively) and referenced to residual solvent ($CDCl_3$) signals (δ 7.24 for ^{1}H and 77.0 for ^{13}C). Elemental analyses were performed at Michigan State University using a Perkin Elmer Series II 2400 CHNS/O Analyzer. Melting points were measured on a MEL-TEMP® capillary melting point apparatus and are uncorrected. High-resolution mass spectra were acquired at the Michigan State University Mass Spectrometry facility using a Waters QTOF Ultima mass spectrometer equipped with an electrospray ionization (ESI) source.

Preparation of (5-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)trimethyl-silane (2):[2] To a solution of *n*-butyllithium (69 mL, 124 mmol, 1.8 M in hexanes) in THF (100 mL) was added dropwise at –78 °C diisopropylamine (14.9 g, 20.5 mL, 147 mmol, 1.4 equiv). The mixture was warmed to 0 °C for 10 min and then recooled to –78 °C. This solution was cannula transferred to a

mixture of 2-chlorothiophene (12.5 g, 9.7 mL, 105 mmol, 1.0 equiv) and chlorotrimethylsilane (34.2 g, 40.3 mL, 315 mmol, 3.0 equiv) at –78 °C. The solution was allowed to warm to room temperature and stir at room temperature for 1 h. The reaction mixture was then poured into 600 mL of water containing 10 mL 3 N HCl. The aqueous layer was extracted twice with 550 mL of diethylether. The combined organic layers were washed with saturated sodium bicarbonate and then brine. After drying over anhydrous sodium sulfate the solvent was removed by rotary evaporation. Vacuum distillation (70 °C at 25 mm Hg) afforded 2-chloro-5-trimethylsilylthiophene (**3**) as a colorless oil (14.7 g, 73% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.98 (d, J = 3.5 Hz, 1 H), 6.93 (d, J = 3.5 Hz, 1 H), 0.27 (s, 9 H, CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz) δ 140.2 (C), 134.5 (C), 133.3 (CH), 127.4 (CH), -0.3 (3 CH_3 of TMS); IR (neat) $\tilde{\nu}_{max}$ = 2959, 1415, 1251, 1205, 1072, 964, 841 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 190 (34), 192 (13), 175 (100); Anal. Calcd for $C_7H_{11}ClSSi$: C, 44.07; H, 5.81. Found: C, 43.59; H, 5.90; HRMS (EI): *m/z* 190.0036 [M^+; Calcd for $C_7H_{11}ClSSi$: 190.0039].

In a glove box, a 250 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (424 mg, 0.64 mmol, 3 mol % Ir) and 20 mL heptane. HBPin (9.3 mL, 8.2 g, 64 mmol 1.5 equiv) was then added and the resulting mixture was stirred for 5 min. The dtbpy (343 mg, 1.3 mmol, 3 mol %) dissolved in 20 mL of heptane was then added and this mixture was stirred for 10 min. 2-Chloro-5-trimethylsilylthiophene (**3**) (8.1 g, 43 mmol, 1 equiv) was added along with an additional 60 mL of heptane. The reaction was left to stir in the glove box for 42 h. The solvent was removed under vacuum and the concentrated reaction mixture was passed through a plug of silica gel eluting with CH_2Cl_2. Evaporation of the CH_2Cl_2 afforded the product as a white solid (12.5 g, 93% yield, mp 68–69 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (s, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), 0.26 (s, 9 H, 3 CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz) δ 144.7 (C), 139.42 (CH), 139.37 (C), 83.7 (2 C), 24.8 (4 CH_3 of BPin), –0.24 (3 CH_3 of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz) δ 29.1; IR (neat) $\tilde{\nu}_{max}$ = 2980, 1525, 1415, 1363, 1307, 1253, 1238, 1143, 993, 841, 758, 696 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity) 316 (33), 301 (100), 281 (6), 201 (15); Anal. Calcd for $C_{13}H_{22}BClO_2SSi$: C, 49.30; H, 7.00; Found: C, 49.16; H, 7.16.

General Procedures

Procedure A: Suzuki coupling of 2 with bromide and triflate partners. In an air-free flask equipped with a magnetic stir bar were mixed **2** (158 mg, 0.5 mmol), the coupling partner (0.6 mmol), K_3PO_4•nH_2O (186 mg, 0.75 mmol), and $PdCl_2$•dppf•CH_2Cl_2 (8.2 mg, 10 μmol). The flask with the solid mixture was purged and refilled with nitrogen several times. Degassed DME (1 mL) was added under a nitrogen atmosphere and the reaction mixture was heated to 80 °C. The progress of the reaction was monitored by TLC. Once finished, usually after 2.5 h for bromide partners and 6 h for triflates, the

reaction mixture was filtered through a short plug of silica gel eluting with acetone. The filtrate was concentrated in vacuo and the crude product was purified by column chromatography.

Procedure B: Suzuki coupling using Pd_2dba_3 and X-phos. To an air-free flask equipped with a magnetic stir bar were added the chloride substrate (0.5 mmol), borylated partner (0.75 mmol), anhydrous potassium phosphate (212 mg, 1.0 mmol), Pd_2dba_3 (5 mg, 5 μmol), and X-phos (10 mg, 20 μmol), and the flask with the solid mixture was purged and refilled with nitrogen multiple times. To the flask was added degassed *t*-BuOH (1.0 mL), and the resulting suspension was heated to 80 °C. The progress of the reaction was monitored by TLC. After completion, usually after more than 6 h, the reaction mixture was filtered through a short plug of silica gel eluting with acetone. The filtrate was concentrated in vacuo and the crude product was purified by column chromatography.

Procedure C: Suzuki coupling using $Pd(OAc)_2$ and S-phos. To an air-free flask provided with a stir bar was added chloride substrate (0.50 mmol), borylated partner (0.75 mmol), $K_3PO_4 \bullet nH_2O$ (248 mg, 1.0 mmol), palladium(II) acetate (1 mg, 5 μmol), and S-phos (4 mg, 10 μmol), and the flask with the solid mixture was purged and refilled with nitrogen several times. Under nitrogen atmosphere, degassed toluene and water (9:1) (1 mL) were added to the flask, and the resulting suspension was heated up to 100 °C. The progress of the reaction was monitored by TLC. After completion, usually after 30 min to 1 h, the reaction mixture was filtered through a short plug of silica gel eluting with acetone. The filtrate was concentrated in vacuo and the crude product was purified by column chromatography.

Procedure D: Desilylative bromination. *N*-bromosuccinimide (18 mg, 0.10 mmol) was added to a solution of silylated substrate (0.1 mmol) in acetonitrile (2 mL), and the mixture was stirred at room temperature until TLC confirmed completion, usually after 12 h. The reaction mixture was filtered through a short plug of silica gel eluting with dichloromethane. The filtrate was concentrated in vacuo and purified by column chromatography.

Procedure E: Desilylation. At room temperature, tetrabutylammonium fluoride (1 M in THF, 0.2 mL, 0.2 mmol) was added dropwise to a solution of silylated substrate (0.1 mmol) in THF (2 mL) or THF/water (4:1) (2 mL). Completion of the reaction, usually after 2.5–3 h, was confirmed by TLC. When THF/water (4:1) was used as solvent, the reaction mixture was passed through a short plug of silica gel eluting with DCM, and the filtrate was concentrated. When THF was used as solvent, the reaction mixture was quenched with aqueous saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate (3 x 5 mL); combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The desilylation product was purified by column chromatography.

Preparation of DuP 697 (1): Using procedure A, **2** (1.58 g, 5.0 mmol) was coupled with 1-bromo-4-

(methylsulfonyl)benzene (1.41 g, 6.0 mmol, 1.2 equiv). After 1 h, the reaction mixture was passed through a short plug of silica gel eluting with ethyl acetate. Concentration of the filtrate followed by column chromatography eluting with ethyl acetate/hexanes 2:3 furnished **4a** (1.51 g, 87% yield) as a white solid. R_f (**4a**) = 0.6 (2:3 ethyl acetate/hexanes); mp 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 8.8 Hz, 2 H), 7.14 (s, 1 H), 3.08 (s, 3 H, SO_2CH_3), 0.32 (s, 9 H, 3 CH_3 of TMS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8 (C), 139.6 (C), 139.2 (C), 137.5 (C), 134.4 (CH), 131.1(C), 129.3 (CH), 127.5 (CH), 44.5 (CH_3), –0.3 (3 CH_3 of TMS); IR (neat) $\tilde{\nu}_{max}$ = 3019, 2957, 1599, 1533, 1397, 1312, 1252, 1153, 1088, 991, 957, 839, 770 cm^{-1}; Anal. Calcd for $C_{14}H_{17}ClO_2S_2Si$: C, 48.75; H, 4.97; Found: C, 48.34; H, 5.36. **4a** (690 mg, 2.0 mmol) was then coupled with 4-fluorophenylboronic acid (420 mg, 3.0 mmol, 1.5 equiv) using procedure B with *t*-AmOH as a solvent. Column chromatography eluting with hexanes/ether 3:7 furnished **5a** as a light cream colored solid (689 mg, 85% yield); R_f (**5a**) = 0.5 (3:7 hexanes/ether); mp 141–143 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2 H), 7.44 (d, *J* = 8.2 Hz, 2 H), 7.24 (s, 1 H), 7.21 (m, 2 H), 6.97 (m, 2 H), 3.05 (s, 3 H, SO_2CH_3), 0.36 (s, 9 H, 3 CH_3 of TMS); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (163.44, 161.47) (d, $^1J_{C–F}$ = 248.5 Hz, C), 144.7 (C), 142.2 (C), 140.4 (C), 138.6 (C), 137.4 (C), 136.5 (CH), (130.92, 130.86) (d, $^3J_{C–F}$ = 8.3 Hz, CH), 129.8 (CH), (129.75, 129.72) (d, $^4J_{C–F}$ = 3.6 Hz, C), 127.5 (CH), (115.88, 115.70) (d, $^2J_{C–F}$ = 21.7 Hz, CH), 44.5 (CH_3), –0.2 (3 CH_3 of TMS); IR (neat) $\tilde{\nu}_{max}$ = 3065, 2957, 2930, 2897, 1599, 1537, 1506, 1314, 1252, 1235, 1154, 1094, 1001, 957, 833, 772 cm^{-1}; Anal. Calcd for $C_{20}H_{21}FO_2S_2Si$: C, 59.37; H, 5.23; Found: C, 58.47; H, 5.64. HRMS (ESI+): *m/z* calculated for $[C_{20}H_{22}FO_2S_2Si]^+$ 405.0815, found 405.0816. **5a** (404 mg, 1.0 mmol) was finally subjected to bromination following procedure D. The crude material was passed through a short plug of silica gel, the filtrate was concentrated and the resulting solid was washed with hexanes and dried to afford DuP 697 (**1**) as a white solid (358 mg, 87% yield). mp 129–131 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.7 Hz, 2 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.16 (m, 2 H), 7.11 (s, 1 H), 6.98 (m, 2 H), 3.05 (s, 3 H, SO_2CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (164.38, 161.07) (d, $^1J_{C–F}$ = 249.5 Hz, C), 140.8 (C), 140.7 (C), 139.2 (C), 136.5 (C), 132.2 (C), (131.10, 130.99) (d, $^3J_{C–F}$ = 8.2 Hz, CH), 129.7 (CH), (128.54, 128.49) (d, $^4J_{C–F}$ = 3.6 Hz, C), 127.6 (CH), (116.22, 115.93) (d, $^2J_{C–F}$ = 21.9 Hz, CH), 111.9 (CH), 44.4 (CH_3); IR (neat) $\tilde{\nu}_{max}$ = 3069, 2926, 1597, 1506, 1489, 1439, 1312, 1282, 1235, 1152, 1094, 983, 957, 860, 830, 772, 735, 681, 558, 544 cm^{-1}; Anal. Calcd for $C_{17}H_{21}BrFO_2S_2$: C, 49.64; H, 2.94; Found: C, 49.50; H, 3.06.

Preparation of analog 6a: Using procedure C, **4a** (173 mg, 0.5 mmol) (see preparation of **1**) was coupled with 2-(3,5-bis(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (255 mg, 0.75 mmol). Column chromatography eluting with hexanes/ethyl acetate 5:1 afforded **5a** (201 mg, 0.39 mmol, 77% yield) as an off-white solid. R_f (**5a**) = 0.3 (hexanes/ethyl acetate 5:1); mp 118–119 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.75 Hz, 2 H), 7.69 (s, 1 H), 7.57 (s, 2 H), 7.38 (d, *J* = 8.75 Hz, 2 H), 7.20 (s,

1 H), 2.98 (s, 3 H), 0.34 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 141.5, 141.4, 139.6, 139.5, 136.8, 136.0, (132.4, 132.1, 131.9, 131.6) (q, $^2J_{C–F}$ = 33.7 Hz), 129.9, 129.0 (m), 127.9, (126.2, 124.0, 121.9, 119.7) (q, $^1J_{C–F}$ = 274.2 Hz), 121.1 (septet, $^3J_{C–F}$ = 3.7 Hz), 44.6, –0.2; IR (neat) $\tilde{\nu}_{max}$ = 3091, 2963, 2933, 1599, 1368, 1319, 1281, 1254, 1237, 1181, 1138, 1099, 1087, 1024, 999, 957, 897, 841, 791, 772, 713 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{22}H_{21}F_6O_2S_2Si]^+$ 523.0651, found 523.0653. **5b** (31 mg, 0.063 mmol) was then brominated using procedure D to afford **6a** (26 mg, 0.049 mmol, 77% yield) as a white solid after purification by column chromatography eluting with hexanes/ethyl acetate 5:1. R_f (**6a**) = 0.21 (hexanes/ethyl acetate 5:1); mp 53–54 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.75 Hz, 2 H), 7.76 (s, 1 H), 7.55 (s, 2 H), 7.38 (d, *J* = 8.75 Hz, 2 H), 7.18 (s, 1 H), 3.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 139.9, 138.7, 137.6, 134.7, (132.9, 132.5, 132.0, 131.6) (q, $^2J_{C–F}$ = 34.1 Hz), 132.7, 129.9, 129.0 (m), (128.2, 124.6, 121.0, 117.3) (q, $^1J_{C–F}$ = 273.3 Hz), 128.0, 121.7 (septet, $^3J_{C–F}$ = 3.6 Hz), 114.2, 44.5; IR (neat) $\tilde{\nu}_{max}$ = 3087, 2930, 1599, 1469, 1432, 1375, 1279, 1155, 1023, 957, 898, 866, 841, 790, 771, 738 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{19}H_{12}BrF_6O_2S_2]^+$ 528.9366, found 528.9366.

Preparation of analog 6b: Using procedure A, **2** (986 mg, 3.1 mmol) was coupled with 4-bromo-2-fluorobenzonitrile (745 mg, 3.7 mmol). Column chromatography eluting with hexanes/ethyl acetate 19:1 afforded **4b** (752 mg, 2.4 mmol, 78% yield) as a white solid. R_f (**4b**) = 0.62 (hexanes/ethyl acetate 5:1); mp 74–76 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.46 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.44 (dd, *J* = 10.25, 1.5 Hz, 1 H), 7.11 (s, 1 H), 0.32 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (164.1, 162.0) (d, $^1J_{C–F}$ = 256.6 Hz), (141.5, 141.4) (d, $^3J_{C–F}$ = 8.5 Hz), 140.0, 136.3, 134.0, 133.4, 131.7, (124.7, 124.7) (d, $^3J_{C–F}$ = 3.5 Hz), (116.2, 116.1) (d, $^2J_{C–F}$ = 21.3 Hz), 113.9, (100.0, 99.9) (d, $^2J_{C–F}$ = 17.0 Hz), –0.4; IR (neat) $\tilde{\nu}_{max}$ = 2963, 2917, 2856, 2239, 1618, 835 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{14}H_{14}ClFNSSi]^+$ 310.0283, found 310.0280. Using procedure C, **4b** (124 mg, 0.4 mmol) was coupled with 2-(3,5-bis(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (204 mg, 0.6 mmol). Column chromatography eluting with hexanes/ethyl acetate 19:1 afforded **5c** (160 mg, 0.33 mmol, 82% yield) as an off-white solid. R_f(**5c**) = 0.62 (5:1 hexanes/ethyl acetate); mp 98–100 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.65 (s, 1 H), 7.53 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.24 (s, 1 H), 7.12 (dd, *J* = 9.5, 1.5 Hz, 1H), 7.07 (dd, *J* = 8.0, 1.5 Hz, 1H), 0.37(s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (164.2, 162.1) (d, $^1J_{C–F}$ = 261.2 Hz), (143.4, 143.4) (d, $^3J_{C–F}$ = 8.5 Hz), 143.0, 142.1, 138.2, 136.4, 135.6, 133.6, (132.7, 132.4, 132.1, 131.9) (q, $^2J_{C–F}$ = 33.6 Hz), 129.0, (126.1, 124.0, 121.8, 119.6) (q, $^1J_{C–F}$ = 273.8 Hz), (125.4, 125.4) (d, $^3J_{C–F}$ = 3.5 Hz), 121.6 (m), (116.8, 116.6) (d, $^2J_{C–F}$ = 20.3 Hz), 113.7, (100.3, 100.2) (d, $^3J_{C–F}$ = 16.5 Hz), –0.3; IR (neat) $\tilde{\nu}_{max}$ = 2961, 2237, 1618, 1564, 1497, 1370, 1346, 1311, 1279, 1254, 1181, 1138, 1026, 1001, 949, 897, 841, 758 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{22}H_{17}F_7NSSi]^+$ 488.0734, found 488.0729. Finally **5c** (50 mg, 0.10 mmol) was brominated according to procedure D to give **6b** (34 mg, 0.068 mmol, 66% yield) as a white solid after purification by column chromatography eluting with

hexanes/ethyl acetate (19:1 to 5:1). R_f (**6b**) = 0.57 (hexanes/ethyl acetate 5:1); mp 148–150 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.60 (s, 1 H), 7.55 (dd, J = 8.0, 6.5 Hz, 1H), 7.15 (s, 1 H), 7.07 (dd, J = 8.5, 1.5 Hz, 1H), 7.04 (dd, J = 8.0, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (164.2, 162.1) (d, $^1J_{C–F}$ = 260.2 Hz), (141.4, 141.4) (d, $^3J_{C–F}$ = 8.4 Hz), 138.3, (137.3, 137.3) (d, $^4J_{C–F}$ = 2.3 Hz), 134.4, 133.9, (133.0, 132.7, 132.4, 132.2) (q, $^2J_{C–F}$ = 33.8 Hz), 132.4, 129.0 (m), (126.0, 123.8, 121.6, 119.5) (q, $^1J_{C–F}$ = 273.4 Hz), (125.3, 125.2) (d, $^3J_{C–F}$ = 3.6 Hz), 122.1 (septet, $^3J_{C–F}$ = 3.4 Hz), (116.8, 116.6) (d, $^2J_{C–F}$ = 20.7 Hz), 114.6, 113.4, (101.0, 100.9) (d, $^2J_{C–F}$ = 15.4 Hz); IR (neat) $\tilde{\nu}_{max}$ = 2923, 2853, 2237, 1727, 1620, 1354, 1205, 1179, 1129 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{19}H_8BrF_7NS]^+$ 493.9444, found 493.9448.

Preparation of analog 6c: Using procedure A, **2** (200 mg, 0.63 mmol) was coupled with 4-bromo-1-methyl-1*H*-pyrazole (122 mg, 0.76 mmol). Column chromatography eluting with hexanes/ethyl acetate 9:1 to 3:1 afforded **4c** (125 mg, 0.46 mmol, 73% yield) as a white solid. R_f (**4c**) = 0.3 (hexanes/ethyl acetate 5:1); mp 82–83 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.79 (s, 1 H), 7.13 (s, 1 H), 3.93 (s, 3 H), 0.29 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 137.8, 133.2, 133.2, 131.0, 128.0, 115.9, 39.1, –0.4; IR (neat) $\tilde{\nu}_{max}$ = 3139, 3091, 3052, 2957, 2898, 1420, 1385, 1312, 1277, 1120, 984, 839, 804, 756 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{11}H_{16}N_2SiSCl]^+$ 271.0492, found 271.0493. **4c** (32 mg, 0.12 mmol) was then coupled with 4-fluorophenylboronic acid (25 mg, 0.18 mmol) following procedure B. Column chromatography eluting with hexanes/ethyl acetate 3:1 to 2:1 afforded **5d** (32 mg, 0.096 mmol, 82% yield) as a very thick colorless oil. R_f(**5d**) = 0 .21 (hexanes/ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 3 H), 7.19 (s, 1 H), 7.15 (s, 1 H), 7.02 (m, 1 H), 3.82 (s, 3 H), 0.33 (s, 9 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ (163.4, 161.4) (d, $^1J_{C–F}$ = 247.7 Hz), 141.1, 138.2, 135.9, (131.0, 131.0) (d, $^3J_{C–F}$ = 8.7 Hz), (130.8, 130.8) (d, $^4J_{C–F}$ = 3.5 Hz), 130.6, 128.0, 117.5, (115.6, 115.5) (d, $^2J_{C–F}$ = 22.0 Hz), 38.9, –0.1; IR (neat) $\tilde{\nu}_{max}$ = 3029, 2955, 2897, 2855, 1601, 1527, 1502, 1448, 1265, 1250, 1222, 1157, 1018, 983, 843, 821 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{17}H_{20}N_2SiSF]^+$ 331.1101, found 331.1101. Using procedure D, **5d** (23 mg, 0.069 mmol) was brominated to afford **6c** (18 mg, 0.053, 76% yield) as a very thick colorless oil after purification by column chromatography eluting with hexanes/ethyl acetate (5:1 to 2:1). R_f(**6c**) = 0.17 (hexanes/ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 2 H), 7.29 (d, J = 0.5 Hz, 1 H), 7.09 (d, J = 0.5 Hz, 1 H), 7.05 (s, 1 H), 7.03 (m, 2 H), 3.81 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (163.7, 161.7) (d, $^1J_{C–F}$ = 247.9 Hz), 138.1, 136.8, 131.4, (131.3, 131.2) (d, $^3J_{C–F}$ = 8.4 Hz), 129.8, (129.6, 129.6) (d, $^4J_{C–F}$ = 3.2 Hz), 128.0, 116.5, (115.9, 115.7) (d, $^2J_{C–F}$ = 22.0 Hz), 111.1, 39.0; IR (neat) $\tilde{\nu}_{max}$ = 3100, 3071, 2932, 2855, 1603, 1586, 1533, 1504, 1448, 1417, 1288, 1234, 1157, 1100, 1093, 985, 972, 841, 810 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{14}H_{11}N_2FSBr]^+$ 336.9810, found 336.9810.

Preparation of intermediate 4d: 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzonitrile (600 mg, 2.0 mmol) was weighed into a 20 mL vial and 2 mL of MeOH was added followed by aqueous H_2O_2 (0.5 mL, 5 mmol). The mixture was stirred for 4 h at room temperature. The progress of the reaction was monitored by TLC eluting with hexanes/EtOAc (3:1). Once finished, the volatiles were removed by rotatory evaporation, and the resulting white solid was stirred with water (10 mL) for 2 h. The resulting fine powder was separated by filtration, washed with cold water, and dried in vacuo to give 2-hydroxy-4-(trifluoromethyl)benzonitrile (337 mg, 90% yield), mp 118–119 °C, and this phenol was used without further purification. The phenol and K_3PO_4•nH_2O (1.34 g, 5.4 mmol) were weighed into a 20 mL vial and there dissolved in water (3 mL) and toluene (3 mL), and cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.47 mL) was added and the resulting mixture was stirred at 0 °C for 10 min, and then allowed to warm to room temperature and stirred for 4 h. The progress of the reaction was monitored by TLC (hexanes/EtOAc 5:1). The reaction mixture was then extracted with diethyl ether, the combined organic layers were passed through a short plug with silica gel and then dried over $MgSO_4$. Concentration in vacuo gave 2-cyano-5-(trifluoromethyl)phenyl trifluoromethanesulfonate (479 mg, 75% yield for two steps) as a slightly yellow clear thick liquid and this triflate was used in following Suzuki couplings without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95–7.90 (d, J = 8.3 Hz, 1 H), 7.81–7.76 (dd, J = 8.3 Hz, 1.0 Hz, 1 H), 7.73 (d, J = 1.0 Hz, 1 H). Following procedure A, **2** (408 mg, 1.3 mmol) was coupled with the crude triflate (493 mg, 1.5 mmol) using $PdCl_2$•dppf•CH_2Cl_2 (25 mg, 0.027 mmol) and K_3PO_4•nH_2O (479 mg, 1.9 mmol). Column chromatography eluting with hexane/EtOAc 9:1 afforded **4d** (388 mg, 84% yield) as a white wax. mp 85.5–87.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.85 (d, J = 8.3 Hz, 1 H), 7.80–7.77 (d, J = 1.2 Hz, 1 H), 7.72–7.68 (dd, J = 8.3, 1.2 Hz, 1 H), 0.34–0.30 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 139.2, 135.0, (134.8, 134.4, 134.1 133.7) (q, $^2J_{C–F}$ = 33.4 Hz), 134.2, 134.0, 133.2, (127.80, 127.77, 127.73, 127.70) (q, $^3J_{F–C}$ = 3.8 Hz), (124.89, 124.86, 124.83, 124.80) (q, $^3J_{F–C}$ = 3.7 Hz), (126.3, 124.1, 121.9, 119.7) (q, $^1J_{F–C}$ = 273.3 Hz), 116.867, 115.984, –0.382; IR (neat) $\tilde{\nu}_{max}$ = 2232 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{15}H_{14}ClF_3NSSi]^+$ 360.0257, found 360.0255.

Preparation of intermediate 4e: 4-(dimethylamino)-2-hydroxybenzonitrile (81 mg, 0.5 mmol) and K_3PO_4•nH_2O (372 mg, 1.5 mmol) were weighted in a 20 mL vial, dissolved in 1.5 mL water and 1.5 mL toluene, and cooled to 0 °C. Trifluoromethanesulfonic anhydride (100 μL, 0.6 mmol) was added and the resulting mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature. Completion of the reaction after 4 h was confirmed by TLC eluting with 5:1 hexanes/EtOAc. The reaction mixture was then extracted with diethyl ether; combined organic layers were passed through a short plug of silica gel and then dried over $MgSO_4$. Concentration gave 2-cyano-5-(dimethylamino)phenyl trifluoromethanesulfonate (77 mg, 52% yield) as a slightly yellow gel and this

triflate was used in following Suzuki coupling without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.42 (d, *J* = 8.9 Hz, 1 H), 6.61–6.59 (dd, *J* = 8.9, 2.6 Hz, 1 H), 6.58–6.57 (d, *J* = 2.6 Hz, 1 H). Following procedure A, **2** (32 mg, 0.099 mmol) was coupled with the crude triflate (38 mg, 0.13 mmol). Column chromatography eluting with hexane/EtOAc (3:1) afforded **4e** (19 mg, 57% yield) as a yellow gel. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.52 (d, *J* = 8.9 Hz, 1 H), 7.18–7.16 (s, 1 H), 6.67–6.65 (d, *J* = 2.6 Hz, 1 H), 6.65–6.62 (dd, *J* = 2.6, 8.9 Hz, 1 H).

Preparation of 5e: Following procedure B, **4d** (180 mg, 0.5 mmol) was coupled with 2-(benzo[b]thiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (195 mg, 0.75 mmol), using $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and X-phos (48 mg, 0.1 mmol), and K_3PO_4•nH_2O (248 mg, 1 mmol). Column chromatography (3:1 hexane/DCM) afforded **5e** (191 mg, 83%) as a white wax. mp 192 °C (decomposed). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.81 (d, *J* = 8.2 Hz, 1 H), 7.81–7.78 (d, *J* = 1.0 Hz, 1 H), 7.75–7.71 (dd, *J* = 8.2, 1.0 Hz, 1 H), 7.32–7.23 (m, 2 H), 7.23–7.19 (2br s, 2 H), 0.41–0.39 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 141.5, 140.5, 140.2, 139.6, 136.4, 135.1, (134.8, 134.5, 134.2, 133.9, q $^2J_{F–C}$ = 33.4 Hz), 134.7, 133.8, 128.3, (126.3, 124.1, 122.0, 119.8, q, $^1J_{F–C}$ = 272.1 Hz), 124.9, 124.8, 124.7, 123.7, 123.2, 122.0, 117.0, 116.6, –0.2; IR (neat) $\tilde{\nu}_{max}$ = 2232 cm^{-1}; HRMS (ESI+) calculated for $[C_{23}H_{19}F_3NS2Si]^+$ 450.0680, found 450.0682.

Preparation of 5g: Following procedure B, **4d** (70 mg, 0.19 mmol) was coupled with 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (71 mg, 0.29 mmol), using $Pd_2(dba)_3$ (9 mg, 0.01 mmol), X-phos (19 mg, 0.039 mmol), and K_3PO_4•nH_2O (97 mg, 0.39 mmol). Column chromatography eluting with hexanes/diethyl ether 9:1 afforded **5g** (65 mg, 78% yield) as a white solid. mp 116.5–117.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.70 (d, *J* = 8.1 Hz, 1 H), 7.60–7.55 (d, *J* = 8.1 Hz, 1 H), 7.54–7.51 (s, 1 H), 7.44–7.40 (d, *J* = 8.0 Hz, 1 H), 7.38–7.36 (s, 1 H), 7.36–7.33 (s, 1 H), 7.22–7.16 (d, *J* = 8.0 Hz, 2 H), 2.42–2.35 (s, 3 H), 0.42–0.34 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 143.3, 143.0, 140.8, 137.1, 136.6, (134.5, 134.3, 134.0, 133.7) (q, $^2J_{F–C}$ = 33.0 Hz), 133.9, 133.3, 133.0, 129.5, (128.44, 128.42, 128.39, 128.36) (q, $^3J_{F–C}$ = 3.4 Hz), (124.28, 124.25, 124.22, 124.19) (q, $^3J_{F–C}$ = 3.7 Hz), (126.2, 124.0, 121.8, 119.7) (q, $^1J_{F–C}$ = 273.6 Hz), 117.7, 117.0, 116.1, 110.0, 21.6, –0.2; IR (neat) $\tilde{\nu}_{max}$ = 2233 cm^{-1}.

Preparation of 5i: Following procedure B, **4e** (18 mg, 0.054 mmol) was coupled with 2-(3,5-bis(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (28 mg, 0.083 mmol), using $Pd_2(dba)_3$ (3 mg, 0.003 mmol), X-phos (6 mg, 0.01 mmol), and K_3PO_4•nH_2O (27 mg, 0.11 mmol). Column chromatography eluting with hexane/EtOAc 9:1 gave **5i** (17 mg, 63% yield) as a yellow gel. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.67 (s, 1 H), 7.66–7.64 (s, 1 H), 7.46–7.43 (d, *J* = 9.0 Hz, 1 H), 7.73–7.29 (s, 1 H), 6.63–6.59 (dd, *J* = 9.0, 2.6 Hz, 1 H), 6.48–6.46 (d, *J* = 2.6 Hz, 1 H), 2.98–2.95 (s, 6 H,),

0.40–0.35 (s, 9 H); IR (neat) $\tilde{\nu}_{max}$ = 2210 cm^{-1}; HRMS (ESI+) calculated for $[C_{24}H_{23}N_2F_6SSi]^+$ 513.1255, found 513.1250.

Preparation of 8a: Following procedure B, **4d** (90 mg, 0.25 mmol) was coupled with 4-(dimethylamino)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (102 mg, 0.38 mmol), using $Pd_2(dba)_3$ (12 mg, 0.013 mmol), X-phos (24 mg, 0.050 mmol), and K_3PO_4•nH_2O (124 mg, 0.50 mmol). Purification by column chromatography eluting with 3:1 hexane/EtOAc afforded 89 mg of a mixture 2.5:1 of **5f** (corresponding to 67% yield) and 4-(*N*,*N*-dimethylamino)benzonitrile, which arose from deborylation of the coupling partner. HRMS (**5f**, ESI+) calculated for $[C_{24}H_{23}F_3N_3SSi]^+$ 470.1334, found 470.1331. Impure **5f** was subjected to desilylation according to procedure E without further purification. The mixture was dissolved in THF (0.67 mL) and water (0.17 mL), TBAF (1M solution in THF, 340 μL, 0.34 mmol) was added and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was passed through a short plug of silica gel eluting with DCM. After concentration, the crude material was purified by column chromatography eluting with DCM to give **8a** (57 mg, 58% yield for two steps) as a white gel. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.71 (d, *J* = 8.0 Hz, 1 H), 7.61–7.55 (2 H, signals overlapping), 7.53–7.49 (d, 1 H, *J* = 5.1 Hz), 7.36–7.31 (d, *J* = 8.8 Hz, 1 H), 7.31–7.28 (d, *J* = 5.1 Hz, 1 H), 6.65–6.62 (d, *J* = 2.7 Hz, 1 H), 6.59–6.55 (dd, *J* = 8.8, 2.7 Hz, 1 H), 2.98–2.95 (s, 6 H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 152.1, 140.9, 139.2, 137.1, 135.3, 134.5, (134.3, 134.0, 133.8, 133.5, q, $^2J_{F–C}$ = 33.3 Hz), 133.7, 129.1, (128.35, 128.32, 128.29, 128.26, q, $^3J_{F–C}$ = 3.8 Hz), 126.6, (126.1, 124.0, 121.8. 119.6, q, $^1J_{F–C}$ = 273.1 Hz), (124.28, 124.26, 124.23, 124.20, q, $^3J_{F–C}$ = 3.8 Hz), 119.1, 117.1, 116.0, 114.6, 111.3, 98.5, 39.8; IR (neat) $\tilde{\nu}_{max}$ = 2211 cm^{-1}; HRMS (ESI+) calculated for $[C_{21}H_{15}N_3F_3S]^+$ 398.0939, found 398.0936.

Preparation of 8b: Using procedure B, **4d** (189 mg, 0.53 mmol) was coupled with ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxylate (210 mg, 0.79 mmol), using $Pd_2(dba)_3$ (10 mg, 0.011 mmol), X-phos (20 mg, 0.042 mmol), and K_3PO_4•nH_2O (261 mg, 1.1 mmol). Purification by column chromatography eluting with 3:1 hexane/EtOAc gave **5h** (95 mg, 39% yield) as a yellow gel. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.85 (d, 1 H, *J* = 8.2 Hz), 7.77–7.75 (d, *J* = 1.3 Hz, 1 H), 7.75–7.70 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.18–7.14 (s, 1 H), 7.09–7.04 (d, *J* = 3.7 Hz, 1 H), 6.21–6.17 (d, *J* = 3.7 Hz, 1 H), 4.38–4.29 (q, *J* = 7.1 Hz, 2 H), 1.28–1.22 (t, *J* = 7.1 Hz, 3 H), 0.38–0.35 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 150.9, 143.9, 142.7, 141.3, 136.3, 135.2, 134.8, (134.7, 134.4, 134.1, 133.9, q, $^2J_{F–C}$ = 33.3 Hz), 133.7, (127.76, 127.73, 127.71, 127.68, q, $^3J_{F–C}$ = 3.7 Hz), (124.79, 124.76, 124.73, 124.70, q, $^3J_{F–C}$ = 3.7 Hz), (126.3, 124.1, 121.9, 119.7, q, $^1J_{F–C}$ = 273.0 Hz), 119.4, 116.6, 116.4, 108.9, 60.8, 14.2, –0.3; IR (neat) $\tilde{\nu}_{max}$ = 2232, 1714 cm^{-1}; HRMS (ESI+) calculated for $[C_{22}H_{21}NO_3SiF_3S]^+$ 464.0964, found 464.0959. **5h** (46 mg, 0.10 mmol) was then dissolved in THF (0.40 mL) and water (0.10 mL). TBAF (1M

solution in THF, 200 μL, 0.20 mmol) was added and the reaction mixture was stirred at room temperature. After 3 h, the reaction mixture was passed through a short plug of silica gel eluting with DCM to afford **8b** (37 mg, 95%) as a white gel. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89–7.85 (d, J = 8.4 Hz, 1 H), 7.75–7.71 (overlapping s and d, 2 H), 7.47–7.43 (d, J = 5.2 Hz, 1 H), 7.13–7.10 (d, J = 5.1 Hz, 1 H), 7.08–7.05 (d, J = 3.7 Hz, 1 H), 6.18–6.16 (d, J = 3.7 Hz, 1 H), 4.28–4.20 (q, J = 7.1 Hz, 2 H), 1.30–1.25 (t, J = 7.2 Hz, 3 H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 158.2, 150.6, 144.1, 141.1, 134.8–134.0 (q, $^2J_{F–C}$ = 33.3 Hz), 134.1, 133.7, 130.3, 130.0, 127.9–127.8 (q, $^3J_{F–C}$ = 3.8 Hz), 126.7, 126.2–129.7 (q, $^1J_{F–C}$ = 273.2 Hz), 125.0–124.9 (q, $^3J_{F–C}$ = 3.7 Hz), 119.3, 116.6, 116.4, 109.1, 60.9, 14.2; IR (neat) $\tilde{\nu}_{max}$ = 2233 cm^{-1}; HRMS (ESI+) calculated for $[C_{19}H_{13}NO_3F_3S]^+$ 392.0568, found 352.0569.

Preparation of 8c: Using procedure A, **2** (200 mg, 0.63 mmol) was coupled with ethyl 2-bromo-4-methylthiazole-5-carboxylate (190 mg, 0.76 mmol). Column chromatography eluting with hexanes/ethyl acetate (19:1 to 5:1) afforded **4f** (191 mg, 0.53 mmol, 84% yield) as a pale yellow solid. R_f(**4f**) = 0.54 (hexanes/ethyl acetate 5:1); mp 63–65 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 4.34 (q, J = 7.25 Hz, 2 H), 2.76 (s, 3 H), 1.38 (t, J = 7.25 Hz, 3 H), 0.32 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 161.6, 159.7, 139.4, 133.6, 133.6, 133.0, 121.7, 61.2, 17.3, 14.4, –0.4; IR (neat) $\tilde{\nu}_{max}$ = 2988, 2959, 2927, 1715, 1539, 1522, 1371, 1321, 1259, 1093, 991, 843, 760 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{14}H_{19}NO_2SiS_2Cl]^+$ 360.0315, found 360.0315. Using procedure C, **4f** (37 mg, 0.10 mmol) was coupled with 4-(dimethylamino)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (22 mg, 0.15 mmol). Column chromatography eluting with hexanes/ethyl acetate (5:1 to 2:1) afforded **5j** (37 mg, 0.080 mmol, 78% yield) as a pale yellow solid. R_f(**5j**) = 0.26 (hexanes/ethyl acetate 3:1); mp 177–178 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1 H), 7.54 (d, J = 9.0 Hz, 1 H), 6.70 (dd, J = 9.0, 3.0 Hz, 1 H), 6.66 (d, J = 3.0 Hz, 1 H), 4.25 (q, J = 7.0 Hz , 2 H), 3.03 (s, 6 H), 2.67 (s, 3 H), 1.30 (t, J = 7.0 Hz, 3 H), 0.36 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 162.5, 159.6, 152.4, 144.5, 141.5, 137.8, 134.8, 134.6, 134.3, 122.2, 119.0, 113.9, 111.9, 99.1, 61.1, 40.0, 17.5, 14.3, –0.2; IR (neat) $\tilde{\nu}_{max}$ = 2957, 2926, 2857, 2820, 2214, 1711, 1599, 1554, 1516, 1442, 1372, 1323, 1264, 1124, 1093, 1003, 843 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{23}H_{28}N_3O_2SiS_2]^+$ 470.1392, found 470.1390. Following procedure E using THF as solvent, **5j** (51 mg, 0.11 mmol) was desilylated to afford **8c** (35 mg, 0.088 mmol, 81% yield) as a white solid after purification by column chromatography eluting with hexanes/ethyl acetate (3:1). R_f(**8c**) = 0.25 (hexanes/ethyl acetate 3:1); mp 185 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 5.0 Hz, 1 H), 7.55 (d, J = 9.0 Hz, 1 H), 7.39 (d, J = 5.0 Hz, 1 H), 6.72 (dd, J = 9.0, 3.0 Hz, 1 H), 6.68 (d, J = 3.0 Hz, 1 H), 4.26 (q, J = 7.5, 2 H), 3.04 (s, 6 H), 2.66 (s, 3 H), 1.30 (t, J = 7.5, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 162.5, 159.6, 152.4, 139.5, 137.4, 134.6, 133.1, 128.3, 125.8, 122.3, 118.9, 114.1, 112.0, 99.5, 61.1, 40.0, 17.5, 14.3; IR (neat) $\tilde{\nu}_{max}$ = 3108, 2964, 2928, 2859, 2213, 1716, 1701, 1684, 1653, 1601, 1558, 1522,

1506, 1437, 1373, 1263 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{20}H_{20}N_3O_2S_2]^+$ 398.0997, found 398.0997.

Preparation of 8d: Using procedure D, **5j** (50 mg, 0.11 mmol) (see preparation of **8c**) was brominated to afford **7c** (49 mg, 0.089, 83% yield) as white solid after purification by column chromatography eluting with hexanes/EtOAc (7:1 to 5:1). R_f(**7c**) = 0.22 (hexanes/EtOAc 5:1); mp 134–136 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1 H), 7.65 (d, *J* = 8.5 Hz, 1 H), 7.14 (d, *J* = 8.5 Hz, 1 H), 4.23 (q, *J* = 7.3 Hz , 2 H), 2.92 (s, 6 H), 2.64 (s, 3 H), 1.28 (t, *J* = 7.3 Hz, 3 H), 0.38 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 162.3, 159.7, 156.8, 143.4, 142.7, 139.8, 134.9, 134.0, 132.9, 122.0, 121.5, 120.4, 116.9, 108.1, 61.0, 43.7, 17.4, 14.2, –0.2; IR (neat) $\tilde{\nu}_{max}$ = 2954, 2924, 2853, 2224, 1717, 1653, 1578, 1523, 1501, 1456, 1437, 1261 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{23}H_{27}N_3O_2SiS_2Br]^+$ 548.0497, found 548.0498. Following procedure E with THF as solvent, **7c** (54 mg, 0.099 mmol) was desilylated to afford **8d** (39 mg, 0.082 mmol, 83% yield) as a wax after purification by column chromatography eluting with hexanes/ethyl acetate (1:1 to 3:1). R_f(**8d**) = 0.4 (hexanes/ethyl acetate 3:1); mp 53–54 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 5.25 Hz, 1 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 7.50 (d, *J* = 5.25 Hz, 1 H), 7.15 (d, *J* = 8.5 Hz, 1 H), 4.24 (q, *J* = 7 Hz, 2 H), 2.93 (s, 1 H), 2.62 (s, 1 H), 1.28 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 162.3, 159.8, 156.8, 139.4, 138.5, 133.7, 132.9, 127.7, 126.9, 122.1, 121.7, 120.6, 116.9, 108.3, 61.1, 43.7, 17.4, 14.3; IR (neat) $\tilde{\nu}_{max}$ = 3110, 2926, 2795, 2224, 1714, 1579, 1522, 1485, 1437, 1373, 1327, 1263, 1128, 1093 cm^{-1}; HRMS (ESI+): *m/z* calculated for $[C_{20}H_{19}N_3O_2S_2Br]^+$ 476.0102, found 476.0105.

Preparation of 8f: Following procedure E, **5e** (63 mg, 0.14 mmol) was desilylated using THF/water (4:1) as solvent. The reaction mixture was passed through a shot plug of silica gel eluting with DCM. Due to the poor solubility of **8f** in DCM, the eluent was monitored under UV light on a TLC plate until no positive detection was observed. The solvent was evaporated and the resulting solid was washed with hexanes to give **8f** (44 mg, 83%) as a white powder. mp 220–223°C (decomposed). ^{1}H NMR (500 MHz, THF-$CDCl_3$) δ 7.95–7.90 (d, 1 H, *J* = 8.3 Hz), 7.85–7.82 (d, *J* = 1.1 Hz, 1 H), 7.82–7.78 (dd, *J* = 1.1, 8.3 Hz, 1 H), 7.65–7.60 (2 H, signals overlapping), 7.55–7.51 (d, *J* = 5.2 Hz, 1 H), 7.26–7.16 (m, 1 H), 7.16–7.12 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR (125 MHz, THF-$CDCl_3$) δ 141.2, 140.1, 139.5, 135.7, (134.8, 134.5, 134.3, 134.0, q, $^2J_{F-C}$ = 33.0 Hz), 134.4, 133.8, 133.7, 129.9, (128.44, 128.41, 128.38, 128.35, q, $^3J_{F-C}$ = 3.8 Hz), (126.2, 124.0, 121.9, 119.7, q, $^1J_{F-C}$ = 272.9 Hz), 126.1, (125.15, 125.12, 125.09, 125.06, q, $^3J_{F-C}$ = 3.8 Hz), 124.9, 124.7, 123.7, 123.5, 122.0, 116.9, 116.6; IR (neat) $\tilde{\nu}_{max}$ = 2233 cm^{-1}; HRMS (ESI+) calculated for $[C_{20}H_{11}NF_3S_2]^+$ 386.285 found 386.292.

Preparation of 9: Compound **5e** (28 mg, 0.062 mmol) and NBS (22 mg, 0.12 mmol) were mixed in a 20 mL vial with 0.5 mL CCl_4 and stirred for 5 h at room temperature. The resulting mixture is washed

through a short plug with silica gel. Concentration in vacuo afforded **7a** (35 mg, 0.056 mmol, 91% yield), which was directly used in the following step. Crude **7a** was dissolved in 224 μL of THF and 56 μL of water, TBAF (1M solution in THF, 112 μL, 0.11 mmol) was added, and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was passed through a short plug of silica gel and the filtrate was concentrated to give **8e** (21 mg, 0.045 mmol, 80% yield). Finally, crude **8e** was mixed with Br_2 (0.5 M stock solution in benzene, 270 μL, 0.14 mmol). The resulting crude material was passed through a short plug with silica gel and purified by column chromatography to afford **9** (23 mg, 87% yield or 64% yield for 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.76 (d, J = 8.1 Hz, 1 H), 7.75–7.71 (d, J = 7.7 Hz, 1 H), 7.70–7.66 (d, J = 7.7 Hz, 1 H), 7.64–7.61 (d, J = 8.1 Hz, 1 H), 7.61–7.59 (s, 1 H), 7.44–7.36 (m, 2 H), 7.27–7.25 (s, 1 H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 139.7, 138.6, 137.9, 137.2, (134.8, 134.5, 134.3, 134.0, q, $^2J_{F–C}$ = 32.7 Hz,) 134.0, 131.6, 128.1 (128.00, 127.98, 127.94, 127.92, q $^3J_{F–C}$ = 3.7 Hz), 126.5, 125.6, (125.15, 125.12, 125.09, 125.06, q $^3J_{F–C}$ = 3.7 Hz), (126.0, 123.8, 121.6, 119.4, q $^1J_{F–C}$ = 273.2 Hz), 124.0, 122.2, 116.5, 116.1, 115.7, 110.2; IR (neat) $\tilde{\nu}_{max}$ = 2233 cm^{-1}; HRMS (ESI+) calculated for $[C_{20}H_9NF_3S_2Br_2]^+$ 541.8495, found 541.8501.

Preparation of 10 and 11: Compound **5f** (0.12 mmol from 65 mg of a mixture 2.5:1 of **5f** and 4-(*N*,*N*-dimethylamino)benzonitrile, see preparation of **8a**) was dissolved in CCl_4 (0.5 mL) and NBS (44 mg, 0.24 mmol) was added. The resulting solution was stirred for 5 h in an 80 °C oil bath. The reaction mixture was passed through a plug of silica gel eluting with dichloromethane. Concentration and purification by column chromatography (3:1 hexanes/EtOAc) gave **7b** (30 mg, 46% yield) as a white gel that was used in the following reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.70 (d, J = 8.4 Hz, 2 H), 7.67–7,64 (two overlapping s, 2 H), 7.63–7.59 (dd, J = 8.4, 1.4 Hz, 1 H), 7.31–7.29 (s, 1H), 6.99–6.97 (s, 1H), 2.83–2.80 (s, 6H), 0.40–0.37 (s, 9H). Compound **7b** (30 mg, 0.055 mmol) was desilylated according to procedure E using THF/water (4:1) as solvent to give **8g**. Crude **8g** was mixed with Br_2 (0.5M stock solution, 0.33 mL, 0.17 mmol) and stirred at room temperature of 6 h. The reaction mixture was passed through a plug of silica gel eluting with DCM and the filtrate was concentrated and purified by column chromatography eluting with 1:1 hexanes/DCM to give **10** (26 mg, 28% yield over 2 steps) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.79 (d, J = 8.1 Hz, 1 H), 7.71–7.69 (s, 1 H), 7.65–7.62 (d, J = 5.3 Hz, 1 H), 7.61–7.57 (dd, J =8.1, 1.7 Hz, 1 H), 7.46–7.44 (d, J = 1.7 Hz, 1 H), 4.82–4.74 (q, J = 5.5 Hz, 1 H), 3.14–3.08 (d, J = 5.6 Hz, 3H); IR (neat) $\tilde{\nu}_{max}$ = 2211 cm^{-1}; HRMS (ESI+) calculated for $[C_{20}H_{11}N_2F_3SBr_2]^+$ 539.8988, found 539.8993 and **11** (34 mg, 32% yield over 2 steps) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.79 (d, J = 8.2 Hz, 1 H), 7.79–7.68 (s, 1H), 7.63–6.59 (dd, J = 8.2, 1.0 Hz, 1 H), 7.47–7.45 (d, J = 1.0 Hz, 1 H) 7.35–7.34 (s, 1 H), 4.85–4.76 (br s, 1 H), 3.15–3.10 (s, 3 H); IR (neat) $\tilde{\nu}_{max}$ = 2210 cm^{-1}.

ACKNOWLEDGEMENTS

We thank BASF, Inc. for gifts of HBPin and B_2Pin_2, and the Michigan Economic Development Corp., the NIH (GM63188 to M.R.S.), the Astellas USA Foundation (to R.E.M.) the ACS Green Chemistry Institute's Pharmaceutical Roundtable, and Pfizer for kind financial support.

REFERENCES

1. J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., and M. R. Smith, III, *Science,* 2002, **295**, 305.
2. G. A. Chotana, V. A. Kallepalli, R. E. Maleczka, Jr., and M. R. Smith, III, *Tetrahedron,* 2008, **64**, 6103.
3. D. Holmes, G. A. Chotana, R. E. Maleczka, Jr., and M. R. Smith, III, *Org. Lett.,* 2006, **8**, 1407.
4. T. Ishiyama and N. Miyaura, *Pure Appl. Chem.,* 2006, **78**, 1369.
5. T. Ishiyama, J. Takagi, Y. Yonekawa, J. F. Hartwig, and N. Miyaura, *Adv. Synth. Catal.,* 2003, **345**, 1103.
6. R. E. Maleczka, Jr., F. Shi, D. Holmes, and M. R. Smith, III, *J. Am. Chem. Soc.,* 2003, **125**, 7792.
7. J. M. Murphy, C. C. Tzschucke, and J. F. Hartwig, *Org. Lett.,* 2007, **9**, 757.
8. S. Paul, G. A. Chotana, D. Holmes, R. C. Reichle, R. E. Maleczka, Jr., and M. R. Smith, III, *J. Am. Chem. Soc.,* 2006, **128**, 15552.
9. F. Shi, M. R. Smith, III, and R. E. Maleczka, Jr., *Org. Lett.,* 2006, **8**, 1411.
10. K. Gans, W. Galbraith, R. Roman, S. Haber, J. Kerr, W. Schmidt, C. Smith, W. Hewes, and N. Ackerman, *J. Pharmacol. Exp. Ther.,* 1990, **254**, 180.
11. S. B. Haber, U.S. Patent 4 820 827, *Chem. Abstr.,* 1989, **111**, 153613.
12. Y. Leblanc, J. Gauthier, D. Ethier, J. Guay, J. Mancini, D. Riendeau, P. Tagari, P. Vickers, E. Wong, and P. Prasit, *Bioorg. Med. Chem. Lett.,* 1995, **5**, 2123.
13. D. J. P. Pinto, R. A. Copeland, M. B. Covington, W. J. Pitts, D. G. Batt, M. J. Orwat, G. N. Lam, A. Joshi, Y.-C. Chan, S. Wang, J. M. Trzaskos, R. L. Magolda, and D. M. Kornhauser, *Bioorg. Med. Chem. Lett.,* 1996, **6**, 2907.
14. A. Suzuki, *J. Organomet. Chem.,* 1999, **576**, 147.
15. N. Miyaura and A. Suzuki, *Chem. Rev.,* 1995, **95**, 2457.
16. R. Wu, J. S. Schumm, D. L. Pearson, and J. M. Tour, *J. Org. Chem.,* 1996, **61**, 6906.
17. K. Billingsley and S. L. Buchwald, *J. Am. Chem. Soc.,* 2007, **129**, 3358.