Copper-Catalyzed Synthesis of Trifluoroethylarenes from Benzylic Bromodifluoroacetates

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Abstract

Trifluoroethylarenes are found in a variety of biologically active molecules, and strategies for accessing this substructure are important for developing therapeutic candidates and biological probes. Trifluoroethylarenes can be directly accessed via nucleophilic trifluoromethylation of benzylic electrophiles; however, current catalytic methods do not effectively transform electron-deficient substrates and heterocycles. To address this gap, we report a Cu-catalyzed decarboxylative trifluoromethylation of benzylic bromodifluoroacetates. To account for the tolerance of sensitive functional groups, we propose an inner-sphere mechanism of decarboxylation.

Graphical abstract
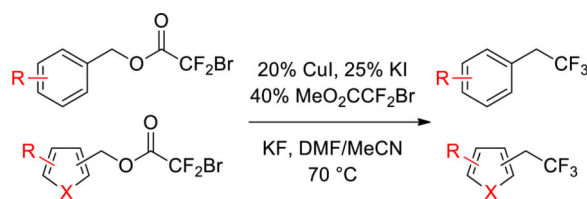
- 20 examples: 44–90% yield
- Tolerates EDG and EWG

The trifluoromethyl group (CF_3) is commonly utilized in medicinal chemistry, agricultural chemistry and materials sciences to modulate the physical and biological properties of molecules.[1,2] Among trifluoromethyl-containing substructures, trifluoroethyl(hetero)arenes represent an important motif, with over 30,000 trifluoroethyl(hetero)arenes possessing documented biological activity or being precursors to bioactive compounds.[3] Thus, general strategies for preparing this substructure are important for accessing biological probes and therapeutics. While several approaches for preparing this group have been reported,[4] one direct route involves the trifluoromethylation of benzylic electrophiles; however, no general

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ASSOCIATED CONTENT

Supporting Information: Supplementary experiments including time-course analysis of benzylic trifluoromethylation, as well as NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

catalytic system can transform a broad spectrum of (hetero)benzylic electrophiles. Current systems for benzylic trifluoromethylation require either stoichiometric Cu (eq 1),[4b,5] or exclusively transform electron-neutral (eq 2)[6] or electron-rich substrates (eq 3).[7] Thus, a need remains for a catalytic system that can transform electron-deficient benzylic electrophiles and heterocyclic derivatives into trifluoroethyl(hetero)arenes. Herein, we report such a general catalytic system that enables access to a broad array of trifluoroethyl(hetero)arenes. Further, we propose a revised mechanism that accounts for the expanded functional group tolerance.

To address the aforementioned gap, we sought to develop a broadly applicable catalytic method for converting benzylic electrophiles into trifluoroethyl(hetero)arenes. As a starting point for this transformation, we considered Chen's decarboxylative trifluoromethylation of benzyl bromodifluoroacetates using stoichiometric Cu.[5f] Beneficial features of this early system included: (1) facile access to substrates derived from simple benzylic alcohols, which are synthetically accessible and already found in a wide variety of synthetic intermediates and building blocks; (2) the formation of just CO_2 and KBr as benign, easily separable by-products. However, this previous transformation was not shown to convert a broad spectrum of substrates,[5f] potentially because the proposed mechanism invoked an outer-sphere decarboxylation that generated free $^-CF_3$ (Scheme 2).[5d–f] If generated, this reactive intermediate would react with carbonyl-based functional groups via 1,2-addition and acidic functional groups via deprotonation, which would severely limit the functional group compatibility of the transformation. However, we hypothesized that a catalytic inner-sphere decarboxylation might generate the critical $Cu–CF_3$ intermediate, which would enable the conversion of substrates bearing sensitive carbonyl and acidic functional groups.

Rational optimization of Chen's CuI-mediated reaction provided a system capable of transforming benzylic electrophiles with only catalytic quantities of Cu. Chen's original reaction of **1a** with stoichiometric CuI provided trifluoroethylarene **2a** in 71% yield;[5f] however, according to the previous protocol, **1a** was slowly added to the reaction mixture over 2 h, which can be labor intensive and operationally challenging for small scale reactions.[5f] To explore a more user-friendly protocol, we charged the vessel with the full quantity of **1a** at the outset of the reaction. Using stoichiometric CuI, this procedure lowered the yield of **2a** and formed benzylic bromide **3a** as a side product (Table 1, entry 1). Given our aim of developing a Cu-catalyzed process, we adapted conditions that effectively catalyzed the decarboxylative trifluoromethylation of allylic bromodifluoroacetates (cat. CuI, *N,N'*-dimethylethylenediamine, NaO_2CCF_2Br, DMF).[8a] However, benzylic bromodifluoroacetates proved less reactive than their allylic counterparts, and optimization of our previous catalyst system provided poor yields of **2a** (entry 2), along with several side products, generally in 2–10% yield (Bn–CF_2CF_3, Bn–I, Bn–F, Bn–Bn, and Bn–O_2CCF_3). Subsequent screening of various N-, O-, and P-based ligands, and attempted modulation of reaction parameters did not improve the transformation. Further, in many cases, addition of a chelating ligand impaired the reaction. Thus, we pursued a system that did not employ a chelating ligand. Using a DMF-ligated system, and MeO_2CCF_2Br as an additive,[5d] a modest yield of **2a** was observed, and benzylic bromide **3a** was identified as the major side-product (entry 3). The formation of **3a** could be suppressed by replacement of DMF with MeCN, but

this change also afforded a less active system (entry 4). Based on these observations, we hypothesized that the use of a DMF/MeCN solvent mixture would provide an active system that would minimize the formation of **3a**. Indeed, employment of a 1:1 mixture of DMF/MeCN improved the yield of desired product **2a**, and minimized formation of the benzylic bromide side-product **3a** (entry 5).

In addition to the solvent, the presence of I^- had a profound effect on the present reaction. In previous reports of Cu-mediated trifluoromethylation of benzylic bromodifluoroacetates, stoichiometric quantities of I^- played an essential role in generating the desired products.[5f] In contrast, a recent Cu-catalyzed trifluoromethylation of allylic bromodifluoroacetates could occur in the complete absence of I^-.[8a] Thus, for the present system, the loading of I^- merited investigation. Addition of catalytic KI (45% total I^-) provided the highest yield of desired product **2a**, and minimized formation of benzylic bromide **3a** and other side-products ($< 2\%$ by GC and ^{19}F NMR analysis; entry 6). In contrast, complete removal of I^- from the system $\{[Cu(MeCN)_4]PF_6\}$ decreased the yield of trifluoroethylarene, and generated additional bromide **3a** (entry 7). However, the catalytic activity using $[Cu(MeCN)_4]PF_6$ could be restored by reintroducing 45% I^- to the system (entry 6 vs. entry 8). Further increase of the I^- content beyond 45% decreased the yield of desired product **2a** (entry 9). In addition, removal of the MeO_2CCF_2Br additive from the system resulted in decreased yield of **2a**, and increased benzyl bromide **3a** (entry 10). Ultimately, we selected a general system that employed 20% CuI, 25% KI, 40% MeO_2CCF_2Br and super-stoichiometric KF in MeCN/DMF (1:1), which minimized the formation of side-products ($<2\%$) and provided good yield of trifluoroethylarene **2a**.

The present Cu-catalyzed reaction tolerated a broad array of useful functional groups (Table 2), including: ethers (**2b, 2e–f, 2l**), a secondary amide (**2c**), a substituted aniline (**2d**), an aryl bromide (**2e**), an alkene (**2h**), a mesylate (**2j**), esters (**2k, 2n**), and a ketone (**2m**). Substrates bearing (pseudo)ortho substituents provided lower yields of products (**2e–f, 2q–s**), and a sterically hindered 2,6-disubstitued benzylic electrophile afforded product in modest yield (**2g**). The present reaction also tolerated heterobenzylic substrates that incorporated N, O, and S atoms (**2o–s**). When the reaction was conducted on gram-scale, the yield of the reaction was maintained (**2b**), which indicates that this process would be useful for the preparation of larger quantities of target trifluoroethyl(hetero)arene compounds.

The broad functional group compatibility implicates a metal-centered decarboxylation that does not involve solvent-separated reactive intermediates. If free in solution, $^-CF_3$ ($pk_a = 27$ in H_2O)[9] would react with sensitive functional groups. However, the tolerance of carbonyls (**2k, 2m–o**) and an acidic amide (**2c**, pk_a ca. 13.8 in H_2O),[10] suggest that free $^-CF_3$ must not exist in solution.[4b] Additionally, in the reaction of **1m–n**, ^{19}F NMR spectra of the crude reaction mixtures did not show products deriving from 1,2-addition or addition-elimination processes. Further, the reaction of **1a** was conducted in the presence of 2-naphthaldehyde (1.0 equiv) with minimal loss of yield (68%) and no evidence of 1,2-addition of $^-CF_3$ to the aldehyde, further discounting the existence of free $^-CF_3$ in solution.[11] Thus, decarboxylation must be a process that either converts $Cu–O_2CCF_2Br$ to $Cu–CF_3$ directly at the metal-center, or that keeps reactive $^-CF_3$ within the solvent cage surrounding Cu. This proposed

mechanism likely explains the broad functional group compatibility of bromodifluoroacetate-mediated trifluoromethylation reactions.[8]

Circumstantial evidence implicates that, as previously suggested,[5f] the present reaction may involve *in situ* conversion of Bn–O_2CCF_2Br to a Bn–I intermediate prior to trifluoromethylation. First, the catalytic system required I^- for turnover, and added I^- facilitated the transformation (*vide supra*). Second, a steady-state concentration of Bn–I persisted throughout the course of the reaction, and the experiment conducted with KI showed higher [Bn–I] than the experiment conducted without KI.[11] Third, the electronic nature of the arene ring noticeably perturbed the reactivity of the substrates, with electron-rich substrates (**2b–f**) providing higher yields than electron-neutral (**2i–l**) and electron-deficient substrates (**2j–k**). The latter trend may suggest that the benzylic position develops cationic character at a transition state of the reaction, which may implicate a S_N1- or S_N2-like step in the mechanism. Based on these pathways, the more slowly reacting electron-deficient electrophiles may allow decomposition of Cu–CF_3[12] to compete with productive trifluoromethylation, thus providing decreased yields for the e^--deficient substrates. Combined, these data fit a mechanism in which Bn–O_2CCF_2Br converts to Bn–I, prior to undergoing trifluoromethylation (Figure 1). Further, the added I^- may play an additional role by converting the less reactive Bn–Br side product into a more active Bn–I electrophile. Regardless, the loading of I^- enabled optimal performance of the catalytic system, and for any given substrate, future users may wish to optimize the loading of I^-.

To illustrate the utility of this protocol, the Cu-catalyzed decarboxylative trifluoromethylation of benzylic bromodifluoroacetates was applied to an intermediate in the synthesis of a fluorinated Tebufenpyrad analogue possessing acaricidal activity (Scheme 3). In a previous report, alcohol **3** was transformed into fluorinated intermediate **5** through a 4-step procedure that employed stoichiometric Mn and Sn and afforded product in 31% overall yield.[13] In contrast, the present 2-step procedure converted **3** to **5** in 60% total yield utilizing catalytic Cu. Thus, the present protocol demonstrated several desirable traits including: 1) improvement of overall yield of trifluoroethylheteroarene; 2) avoidance of oxidation and reduction reactions; 3) decrease in time and resource costs; 4) reduction of metal-containing waste products (stoichiometeric Mn and Sn vs. catalytic Cu). These attractive features should be useful for both agricultural and medicinal chemists.

CONCLUSION

In conclusion, two key features, solvent and I^-, enabled a Cu-catalyzed decarboxylative trifluoromethylation of benzylic and heterobenzylic bromodifluoroacetates. This transformation provided trifluoroethylarenes and heteroarenes from readily available alcohols through a simple and robust two-step procedure. The protocol transformed a variety of benzylic bromodifluoroacetates, including electron-deficient and heterocyclic substrates, and substrates bearing carbonyl groups and acidic protons. The expanded functional group compatibility is rationalized by a metal-centered decarboxylation event, which does not seem to generate free $^-CF_3$ in solution. We envision that this system will be useful for accessing biological probes, therapeutic agents, and agrochemicals. Ongoing work in our laboratory aims to use decarboxylative strategies to address related challenges in synthetic

organofluorine chemistry, such as the conversion of unactivated electrophiles to trifluoromethanes.

EXPERIMENTAL SECTION

Unless otherwise noted, reactions were performed using oven-dried glassware under an atmosphere of dry N_2. Trifluoromethylation reactions were performed in resealable 15 mL test tubes sealed with PTFE septa. All other reactions were performed in round-bottom flasks, which were sealed with rubber septa. Stainless steel syringes were used to transfer air- or moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE™ Silica Gel HLF 250 micron glass plates precoated with 230–400 mesh silica impregnated with a fluorescent indicator (250 nm), visualizing by quenching of fluorescence, $KMnO_4$ solution, or *p*-anisaldehyde solution. Silica gel for chromatographic purifications was purchased from Sorbent Technologies (cat. #30930M-25, 60 Å, 40–63 μm).

Commercial reagents were purchased and used as received with the following exceptions. Anhydrous potassium fluoride (KF) and potassium iodide (KI) were dried in a vacuum-oven at 200 °C for 24 h and stored in a N_2 filled glovebox. Use of non-anhydrous KF resulted in decreased yields of desired products. In the absence of a glovebox, comparable yields were obtained by flame-drying KF and KI under vacuum, and using standard Schlenk techniques. Anhydrous *N,N′*-dimethylformamide (DMF), acetonitrile (MeCN), methanol (MeOH), dichloromethane (DCM), tetrahydrofuran (THF), and triethylamine (NEt_3) were dispensed from a solvent purification system, in which the solvent was dried by passage through two columns of activated alumina under argon. Some benzylic alcohols were acquired by reduction of the corresponding aldehydes using $NaBH_4$ (1.5 equiv) in anhydrous MeOH at 0 °C or the corresponding carboxylic acid using lithium aluminum hydride (2.0 equiv) at 0 °C.

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 400 or 500 MHz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 101 or 126 MHz. Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded at 376 MHz. Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to the proton resonance of residual $CHCl_3$ in the NMR solvent (δ = 7.27 ppm). Chemical shifts (δ) for carbon are reported in parts per million downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent peak (δ = 77.16 ppm). Chemical shifts (δ) for fluorine are reported in parts per millions, and are referenced to $PhCF_3$ (δ = −63.72 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constant in Hertz (Hz), and integration.

Exact mass determinations were obtained by the following methods; electron impact ionization (EI) using a magnetic and electrostatic sector mass analyzer, electrospray ionization (ESI) using a TOF mass analyzer, or atmospheric-pressure chemical ionization (APCI–hexane/PhMe) using a QTOF mass analyzer, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were

used as ionization solvent. Melting points were uncorrected and measured on a Thomas Hoover Capillary Melting Point Apparatus.

General Procedure A

HO_2CCF_2Br (1.45 equiv) was added to a round-bottom flask, which was sealed with a rubber septum and attached to an oil bubbler. DCM and DMF were injected, and the solution was cooled to 0 °C. Oxalyl chloride (1.4 equiv) was injected (caution: evolution of noxious gas), and after 5 min, the mixture was allowed to warm to rt. After 2 h, the mixture was cooled to 0 °C, and a solution of benzylic alcohol (1.0 equiv) and NEt_3 (2–3 equiv) in DCM was added. The reaction was monitored by TLC analysis, and after consumption of the benzylic alcohol (usually within 1–2 h), the reaction was quenched with water, and the aqueous layer was extracted with DCM or EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the removal of solvent, the residue was purified by flash column chromatography to afford bromodifluoroacetates **1a–s**.

4-Methylbenzyl 2-bromo-2,2-difluoroacetate (1a)—General Procedure A was followed using 4-methylbenzyl alcohol (1.5 g, 12 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless oil (2.9 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2 H), 7.22 (d, J = 7.9 Hz, 2 H), 5.33 (s, 2 H), 2.38 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.72 (s, 2 F). Spectroscopic data are consistent with the previous report.[5f]

4-(Benzyloxy)benzyl 2-bromo-2,2-difluoroacetate (1b)—General Procedure A was followed using 4-(benzyloxy)benzyl alcohol (0.65 g, 3.0 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→19:1) afforded the title compound as a colorless solid (0.88 g, 79%). mp 64–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.31 (m, 7 H), 7.01 (d, J = 8.4 Hz, 2 H), 5.31 (s, 2 H), 5.10 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.7, 159.6 (t, J = 31.6 Hz), 136.7, 130.8, 128.8, 128.3, 127.6, 125.9, 115.2, 108.9 (t, J = 314.5 Hz), 70.2, 69.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.7 (s, 2 F). HRMS (EI): m/z [M]+ calcd for $C_{16}H_{13}BrF_2O_3$: 370.0016; found: 370.0012 (1.1 ppm). IR (film): 2945, 2866, 1769, 1609, 1585, 1518, 1454, 1302, 1246, 1161, 1126, 1018, 955, 870, 814, 742, 706, 613 cm^{-1}.

4-Pivalamidobenzyl 2-bromo-2,2-difluoroacetate (1c)—General Procedure A was followed using *N*-[4-(hydroxymethyl)phenyl] pivalamide (0.83 g, 4.0 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→25:4) afforded the title compound as a yellow solid (1.2 g, 85%). mp 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.56 (m, 2 H), 7.42 (s, 1 H), 7.39–7.34 (m, 2 H), 5.31 (s, 2 H), 1.32 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.9, 159.5 (t, J = 31.4 Hz), 139.1, 129.9, 129.1, 120.2, 108.8 (t, J = 314.3 Hz), 69.6, 39.8, 27.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.8 (s, 2 F). HRMS (APCI–hexane/ PhMe): m/z [M+H]+ calcd for $C_{14}H_{17}BrF_2NO_3$: 364.0360; found: 364.0362 (0.5 ppm). IR (film): 3292, 2975, 1771, 1655, 1599, 1520, 1460, 1294, 1157, 955, 820, 700, 604 cm^{-1}.

3-(Dibenzylamino)benzyl 2-bromo-2,2-difluoroacetate (1d)—General Procedure A was followed using [3-(dibenzylamino)phenyl]methanol (0.83 g, 4.0 mmol). Workup and

chromatographic purification (hexanes/EtOAc, 1:0→21:4) afforded the title compound as a yellow solid (1.2 g, 85%). mp 67–68 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.34 (m, 4 H), 7.33–7.25 (m, 6 H), 7.25–7.18 (m, 1 H), 6.80–6.72 (m, 3 H), 5.27 (s, 2 H), 4.71 (s, 4 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.5 (t, J = 31.4 Hz), 149.6, 138.2, 134.6, 129.8, 128.9, 127.2, 126.7, 116.6, 113.1, 111.9, 108.8 (t, J = 314.3 Hz), 70.3, 54.3. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.7 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M]$^+$ calcd for C$_{23}$H$_{20}$BrF$_2$NO$_2$: 459.0645; found: 459.0644 (0.2 ppm). IR (film): 3028, 2866, 1774, 1605, 1582, 1495, 1452, 1294, 1167, 1122, 953, 775, 733, 694 cm^{-1}.

2-Bromo-3,4-dimethoxybenzyl 2-bromo-2,2-difluoroacetate (1e)—General Procedure A was followed using (2-bromo-3,4-dimethoxyphenyl) methanol[14] (0.94 g, 3.8 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→9:1) afforded the title compound as a viscous, colorless oil [1.3 g, 83% (after correction for 10 mol% solvent impurity)]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20 (d, J = 8.5 Hz, 1 H), 6.90 (d, J = 8.5 Hz, 1 H), 5.41 (s, 2 H), 3.90 (s, 3 H), 3.88 (s, 3 H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 159.4 (t, J = 31.5 Hz), 154.6, 147.1, 126.5, 125.8, 120.2, 111.2, 108.8 (t, J = 314.4 Hz), 69.6, 60.7, 56.3. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.61 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M]$^+$ calcd for C$_{11}$H$_{10}$Br$_2$F$_2$O$_4$: 401.8914; found: 401.8910 (1.0 ppm). IR (film): 2943, 2839, 1772, 1595, 1493, 1410, 1296, 1122, 1036, 941, 806, 750, 702 cm^{-1}.

2-(Benzyloxy)benzyl 2-bromo-2,2-difluoroacetate (1f)—General Procedure A was followed using [2-(benzyloxy)phenyl]methanol (0.70 g, 3.3 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→19:1) afforded the title compound as a colorless solid (1.1 g, 88%). mp 45–46 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.32 (m, 7 H), 7.05 – 6.97 (m, 2 H), 5.49 (s, 2 H), 5.16 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.6 (t, J = 31.3 Hz), 157.1, 136.7, 130.8, 130.5, 128.7, 128.2, 127.3, 122.3, 120.9, 112.1, 108.9 (t, J = 314.5 Hz), 70.2, 65.9. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.44 (s, 2 F). HRMS (EI): m/z [M]$^+$ calcd for C$_{16}$H$_{13}$BrF$_2$O$_3$: 370.0016; found: 370.0023 (1.9 ppm). IR (film): 3034, 1774, 1605, 1498, 1452, 1379, 1296, 1250, 1165, 1126, 1024, 949, 806, 754, 696 cm^{-1}.

2,4,6-Trimethylbenzyl 2-bromo-2,2-difluoroacetate (1g)—General Procedure A was followed using mesitylmethanol (0.60 g, 4.0 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→19:1) afforded the title compound as a colorless solid (1.1 g, 88%). mp 45–46 °C. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.92 (s, 2 H), 5.45 (s, 2 H), 2.39 (s, 6 H), 2.31 (s, 3 H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 159.9 (t, J = 31.2 Hz), 139.7, 138.7, 129.4, 126.9, 108.9 (t, J = 314.7 Hz), 65.2, 21.2, 19.6. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.51 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M]$^+$ calcd for C$_{12}$H$_{13}$BrF$_2$O$_2$: 306.0067; found: 306.0080 (4.2 ppm). IR (film): 3011, 2974, 2957, 2922, 2866, 1772, 1614, 1583, 1448, 1375, 1302, 1288, 1167, 1126, 1032, 951, 912, 851, 771, 700 cm^{-1}.

(*E*)-4-Styrylbenzyl 2-bromo-2,2-difluoroacetate (1h)—General Procedure A was followed using (*E*)-(4-styrylphenyl) methanol[15] (0.72 g, 3.4 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless solid (1.1 g, 86%). mp 75–76 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (t, J = 7.5 Hz, 4 H), 7.45–7.36

(m, 4 H), 7.34–7.28 (m, 1 H), 7.21–7.09 (m, 2 H), 5.38 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.6 (t, J = 31.6 Hz), 138.5, 137.1, 132.6, 129.9, 129.2, 128.9, 128.1, 127.9, 127.0, 126.8, 108.9 (t, J = 314.4 Hz), 69.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.7 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M]$^+$ calcd for C$_{17}$H$_{13}$BrF$_2$O$_2$: 366.0067; found: 366.0055 (3.3 ppm). IR (film): 3026, 1772, 1514, 1448, 1383, 1296, 1165, 1126, 966, 949, 866, 818, 704, 690 cm^{-1}.

Naphthalen-2-ylmethyl 2-bromo-2,2-difluoroacetate (1i)—General Procedure A was followed using (naphthalen-2-yl)methanol (0.63 g, 4.0 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless solid (1.1 g, 88%). m.p. 32–33 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 – 7.83 (m, 4 H), 7.58 – 7.53 (m, 2 H), 7.51 (d, J = 8.7 Hz, 1 H), 5.54 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.6 (t, J = 31.5 Hz), 133.6, 133.2, 130.9, 129.0, 128.4, 128.3, 127.9, 127.0, 126.8, 125.8, 108.9 (t, J = 315.0 Hz), 70.1. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.68 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M]$^+$ calcd for C$_{13}$H$_9$BrF$_2$O$_2$: 313.9754; found: 313.9763 (2.9 ppm). IR (film): 3056, 2964, 1774, 1508, 1375, 1296, 1171, 1124, 947, 854, 816, 750, 698 cm^{-1}.

4-((Methylsulfonyl)oxy)benzyl 2-bromo-2,2-difluoroacetate (1j)—General Procedure A was followed using 4-(hydroxymethyl)phenyl methanesulfonate (1.4 g, 7.1 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→4:1) afforded the title compound as a colorless solid (2.4 g, 95%). mp 48–49 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 – 7.47 (m, 2 H), 7.38 – 7.33 (m, 2 H), 5.38 (s, 2 H), 3.19 (s, 3 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.4 (t, J = 31.7 Hz), 149.7, 132.9, 130.4, 122.6, 108.7 (t, J = 314.4 Hz), 68.7, 37.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.79 (s, 2 F). HRMS (EI): m/z [M]$^+$ calcd for C$_{10}$H$_9$BrF$_2$O$_5$S: 357.9322; found: 357.9329 (2.0 ppm). IR (film): 3033, 2941, 1774, 1606, 1506, 1456, 1420, 1371, 1298, 1178, 1153, 1122, 970, 872, 835, 710, 679 cm^{-1}.

4-((2-Bromo-2,2-difluoroacetoxy)methyl)phenyl benzoate (1k)—General Procedure A was followed using 4-(hydroxymethyl)phenyl benzoate (0.57 g, 2.5 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→9:1) afforded the title compound as a colorless solid (0.79 g, 82%). mp 65–66 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.27 – 8.18 (m, 2 H), 7.71 – 7.63 (m, 1 H), 7.58 – 7.46 (m, 4 H), 7.32 – 7.27 (m, 2 H), 5.39 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 165.1, 159.5 (t, J = 31.6 Hz), 151.7, 133.9, 131.2, 130.3, 130.1, 129.3, 128.8, 122.4, 108.8 (t, J = 314.3 Hz), 69.2. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.74 (s, 2 F). HRMS (EI): m/z [M]$^+$ calcd for C$_{16}$H$_{11}$BrF$_2$O$_4$: 383.9809; found: 383.9810 (0.3 ppm). IR (film): 3065, 1776, 1740, 1601, 1510, 1452, 1379, 1298, 1265, 1204, 1123, 1061, 1024, 951, 876, 804, 706, 604 cm^{-1}.

3-Phenoxybenzyl 2-bromo-2,2-difluoroacetate (1l)—General Procedure A was followed using (3-phenoxyphenyl)methanol (0.69 g, 3.4 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→19:1) afforded the title compound as a colorless oil (0.99 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.34 (m, 3 H), 7.18 – 7.10 (m, 2 H), 7.07 – 7.00 (m, 4 H), 5.33 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.5 (t, J = 31.6 Hz), 158.0, 156.7, 135.4, 130.4, 130.0, 123.9, 122.9, 119.5, 119.3, 118.3, 108.7 (t, J = 314.4 Hz), 69.2. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.83 (s, 2 F). HRMS (APCI–hexane/

PhMe): m/z [M]$^+$ calcd for $C_{15}H_{11}BrF_2O_3$: 355.9860; found: 355.9845 (4.2 ppm). IR (film): 3065, 3040, 2964, 1778, 1585, 1489, 1448, 1377, 1301, 1259, 1213, 1173, 1122, 945, 874, 847, 777, 692, 604 cm^{-1}.

3-Benzoylbenzyl 2-bromo-2,2-difluoroacetate (1m)—General Procedure A was followed using (3-(hydroxylmethyl)phenyl)(phenyl)methanone. Workup and chromatographic purification (hexanes/EtOAc, 1:0→21:4) afforded the title compound as a pale yellow oil (1.6 g, 88%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 – 7.77 (m, 4 H), 7.67 – 7.59 (m, 2 H), 7.58 – 7.47 (m, 3 H), 5.43 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 196.1, 159.4 (t, $J = 31.5$ Hz), 138.3, 137.3, 133.9, 132.9, 132.3, 130.9, 130.2, 130.0, 129.1, 128.5, 108.7 (t, $J = 314.3$ Hz), 69.2. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.81 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M+H]$^+$ calcd for $C_{16}H_{12}BrF_2O_3$: 368.9938; found: 368.9936 (0.5 ppm). IR (film): 3065, 3040, 2964, 1778, 1585, 1489, 1448, 1377, 1301, 1259, 1213, 1173, 1122, 945, 874, 847, 777, 692, 604 cm^{-1}.

Methyl 4-((2-bromo-2,2-difluoroacetoxy)methyl)benzoate (1n)—General Procedure A was followed using methyl 4-(hydroxymethyl) benzoate (0.55 g, 3.3 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→19:1) afforded the title compound as a colorless oil (0.91 g, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 (d, $J = 7.9$ Hz, 2 H), 7.47 (d, $J = 8.0$ Hz, 2 H), 5.41 (s, 2 H), 3.94 (s, 3 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 166.6, 159.4 (t, $J = 31.7$ Hz), 138.3, 130.9, 130.2, 128.1, 108.6 (t, $J = 314.2$ Hz), 68.9, 52.4. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.86 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M]$^+$ calcd for $C_{11}H_9BrF_2O_4$: 321.9652; found: 321.9639 (4.0 ppm). IR (film): 2955, 1778, 1724, 1616, 1437, 1379, 1283, 1171, 1111, 1020, 955, 847, 756, 708, 602 cm^{-1}.

Tert-butyl 3-((2-bromo-2,2-difluoroacetoxy)methyl)-1H-indole-1-carboxylate (1o)—General Procedure A was followed using *tert*-butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate (1.2 g, 3.0 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→9:1) afforded the title compound as a colorless solid (0.91 g, 85%). mp 47–49 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.18 (d, $J = 8.3$ Hz, 1 H), 7.77 (s, 1 H), 7.64 (dt, $J = 7.8, 1.0$ Hz, 1 H), 7.39 (ddd, $J = 8.5, 7.2, 1.3$ Hz, 1 H), 7.31 (td, $J = 7.6, 1.1$ Hz, 1 H), 5.54 (d, $J = 0.7$ Hz, 2 H), 1.69 (s, 9 H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 159.7 (t, $J = 31.5$ Hz), 149.5, 135.7, 128.9, 127.1, 125.2, 123.3, 119.2, 115.6, 113.3, 108.8 (t, $J = 314.5$ Hz), 84.5, 62.0, 28.3. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.7 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M]$^+$ calcd for $C_{16}H_{16}BrF_2NO_4$: 403.0231; found: 403.0222 (2.2 ppm). IR (film): 3126, 3055, 2980, 2934, 1774, 1736, 1610, 1597, 1572, 1452, 1389, 1371, 1358, 1292, 1273, 1259, 1231, 1159, 1128, 1092, 1020, 945, 854, 768, 746, 704 cm^{-1}.

(1-Phenyl-1*H*-pyrazol-4-yl)methyl 2-bromo-2,2-difluoroacetate (1p)—General Procedure A was followed using (1-phenyl-1*H*-pyrazol-4-yl)methanol[16] (0.87 g, 5.0 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→4:1) afforded the title compound as a colorless solid (1.5 g, 89%). mp 60–61 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (s, 1 H), 7.81 (s, 1 H), 7.71 – 7.66 (m, 2 H), 7.51 – 7.44 (m, 2 H), 7.36 – 7.30 (m, 1 H), 5.36 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.7 (t, $J = 31.7$ Hz), 141.7, 139.8, 129.7, 128.2, 127.2, 119.5, 116.0, 108.9 (t, $J = 314.5$ Hz), 61.0. ^{19}F NMR (376 MHz,

CDCl$_3$) δ −60.90 (s, 2 F). HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{12}$H$_{10}$BrF$_2$N$_2$O$_2$: 330.9781; found: 330.9788 (2.1 ppm). IR (film): 3057, 2970, 1774, 1514, 1489, 1375, 1292, 11689, 1122, 1067, 943, 887, 842, 771, 736, 692, 660 cm^{-1}.

(2-Phenylfuran-3-yl)methyl 2-bromo-2,2-difluoroacetate (1q)—General Procedure A was followed using (2-phenylfuran-3-yl)methanol[17] (0.52 g, 3.0 mmol). Workup provided the title compound as a yellow oil (0.93 g, 93%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 – 7.59 (m, 2 H), 7.51 – 7.45 (m, 3 H), 7.43 – 7.37 (m, 1 H), 6.61 (d, *J* = 1.9 Hz, 1 H), 5.40 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.7 (t, *J* = 31.6 Hz), 153.4, 142.1, 129.9, 129.1, 128.7, 126.6, 113.56, 113.54, 108.8 (t, *J* = 314.6 Hz), 62.6. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.75 (s, 2 F). HRMS (EI): *m/z* [M]$^+$ calcd for C$_{13}$H$_9$BrF$_2$O$_3$: 329.9703; found: 329.9701 (0.6 ppm). IR (film): 3057, 2970, 1774, 1514, 1489, 1375, 1292, 11689, 1122, 1067, 943, 887, 842, 771, 736, 692, 660 cm^{-1}.

Dibenzo[*b,d*]thiophen-4-ylmethyl 2-bromo-2,2-difluoroacetate (1r)—General Procedure A was followed using dibenzo[*b,d*]thiophen-4-ylmethanol (1.2 g, 5.6 mmol). Workup and chromatographic purification (hexanes) provided the title compound as a colorless solid (1.9 g, 89%). mp 90–91 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.22 – 8.15 (m, 2 H), 7.94 – 7.86 (m, 1 H), 7.57 – 7.47 (m, 4 H), 5.63 (s, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.6 (t, *J* = 31.7 Hz), 139.24, 139.15, 136.6, 135.4, 127.7, 127.37, 127.33, 124.90, 124.86, 123.0, 122.6, 122.0, 108.7 (t, *J* = 314.5 Hz), 68.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.52 (s, 2 F). HRMS (APCI–hexane/PhMe): *m/z* [M]$^+$ calcd for C$_{15}$H$_9$BrF$_2$O$_2$S: 369.9475; found: 369.9471 (1.1 ppm). IR (film): 3064, 2931, 1778, 1585, 1443, 1408, 1298, 1180, 1136, 1047, 982, 941, 883, 827, 789, 746, 710, 669 cm^{-1}.

(1-(Methylsulfonyl)-1*H*-indol-2-yl)methyl 2-bromo-2,2-difluoroacetate (1s)—General Procedure A was followed using [1-(methylsulfonyl)-1*H*-indol-2-yl]methanol[18] (1.1 g, 5.0 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→9:1) provided the title compound as a grey solid (1.1 g, 70%). mp 87–88 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (dt, *J* = 8.3, 1.0 Hz, 1 H), 7.66 – 7.61 (m, 1 H), 7.47 – 7.40 (m, 1 H), 7.38 – 7.31 (m, 1 H), 6.91 (s, 1 H), 5.69 (s, 2 H), 3.19 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 158.8 (t, *J* = 31.7 Hz), 137.2, 131.7, 128.3, 126.5, 124.3, 122.0, 114.8, 114.1, 108.7 (t, *J* = 314.3 Hz), 62.7, 41.1. ^{19}F NMR (376 MHz, CDCl$_3$) δ −60.63 (s, 2 F). HRMS (APCI–hexane/PhMe): *m/z* [M]$^+$ calcd for C$_{12}$H$_{10}$BrF$_2$NO$_4$S: 380.9482; found: 380.9479 (0.8 ppm). IR (film): 3028, 1778, 1452, 1369, 1292, 1175, 1121, 964, 916, 823, 771, 748, 719, 685 cm^{-1}.

(5-(Furan-2-yl)-1-methyl-1H-pyrazol-3-yl)methyl 2-bromo-2,2-difluoroacetate (3a)—HO$_2$CCF$_2$Br (0.27 g, 1.5 mmol) was added to a round-bottom flask, which was sealed with a rubber septum and attached to an oil bubbler. DCM (6.0 mL) and DMF (0.30 mL) were injected, and the solution was cooled to −10 °C. Oxalyl chloride (0.13 mL, 1.5 mmol) was injected (caution: evolution of noxious gas), and after 5 min, the mixture was allowed to warm to rt. After 2 h, the mixture was cooled to −10 °C, and a solution of [5-(furan-2-yl)-1-methyl-1*H*-pyrazol-3-yl]methanol[13] (0.19 g, 1.0 mmol) and NEt$_3$ (0.38 mL, 2.7 mmol) in DCM (1.5 mL) was added. After 2.5 h, the reaction was quenched with water,

and the aqueous layer was extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. Chromatographic purification (hexanes/EtOAc 1:0→3:2) provided the title compound as a yellow solid (0.29 g, 82%). m.p. 39–40 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.52 (m, 1 H), 6.59 (d, J = 3.4 Hz, 1 H), 6.57 (s, 1 H), 6.52 (dd, J = 3.4, 1.8 Hz, 1 H), 5.36 (s, 2 H), 4.05 (s, 3 H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.6 (t, J = 31.6 Hz), 144.4, 144.2, 143.1, 135.7, 111.7, 109.1, 108.8 (t, J = 314.9 Hz), 105.4, 63.5, 39.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ –60.64 (s, 2 F). HRMS (APCI–hexane/PhMe): m/z [M + Na]$^+$ calcd for $C_{11}H_9BrF_2N_2O_3Na$: 356.9662; found: 356.9648 (3.9 ppm). IR (film): 3128, 1776, 1531, 1475, 1448, 1362, 1302, 1163, 1124, 1011, 947, 903, 885, 800, 741, 702 cm^{-1}.

General Procedure B (solid substrates)

An oven-dried 15 mL screw-top vial was sealed with a PTFE septum and cooled under an atmosphere of dry N_2. CuI (9.5 mg, 0.050 mmol) and (hetero)benzyl bromodifluoroacetate (0.25 mmol) were added to the vial, which was transferred into a N_2-filled glovebox. Anhydrous KF (58.1 mg, 1.00 mmol) and anhydrous KI (10.4 mg, 0.0625 mmol) were added to the vial, which was sealed with a PTFE septum and removed from the glovebox. MeCN (125 μL), MeO_2CCF_2Br (11.0 μL, 0.100 mmol) and DMF (125 μL) were injected into the vial, which was placed in a pre-heated hot plate (70 °C) and stirred for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc or Et_2O (25 mL). The mixture was washed with H_2O (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified via silica gel chromatography to provide the corresponding trifluoroethyl(hetero)arene.

General Procedure C (liquid substrates)

An oven-dried 15 mL screw-top vial was sealed with a PTFE septum and cooled under an atmosphere of dry N_2. CuI (9.5 mg, 0.050 mmol) was added to the vial, which was transferred into a N_2-filled glovebox. Anhydrous KF (58.1 mg, 1.00 mmol) and anhydrous KI (10.4 mg, 0.0625 mmol) were added to the vial, which was sealed with a PTFE septum and removed from the glovebox. MeCN (125 μL), MeO_2CCF_2Br (11.0 μL, 0.100 mmol), (hetero)benzyl bromodifluoroacetate (0.25 mmol), and DMF (125 μL) were injected into the vial, which was placed in a pre-heated hot plate (70 °C) and stirred for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc or Et_2O (25 mL). The mixture was washed with H_2O (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified via silica gel chromatography to provide the corresponding trifluoroethyl(hetero)arene.

Synthesis of Trifluoroethyl(hetero)arenes

Each decarboxylative trifluoromethylation was run twice, and the yields in manuscript refer to the average of two runs. The procedures described below represent one individual run. $ArCH_2CF_2CF_3$ was observed as a minor side-product (<2%) in many reactions, as evidenced by ^{19}F NMR spectroscopy (δ –85 (s, 3 F), –117 (t, J = 18 Hz, 2 F).

1-(Benzyloxy)-4-(2,2,2-trifluoroethyl)benzene (2b)—General Procedure B was followed using **1b** (92.8 mg, 0.250 mmol). Workup and chromatographic purification

(hexanes/Et$_2$O 39:1) afforded the title compound as a colorless solid (55.7 mg, 84%). mp 78–79 °C (lit.[19] 82–84 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48–7.39 (m, 4 H), 7.39–7.33 (m, 1 H), 7.27–7.21 (m, 2 H), 7.01–6.96 (m, 2 H), 5.09 (s, 2 H), 3.33 (q, J = 10.8 Hz, 2 H). ^{19}F NMR (376 MHz, CDCl$_3$) δ −66.4 (3 F, t, J = 10.9 Hz). Spectroscopic data are consistent with the previous report.[19]

Gram-scale Decarboxylative Trifluoromethylation: An oven-dried 25 mL Schlenk flask was sealed with a rubber septum and cooled under an atmosphere of dry N$_2$. CuI (0.23 g, 1.2 mmol) was added to the vial, which was transferred into a N$_2$-filled glovebox. Anhydrous KF (1.4 g, 24 mmol) and anhydrous KI (0.25 g, 1.5 mmol) were added to the flask, which was sealed with a rubber septum and removed from the glovebox. The flask was attached to a Schlenk line, and remained open to an atmosphere of dry N$_2$ for the remainder of the reaction (CAUTION: CO$_{2\ (g)}$ is generated during the course of the reaction; therefore, the reaction should either be conducted in a pressure-rated vessel, or open to an inert atmosphere). MeCN (3.0 mL), MeO$_2$CCF$_2$Br (0.26 mL, 2.4 mmol), **1b** (2.2 g, 6.0 mmol), and DMF (3.0 mL) were injected into the flask, which was placed in a pre-heated oil bath (70 °C) and stirred for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (75 mL). The mixture was washed with H$_2$O (75 mL) and brine (75 mL). The organic phase was dried over Na$_2$SO$_4$, filtered, and the solvent was removed *in vacuo*. The residue was purified via silica gel chromatography (hexanes/Et$_2$O 39:1) to provide **2b** as a colorless solid (1.4 g, 87%). The ^{1}H and ^{19}F NMR spectrum were consistent with the data described above.

_N_-(4-(2,2,2-Trifluoroethyl)phenyl)pivalamide (2c)—General Procedure B was followed using **1c** (91.0 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→9:1) afforded the title compound as a colorless solid (52.8 mg, 81%). mp 132–133 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, J = 8.4 Hz, 2 H), 7.37 (s, 1 H), 7.25 (d, J = 8.3 Hz, 2 H), 3.33 (q, J = 10.8 Hz, 2 H), 1.32 (s, 9 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 176.8, 138.1, 130.8, 125.9 (q, J = 3.0 Hz), 125.8 (q, J = 276.7 Hz), 120.2, 39.76, 39.74 (q, J = 29.8 Hz), 27.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.65 (t, J = 10.8 Hz, 3 F). HRMS (EI): *m/z* [M]$^+$ calcd for C$_{13}$H$_{16}$F$_3$NO: 259.1184; found: 259.1189 (1.9 ppm). IR (film): 3317, 2978, 2873, 1654, 1599, 1522, 1412, 1315, 1265, 1244, 1138, 1072, 905, 806, 698, 656 cm^{-1}.

_N,N_-Dibenzyl-3-(2,2,2-trifluoroethyl)aniline (2d)—General Procedure B was followed using **1d** (115 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→17:3) afforded the title compound as a colorless oil (80.6 mg, 91%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.33 (m, 4 H), 7.32 – 7.25 (m, 6 H), 7.17 (t, J = 7.9 Hz, 1 H), 6.73 (dd, J = 8.4, 2.7 Hz, 1 H), 6.70 – 6.64 (m, 2 H), 4.68 (s, 4 H), 3.26 (q, J = 11.0 Hz, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 149.6, 138.4, 131.2 (q, J = 2.8 Hz), 129.6, 128.8, 127.1, 126.8, 126.0 (q, J = 277.0 Hz), 118.6, 114.3, 112.3, 54.3, 40.7 (q, J = 29.5 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.68 (t, J = 10.9 Hz, 3 F). HRMS (EI): *m/z* [M]$^+$ calcd for C$_{22}$H$_{20}$F$_3$N: 355.1548; found: 355.1561 (3.7 ppm). IR (film): 3061, 3030, 2922, 2860, 1605, 1582, 1499, 1452, 1358, 1259, 1132, 1078, 1028, 991, 964, 922, 777, 729, 696 cm^{-1}.

2-Bromo-3,4-dimethoxy-1-(2,2,2-trifluoroethyl)benzene (2e)—General Procedure C was followed using **1e** (101 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→17:3) afforded the title compound as a colorless oil (57.9 mg, 78%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.10 (d, J = 8.5 Hz, 1 H), 6.87 (d, J = 8.6 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.60 (q, J = 10.6 Hz, 2 H). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.48 (t, J = 10.5 Hz, 3 F). Spectroscopic data are consistent with the previous report.[4a]

1-(Benzyloxy)-2-(2,2,2-trifluoroethyl)benzene (2f)—General Procedure B was followed using **1f** (92.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→19:1) afforded the title compound as a colorless oil (50.7 mg, 76%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.30 (m, 7 H), 7.07 – 6.93 (m, 2 H), 5.15 (s, 2 H), 3.57 (q, J = 11.0 Hz, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 157.2, 137.0, 132.0, 129.6, 128.7, 128.1, 127.3, 126.3 (q, J = 277.3 Hz), 120.9, 119.3 (q, J = 2.8 Hz), 112.2, 70.3, 33.7 (q, J = 30.2 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.34 (t, J = 10.9 Hz, 3 F). HRMS (EI): m/z [M]$^+$ calcd for C$_{15}$H$_{13}$F$_3$O: 266.0918; found: 266.0920 (0.8 ppm). IR (film): 3005, 2943, 1595, 1494, 1406, 1360, 1285, 1246, 1138, 1092, 1036, 947, 901, 806, 766, 681, 646 cm^{-1}.

1,3,5-Trimethyl-2-(2,2,2-trifluoroethyl)benzene (2g)—General Procedure C was followed using **1g** (76.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless oil (22.4 mg, 46%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.91 (s, 2 H), 3.48 (q, J = 10.8 Hz, 2 H), 2.35 (s, 6 H), 2.29 (s, 3 H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 138.3, 137.7, 129.4, 126.9 (q, J = 278.3 Hz), 125.6 (q, J = 2.47 Hz), 33.6 (q, J = 29.6 Hz), 21.0, 20.4 (q, J = 2.1 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ −63.8 (t, J = 10.8 Hz, 3 F). HRMS (EI): m/z [M]$^+$ calcd for C$_{11}$H$_{13}$F$_3$: 202.0969; found: 202.0978 (4.5 ppm). IR (film): 3007, 2964, 2926, 2868, 2856, 1614, 1481, 1450, 1427, 1381, 1352, 1306, 1248, 1202, 1130, 1099, 1026, 941, 910, 854, 833, 804, 735, 654 cm^{-1}.

(*E*)-1-Styryl-4-(2,2,2-trifluoroethyl)benzene (2h)—General Procedure B was followed using **1h** (91.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→9:1) afforded the title compound as a colorless solid (39.2 mg, 60%). mp 135–136 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 – 7.51 (m, 4 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.36 – 7.29 (m, 3 H), 7.17 – 7.14 (m, 2 H), 3.40 (q, J = 10.8 Hz, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 137.4, 137.2, 130.6, 129.45 (q, J = 2.9 Hz), 129.41, 128.8, 128.0, 127.9, 126.8, 126.7, 125.9 (q, J = 276.9 Hz), 40.1 (q, J = 29.8 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.81 (t, J = 10.8 Hz, 3 F). HRMS (EI): m/z [M]$^+$ calcd for C$_{16}$H$_{13}$F$_3$: 262.0969; found: 262.0968 (0.4 ppm). IR (film): 3022, 1448, 1429, 1420, 1356, 1258, 1147, 1119, 1078, 964, 908, 820, 792, 754, 739, 692, 658 cm^{-1}.

2-(2,2,2-Trifluoroethyl)naphthalene (2i)—General Procedure B was followed using **1i** (78.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless solid (42.3 mg, 81%). mp 51–53 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 – 7.81 (m, 3 H), 7.79 (s, 1 H), 7.55 – 7.48 (m, 2 H), 7.42 (d, J = 8.4 Hz, 1 H), 3.55 (q, J = 10.8 Hz, 2 H). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.65 (t, J = 10.8 Hz, 3 F). Spectroscopic data are consistent with the previous report.[4b]

4-(2,2,2-Trifluoroethyl)phenyl methanesulfonate (2j)—General Procedure B was followed using **1j** (89.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→2:3) afforded the title compound as a colorless solid (43.5 mg, 69%). mp 75–76 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 (d, J = 8.5 Hz, 2 H), 7.29 (d, J = 8.6 Hz, 2 H), 3.39 (q, J = 10.7 Hz, 2 H), 3.15 (s, 3 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 149.1, 132.0, 129.6 (q, J = 3.0 Hz), 125.6 (q, J = 276.8 Hz), 122.4, 39.6 (q, J = 30.1 Hz), 37.5. ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.36 (t, J = 10.7 Hz, 3 F). HRMS (EI): m/z [M]$^+$ calcd for C$_9$H$_9$F$_3$O$_3$S: 254.0225; found: 254.0229 (1.6 ppm). IR (film): 3031, 2945, 1608, 1502, 1456, 1421, 1361, 1302, 1177, 1153, 1132, 974, 876, 832, 707, 681 cm^{-1}.

4-(2,2,2-Trifluoroethyl)phenyl benzoate (2k)—General Procedure B was followed using **1k** (96.3 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→19:1) afforded the title compound as a colorless solid (49.6 mg, 71%). mp 84–85 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.25 (d, J = 7.6 Hz, 2 H), 7.68 (t, J = 7.4 Hz, 1 H), 7.55 (t, J = 7.7 Hz, 2 H), 7.40 (d, J = 8.3 Hz, 2 H), 7.26 (d, J = 8.3 Hz, 2 H), 3.43 (q, J = 10.8 Hz, 2 H). ^{19}F NMR (376 MHz, CDCl$_3$) δ −66.37 (t, J = 10.8 Hz, 3 F). Spectroscopic data are consistent with the previous report.[20]

1-Phenoxy-3-(2,2,2-trifluoroethyl)benzene (2l)—General Procedure C was followed using **1l** (89.3 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→19:1) afforded the title compound as a colorless oil (41.9 mg, 67%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.29 (m, 3 H), 7.14 (t, J = 7.4 Hz, 1 H), 7.09 – 6.95 (m, 5 H), 3.35 (q, J = 10.8 Hz, 2 H). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.46 (t, J = 10.8 Hz, 3 F). Spectroscopic data are consistent with the previous report.[51]

Phenyl(3-(2,2,2-trifluoroethyl)phenyl)methanone (2m)—General Procedure C was followed using **1m** (92.3 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→3:1) afforded the title compound as a colorless oil (40.9 mg, 62%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 – 7.71 (m, 4 H), 7.62 (t, J = 7.4 Hz, 1 H), 7.57 – 7.45 (m, 4 H), 3.45 (q, J = 10.7 Hz, 2 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 196.3, 138.2, 137.4, 134.2, 132.8, 131.8, 130.6 (q, J = 2.9 Hz), 130.2, 130.0, 128.8, 128.5, 125.7 (q, J = 276.9 Hz), 40.2 (q, J = 29.8 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.66 (t, J = 10.7 Hz, 3 F). HRMS (EI): m/z [M]$^+$ calcd for C$_{15}$H$_{11}$F$_3$O: 264.0762; found: 264.0763 (0.4 ppm). IR (film): 3063, 3036, 2947, 1661, 1597, 1585, 1578, 1448, 1362, 1319, 1308, 1288, 1256, 1209, 1138, 1101, 1076, 986, 968, 932, 906, 870, 852, 813, 783, 714, 640, 602 cm^{-1}.

Methyl 4-(2,2,2-trifluoroethyl)benzoate (2n)—General Procedure C was followed using **1n** (80.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→9:1) afforded the title compound as a colorless oil [(29.5 mg, 51% (after correction for 5 mol% ArCH$_2$Br side-product)]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 – 8.02 (m, 2 H), 7.39 (d, J = 8.1 Hz, 2 H), 3.93 (s, 3 H), 3.44 (q, J = 10.7 Hz, 2 H). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.58 (t, J = 10.7 Hz, 3 F). Spectroscopic data are consistent with the previous report.[4b]

***Tert*-butyl 3-(2,2,2-trifluoroethyl)-1*H*-indole-1-carboxylate (2o)**—General Procedure B was followed using **1o** (101 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc, 39:1) afforded the title compound as a colorless solid (58.1 mg, 78%). m.p. 79–80 °C. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.17 (d, *J* = 6.7 Hz, 1 H), 7.61 (s, 1 H), 7.56 (d, *J* = 7.8 Hz, 1 H), 7.37 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1 H), 7.30 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1 H), 3.51 (qd, *J* = 10.6, 0.9 Hz, 2 H), 1.69 (s, 9 H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 149.6, 135.4, 130.0, 125.93 (q, *J* = 276.9 Hz), 125.92, 124.9, 123.0, 119.0, 115.5, 109.5 (q, *J* = 3.3 Hz), 84.2, 30.5 (q, *J* = 31.7 Hz), 28.3. ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.57 (t, *J* = 10.7 Hz, 3 F). HRMS (EI): *m/z* [M]$^+$ calcd for C$_{15}$H$_{16}$F$_3$NO$_2$: 299.1133; found: 299.1122 (3.7 ppm). IR (film): 3057, 2982, 2934, 1736, 1452, 1375, 1350, 1277, 1259, 1229, 1153, 1138, 1101, 1016, 914, 856, 770, 744 cm^{-1}.

1-Phenyl-4-(2,2,2-trifluoroethyl)-1*H*-pyrazole (2p)—General Procedure B was followed using **1p** (82.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→9:1) afforded the title compound as a colorless solid (47.2 mg, 83%). m.p. 45–46 °C. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 (s, 1 H), 7.70 – 7.65 (m, 3 H), 7.49 – 7.42 (m, 2 H), 7.33 – 7.28 (m, 1 H), 3.36 (q, *J* = 10.7 Hz, 2 H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 141.6, 140.0, 129.6, 127.0, 126.9, 125.7 (q, *J* = 276.2 Hz), 119.3, 111.8 (q, *J* = 3.3 Hz), 30.1 (q, *J* = 31.7 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ −66.02 (t, *J* = 10.7 Hz, 3 F). HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{11}$H$_{10}$F$_3$N$_2$: 227.0796; found: 227.0794 (0.9 ppm). IR (film): 3153, 3109, 3053, 2943, 1601, 1576, 1506, 1464, 1404, 1387, 1348, 1259, 1213, 1138, 1084, 1043, 1018, 955, 906, 862, 835, 808, 756, 692, 660 cm^{-1}.

2-Phenyl-3-(2,2,2-trifluoroethyl)furan (2q)—General Procedure C was followed using **1q** (82.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→19:1) afforded the title compound as a colorless oil (31.2 mg, 55%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.61 – 7.57 (m, 2 H), 7.51 – 7.44 (m, 3 H), 7.41 – 7.36 (m, 1 H), 6.53 (s, 1 H), 3.45 (q, *J* = 10.5 Hz, 2 H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 152.1, 142.0, 130.5, 128.9, 128.3, 126.8, 126.1 (q, *J* = 277.0 Hz), 113.5, 109.8 (q, *J* = 3.3 Hz), 31.3 (q, *J* = 31.0 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ −66.81 (t, *J* = 10.7 Hz, 3 F). HRMS (EI): *m/z* [M]$^+$ calcd for C$_{12}$H$_9$F$_3$O: 226.0605; found: 226.0597 (3.5 ppm). IR (film) 3055, 2937, 2856, 1599, 1487, 1447, 1433, 1362, 1298, 1273, 1254, 1140, 1105, 1082, 1053, 1032, 908, 887, 835, 764, 743, 692, 671, 650, 604 cm^{-1}.

4-(2,2,2-Trifluoroethyl)dibenzo[*b,d*]thiophenes (2r)—General Procedure B was followed using **1r** (92.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→19:1) afforded the title compound as a colorless solid (40.9 mg, 61%). mp 102–103 °C (lit.[19] 104–106 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.21 – 8.13 (m, 2 H), 7.92 – 7.85 (m, 1 H), 7.54 – 7.42 (m, 4 H), 3.69 (q, *J* = 10.6 Hz, 2 H). ^{19}F NMR (376 MHz, CDCl$_3$) δ −64.65 (t, *J* = 10.6 Hz, 3 F). Spectroscopic data are consistent with the previous report.[19]

1-(Methylsulfonyl)-2-(2,2,2-trifluoroethyl)-1*H*-indole (2s)—General Procedure B was followed using **1s** (95.5 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 9:1→2:1) afforded the title compound as a colorless solid (42.6 mg, 61%).

m.p. 95–96 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 – 7.99 (m, 1 H), 7.64 – 7.59 (m, 1 H), 7.41 (ddd, J = 8.4, 7.2, 1.4 Hz, 1 H), 7.34 (td, J = 7.5, 1.1 Hz, 1 H), 6.80 (s, 1 H), 4.04 (q, J = 10.2 Hz, 2 H), 3.13 (s, 3 H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 136.8, 129.4 (q, J = 3.5 Hz), 129.0, 125.5, 125.2 (q, J = 277.1 Hz), 124.2, 121.3, 114.3, 113.1, 40.9, 32.8 (q, J = 31.7 Hz). ^{19}F NMR (376 MHz, CDCl$_3$) δ −64.76 (t, J = 10.2 Hz, 3 F). HRMS (EI): m/z [M]$^+$ calcd for C$_{11}$H$_{10}$F$_3$NO$_2$S: 277.0384; found: 277.0382 (0.7 ppm). IR (film) 3022, 2934, 1452, 1366, 1331, 1304, 1275, 1254, 1234, 1175, 1153, 1082, 1057, 1022, 962, 924, 899, 818, 771, 748, 727, 665, 636, 554, 513 cm^{-1}.

5-(Furan-2-yl)-1-methyl-3-(2,2,2-trifluoroethyl)-1H-pyrazole (5)—General Procedure B was followed using **3a** (83.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→4:1) afforded the title compound as a yellow oil (42.6 mg, 73%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (dd, J = 1.9, 0.8 Hz, 1 H), 6.57 (dd, J = 3.4, 0.8 Hz, 1 H), 6.51 (dd, J = 3.4, 1.8 Hz, 1 H), 6.48 (s, 1 H), 4.02 (s, 3 H), 3.45 (q, J = 10.8 Hz, 2 H). ^{19}F NMR (376 MHz, CDCl$_3$) δ −65.72 (t, J = 10.8 Hz). Spectroscopic data are consistent with the previous report.[13]

Supplementary Material

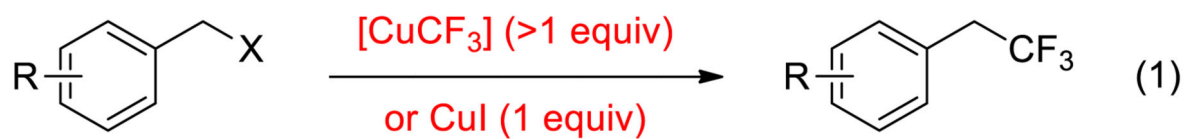Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT

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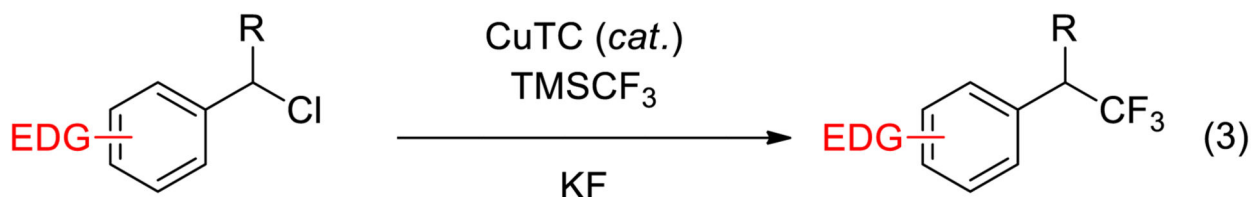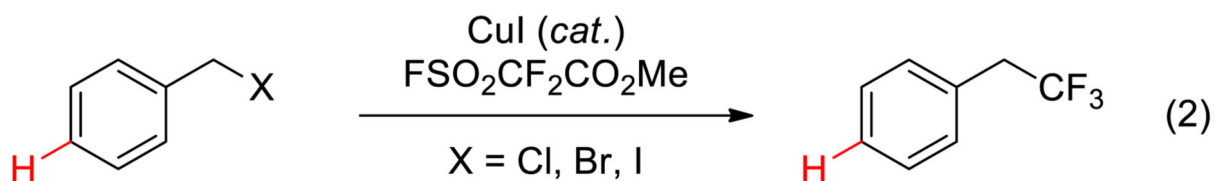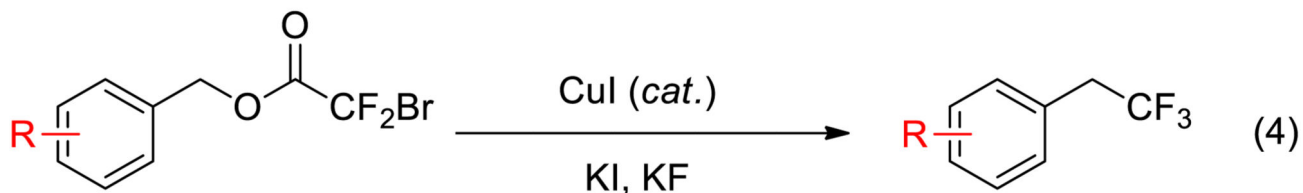Duan J-X. J. Chem. Soc., Chem. Commun. 1993:1389.(f) Duan J-X, Chen Q-Y. J. Chem. Soc. Perkin Trans. 1. 1994:725.(g) Kim J, Shreeve JM. Org. Biomol. Chem. 2004; 2:2728. [PubMed: 15455143] (h) Dubinina GG, Furutachi H, Vicic DA. J. Am. Chem. Soc. 2008; 130:8600. [PubMed: 18543912] (i) Dubinina GG, Ogikubo J, Vicic DA. Organometallics. 2008; 27:6233.(j) Kremlev MM, Mushta AF, Fyrra W, Yagupolskii YF, Naumann D, Möeller A. J. Fluorine Chem. 2012; 133:67.(k) Jiang X, Qing FF. Beilstein. J. Org. Chem. 2013; 9:2862. [PubMed: 24367451] (l) Zhu F, Fm S, Douglas JF, Altman RA. Chem. Eur. J. 2013; 19:12800. [PubMed: 23922222]

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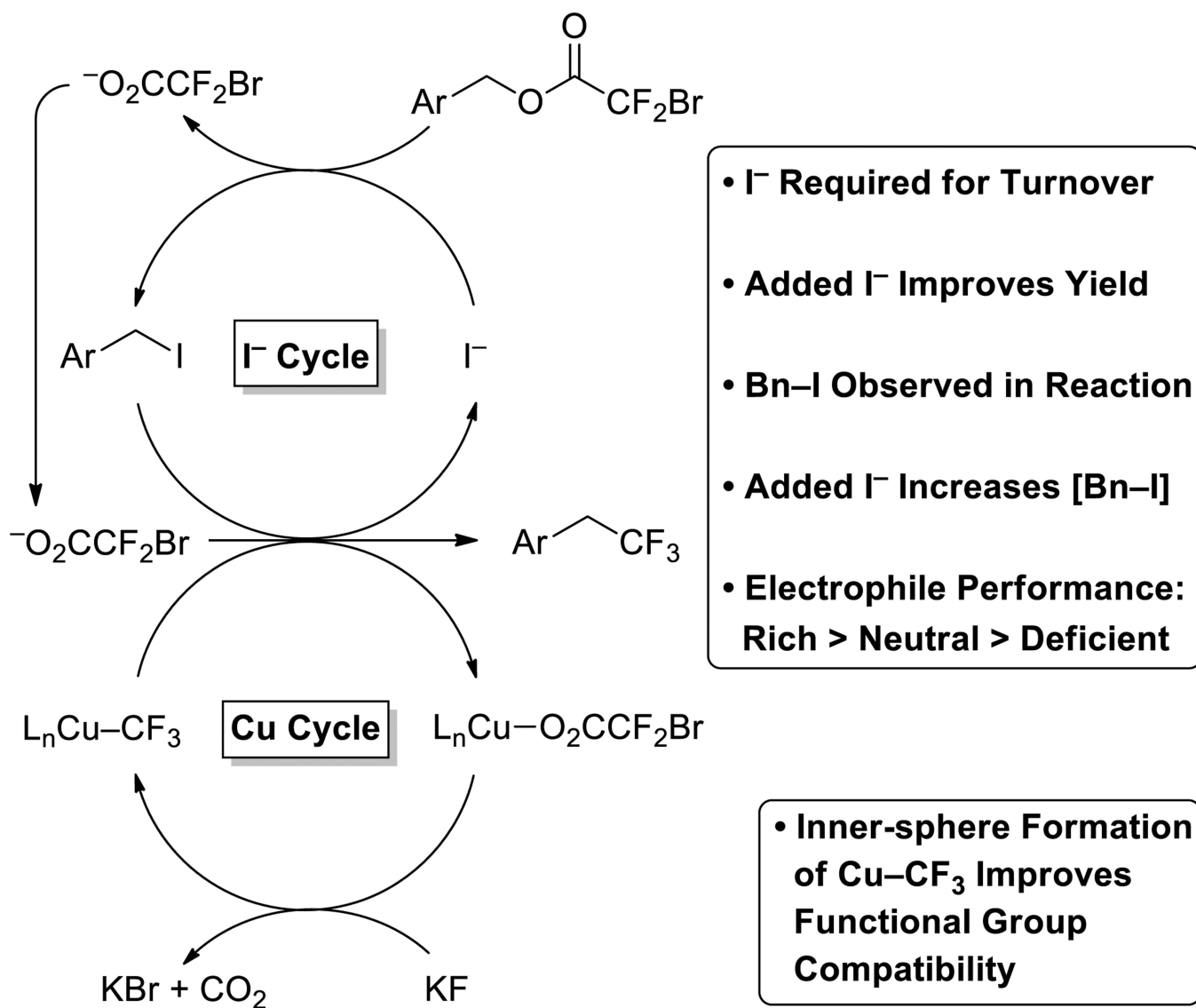
Figure 1.
Iodide plays an essential role in benzylic trifluoromethylation
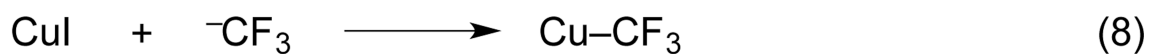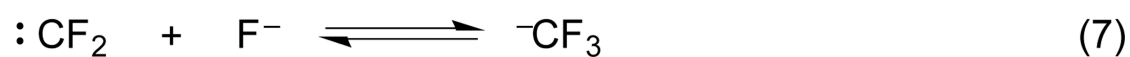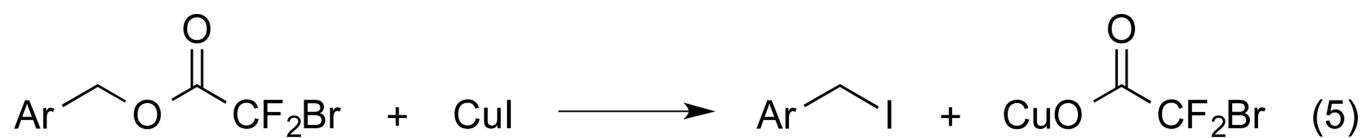
Metal-mediated Processes (Ref. 4b, 5)

$$R \overset{}{\underset{}{\bigcirc}} \diagdown X \xrightarrow[\text{or CuI (1 equiv)}]{\text{[CuCF}_3\text{] (>1 equiv)}} R \overset{}{\underset{}{\bigcirc}} \diagdown CF_3 \quad (1)$$

$$X = Br, I, OMs, OCS_2Me, O_2CCF_2Br, O_2CCF_2Cl$$

- -

Metal-catalyzed Processes (Ref. 6, 7)

$$H \overset{}{\underset{}{\bigcirc}} \diagdown X \xrightarrow[\text{X = Cl, Br, I}]{\substack{\text{CuI (cat.)} \\ \text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}}} H \overset{}{\underset{}{\bigcirc}} \diagdown CF_3 \quad (2)$$

$$EDG \overset{R}{\underset{}{\bigcirc}} \diagup Cl \xrightarrow[\text{KF}]{\substack{\text{CuTC (cat.)} \\ \text{TMSCF}_3}} EDG \overset{R}{\underset{}{\bigcirc}} \diagup CF_3 \quad (3)$$

- -

Present Work: Metal-catalyzed Reaction

$$R \overset{}{\underset{}{\bigcirc}} \diagdown O \diagup \overset{O}{\underset{}{\|}} CF_2Br \xrightarrow[\text{KI, KF}]{\text{CuI (cat.)}} R \overset{}{\underset{}{\bigcirc}} \diagdown CF_3 \quad (4)$$

- *Transforms electron-rich, -neutral, and -deficient substrates*
- *Compatible with heterocyclic substrates*
- *Tolerates sensitive functional groups*

Scheme 1.
Trifluoromethylation of Benzylic Electrophiles Typically Requires Stoichiometric Copper

$$Ar\text{—}CH_2\text{—}O\text{—}C(=O)\text{—}CF_2Br \;+\; CuI \longrightarrow Ar\text{—}CH_2\text{—}I \;+\; CuO\text{—}C(=O)\text{—}CF_2Br \quad (5)$$

$$CuO\text{—}C(=O)\text{—}CF_2Br \longrightarrow CuBr \;+\; CO_2 \;+\; :CF_2 \quad (6)$$

$$:CF_2 \;+\; F^- \rightleftharpoons {}^-CF_3 \quad (7)$$

$$CuI \;+\; {}^-CF_3 \longrightarrow Cu\text{—}CF_3 \quad (8)$$

$$Cu\text{—}CF_3 \;+\; Ar\text{—}CH_2\text{—}I \longrightarrow Ar\text{—}CH_2\text{—}CF_3 \;+\; CuI \quad (9)$$

Beneficial Features:
- **Easily Accessible Substrates**
- **Benign, Easily Separable Byproducts**

Proposed Outer-sphere Decarboxylation:
- **Free $^-CF_3$ in Solution $\rightarrow$ Poor FG Tolerance**

Scheme 2.
Previously proposed mechanism involves generation of free $^-CF_3$

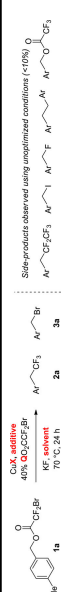## Previous Work – Stoichiometric Mn and Sn (Ref. 13): 4 steps, 31%

1) MnO$_2$, 75%

2) Me$_3$SiCF$_3$, TBAF, 90%

4

3) PhOC(S)Cl DMAP, 61%

4) *n*-Bu$_3$SnH, AIBN, 75%

3

Me—N

OH

Tebufenpyrad analog with acaricidal activity

5

Me—N

CF$_3$

1) HO$_2$CCF$_2$Br, (COCl)$_2$, DMF, NEt$_3$, DCM, −10 °C, 82%

2) 20% CuI, 25% KI, 40% MeO$_2$CCF$_2$Br, KF, DMF/MeCN, 70 °C, 24 h, 73%
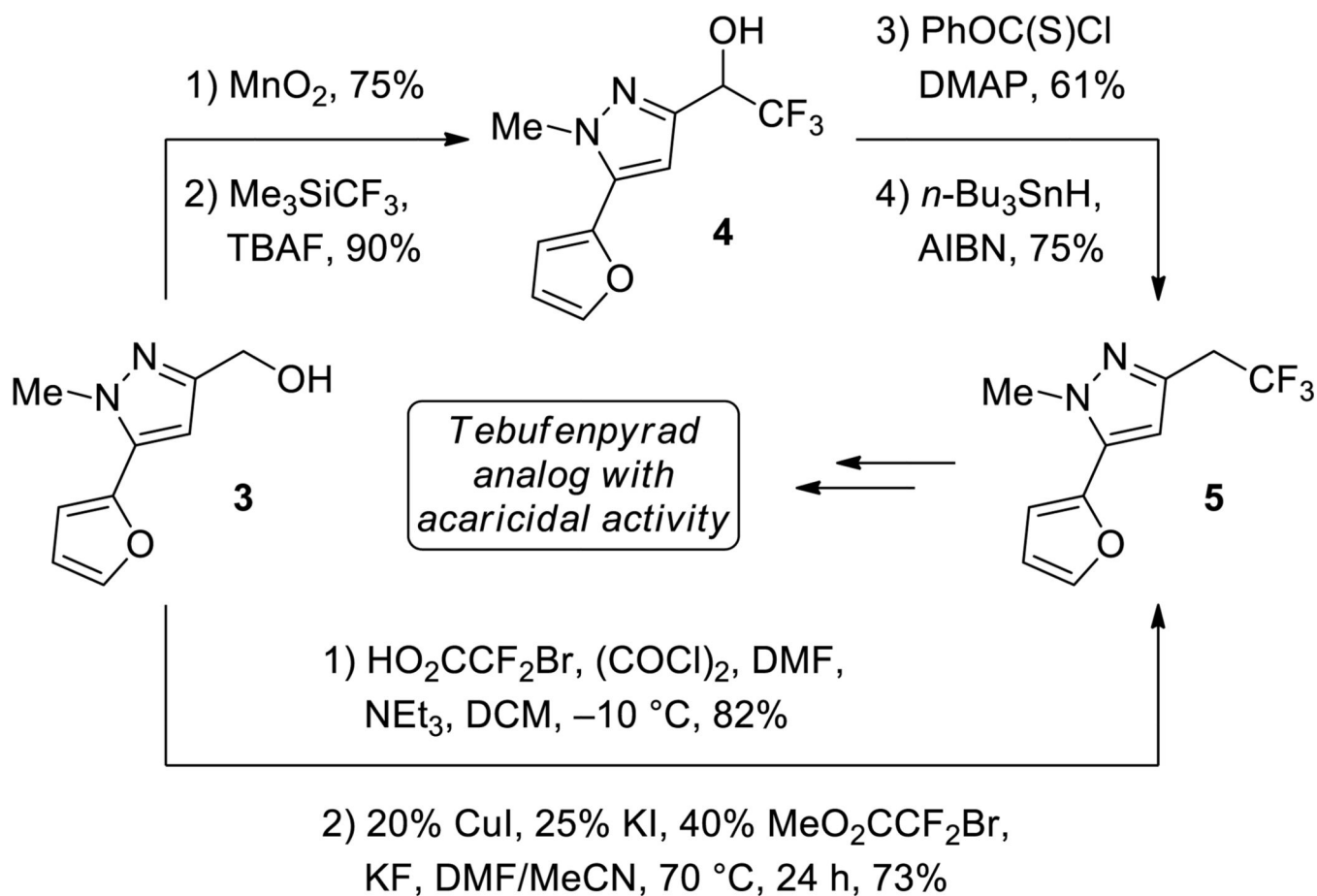
This Work – Catalytic Cu: 2 steps, 60%

Scheme 3.
Copper-catalyzed reaction improves access to target compounds

Table 1

Solvent and I⁻ Critical for Developing a Cu-catalyzed Reaction[a]

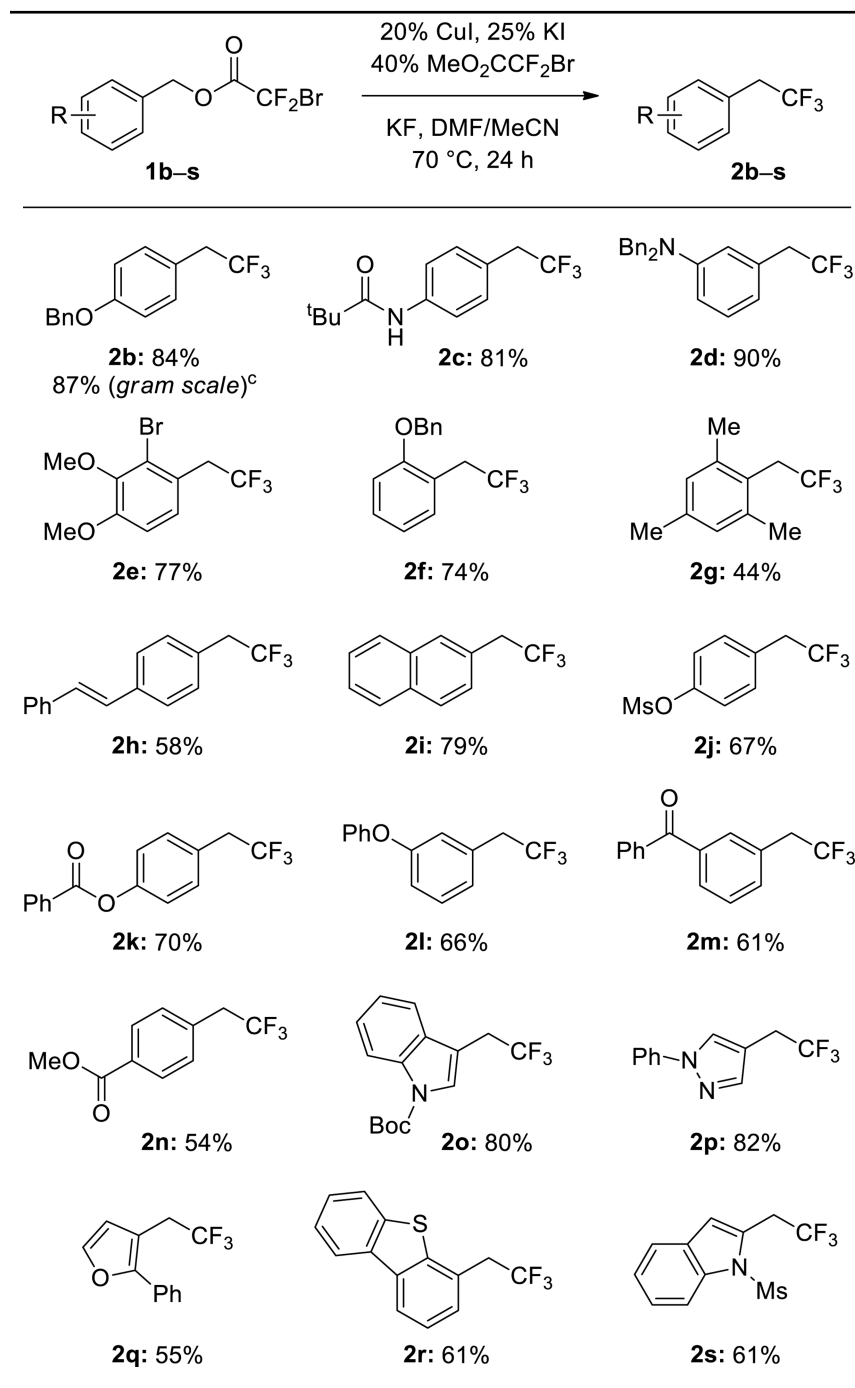| entry	solvent	CuX(mol %)	additive(mol %)	total % I⁻	Q	conversion(%)	2a(%)	3a(%)
1[b]	DMF	CuI (100)	–	100	–	>99	22	8
2	DMF	CuI (20)	DMEDA(20)	20	Na	>99	23	10
3	DMF	CuI (20)	–	20	Me	>99	30	19
4	MeCN	CuI (20)	–	20	Me	35	13	3
5	DMF/MeCN	CuI (20)	–	20	Me	>99	61	5
6[c]	DMF/MeCN	CuI (20)	KI (25)	45	Me	>99	74	1
7	DMF/MeCN	[Cu(MeCN)₄]PF₆ (20)	–	–	Me	92	18	17
8[c]	DMF/MeCN	[Cu(MeCN)₄]PF₆ (20)	KI (45)	45	Me	>99	76	1
9	DMF/MeCN	CuI (20)	KI (80)	100	Me	>99	52	1
10	DMF/MeCN	CuI (20)	KI (25)	45	–	>99	53	6

[a] Reactions were performed with 0.20 mmol of **1a**, 0.080 mmol of QO₂CCF₂Br, 0.80 mmol of KF, 0.20 mL of solvent. Conversion and yield data were determined by GC/FID analysis, and represent the average of a minimum of two independent experiments;

[b] 80 °C;

[c] No side-products > 2% were detected by GC/FID analysis.

Table 2

Copper-catalyzed decarboxylative trifluoromethylation tolerates important functional groups and heterocycles[a,b]

$$\text{1b-s} \xrightarrow[\substack{\text{KF, DMF/MeCN} \\ 70\ °\text{C, 24 h}}]{\substack{20\%\ \text{CuI, 25\%\ KI} \\ 40\%\ \text{MeO}_2\text{CCF}_2\text{Br}}} \text{2b-s}$$

2b: 84%
87% (*gram scale*)[c]

2c: 81%

2d: 90%

2e: 77%

2f: 74%

2g: 44%

2h: 58%

2i: 79%

2j: 67%

2k: 70%

2l: 66%

2m: 61%

2n: 54%

2o: 80%

2p: 82%

2q: 55%

2r: 61%

2s: 61%

[a] 0.25 mmol **1b-s**, 0.050 mmol CuI, 0.063 mmol KI, 0.10 mmol MeO$_2$CCF$_2$Br, 1.0 mmol KF, 0.13 mL DMF, 0.13 mL MeCN;

*b*The yields represent the average of two independent experiments;

*c*6.0 mmol scale, single experiment.