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Copper-Catalyzed Synthesis of Trifluoroethylarenes from Benzylic Bromodifluoroacetates

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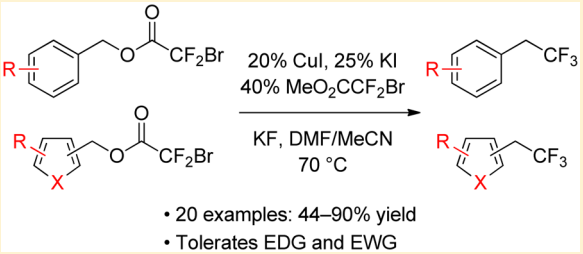
Supporting Information

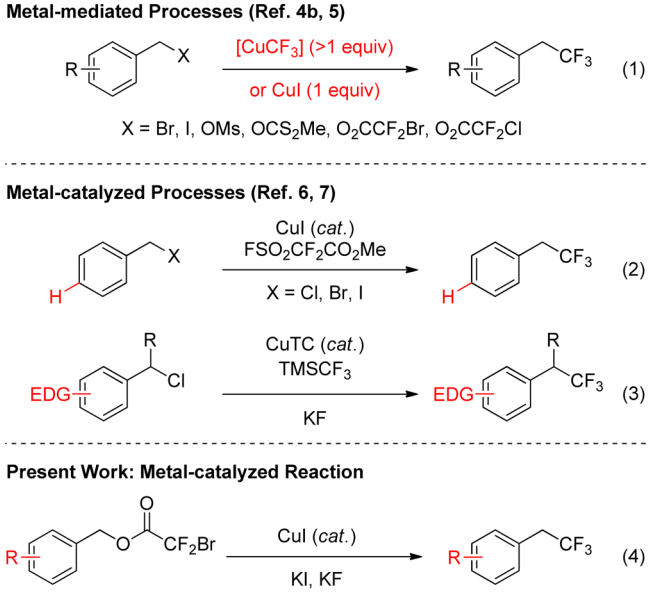
ABSTRACT: Trifluoroethylarenes are found in a variety of biologically active molecules, and strategies for accessing this substructure are important for developing therapeutic candidates and biological probes. Trifluoroethylarenes can be directly accessed via nucleophilic trifluoromethylation of benzylic 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.



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 30000 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 catalytic system can transform a broad spectrum of (hetero)benzylic electrophiles. Current systems for benzylic trifluoromethylation require either stoichiometric Cu (Scheme 1, 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 byproducts. 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

Scheme 1. Trifluoromethylation of Benzylic Electrophiles Typically Requires Stoichiometric Copper



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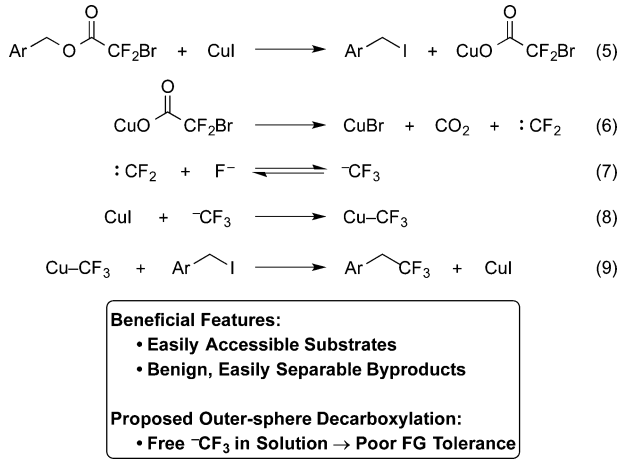
Scheme 2. Previously Proposed Mechanism Involves Generation of Free $^{-}CF_3$

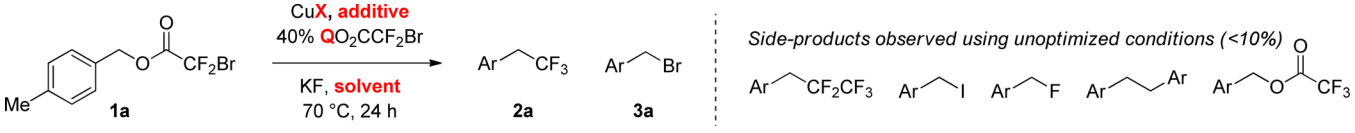


would severely limit the functional group compatibility of the transformation. However, we hypothesized that a catalytic inner-sphere decarboxylation might generate the critical Cu–CF_3 intermediate, which would enable the conversion of substrates bearing sensitive carbonyl and acidic functional groups.

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). On the basis of 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

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	$[Cu(MeCN)_4]PF_6$ (20)		0	Me	92	18	17
8[c]	DMF/MeCN	$[Cu(MeCN)_4]PF_6$ (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 QO_2CCF_2Br, 0.80 mmol of KF, and 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.

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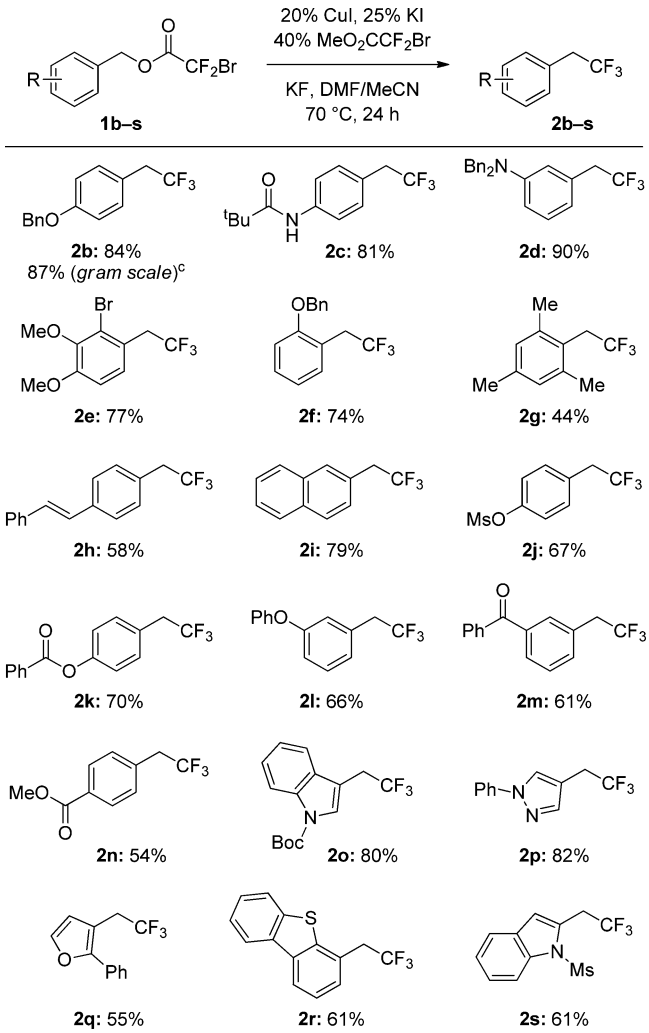
in a decreased yield of **2a** and an increased benzyl bromide **3a** (entry 10). Ultimately, we selected a general system that employed 20% CuI, 25% KI, 40% MeO_2CCF_2Br, and superstoichiometric KF in MeCN/DMF (1:1), which minimized the formation of side products (<2%) and provided a good yield of trifluoroethylarene **2a**.

The present Cu-catalyzed reaction tolerated a broad array of useful functional groups (Table 2), including ethers (**2b,e−f,l**),

Table 2. Copper-Catalyzed Decarboxylative Trifluoromethylation Tolerates Important Functional Groups and Heterocycles[a,b]



[a]0.25 mmol of **1b−s**, 0.050 mmol of CuI, 0.063 mmol of KI, 0.10 mmol of MeO_2CCF_2Br, 1.0 mmol of KF, 0.13 mL of DMF, 0.13 mL of MeCN. [b]The yields represent the average of two independent experiments. [c]6.0 mmol scale, single experiment.

a secondary amide (**2c**), a substituted aniline (**2d**), an aryl bromide (**2e**), an alkene (**2h**), a mesylate (**2j**), esters (**2k,n**), and a ketone (**2m**). Substrates bearing (pseudo)ortho substituents provided lower yields of products (**2e−f,q−s**), and a sterically hindered 2,6-disubstituted 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,m−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 implies 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 an 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 four-step procedure that employed stoichiometric Mn and Sn and afforded product in 31% overall yield.[13] In contrast, the present two-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; and (4) reduction of metal-containing waste products (stoichiometeric Mn and Sn vs catalytic Cu). These attractive

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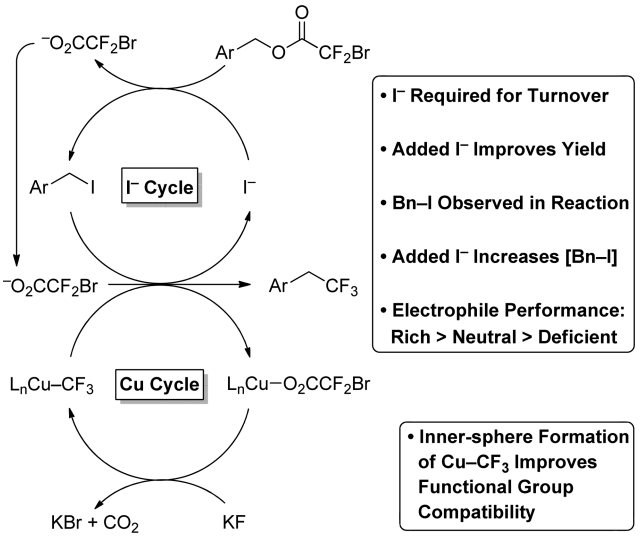
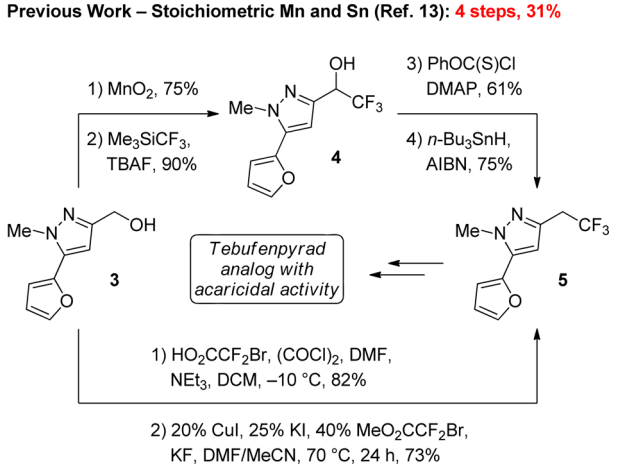


Figure 1. Iodide plays an essential role in benzylic trifluoromethylation.

Scheme 3. Copper-Catalyzed Reaction Improves Access to Target Compounds



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 μm 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. no. 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 nonanhydrous 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 (^{1}H 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 million 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 constants 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 the sample plus near-mass internal exact mass standard were dissolved in hexane and hexane or PhMe/hexane were used as ionization solvent. Melting points are uncorrected and were 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 that 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 (4×). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the removal of

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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 $C_{23}H_{20}BrF_2NO_2$ 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 $C_{11}H_{10}Br_2F_2O_4$ 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 $C_{16}H_{13}BrF_2O_3$ 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 $C_{12}H_{13}BrF_2O_2$ 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 $C_{17}H_{13}BrF_2O_2$ 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%): mp 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 $C_{13}H_9BrF_2O_2$ 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 $C_{10}H_9BrF_2O_5S$ 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 $C_{16}H_{11}BrF_2O_4$ 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

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(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); $^{13}C\{^1H\}$ 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)-phenylmethanone. 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); $^{13}C\{^1H\}$ 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); $^{13}C\{^1H\}$ 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)-1*H*-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); $^{13}C\{^1H\}$ 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-1H-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); $^{13}C\{^1H\}$ 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 $C_{12}H_{10}BrF_2N_2O_2$ 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); $^{13}C\{^1H\}$ 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 $C_{13}H_9BrF_2O_3$ 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]thiophene-4-ylmethyl 2-Bromo-2,2-difluoroacetate (**1r**).* General procedure A was followed using dibenzo[*b*,*d*]-thiophene-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); $^{13}C\{^1H\}$ 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 $C_{15}H_9BrF_2O_2S$ 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)-1H-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 gray 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); $^{13}C\{^1H\}$ 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 $C_{12}H_{10}BrF_2NO_4S$ 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-1*H*-pyrazol-3-yl)methyl 2-Bromo-2,2-difluoroacetate (3a). HO_2CCF_2Br (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%): mp 39−40 °C; ^{1}H 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 preheated hot plate (70 °C) and stirred for 24 h. After being cooled 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 and filtered, and the solvent was removed in vacuo. The residue was purified via silica gel

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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 preheated 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 and 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_2O 39:1) afforded the title compound as a colorless solid (55.7 mg, 84%): mp 78−79 °C (lit.[19] 82−84 °C); ^1H 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_2CCF_2Br (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 preheated oil bath (70 °C) and stirred for 24 h. After being cooled to room temperature, the mixture was diluted with EtOAc (75 mL). The mixture was washed with H_2O (75 mL) and brine (75 mL). The organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The residue was purified via silica gel chromatography (hexanes/Et_2O 39:1) to provide **2b** as a colorless solid (1.4 g, 87%). The ^1H 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; ^1H 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); $^{13}C\{^1H\}$ 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 $C_{13}H_{16}F_3NO$ 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%): ^1H 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); $^{13}C\{^1H\}$ 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 $C_{22}H_{20}F_3N$ 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%): ^1H 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%): ^1H 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); $^{13}C\{^1H\}$ 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 $C_{15}H_{13}F_3O$ 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%): ^1H 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); $^{13}C\{^1H\}$ 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; ^1H 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); $^{13}C\{^1H\}$ 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; ^1H 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; ^1H 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); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 132.0, 129.6 (q, J = 3.0 Hz), 125.6 (q, J =

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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 $C_9H_9F_3O_3S$ 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.[5l]

*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 $C_{15}H_{11}F_3O$ 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 % $ArCH_2Br$ 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)-1H-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%): mp 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 $C_{15}H_{16}F_3NO_2$ 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)-1H-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%): mp 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 $C_{11}H_{10}F_3N_2$ 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 $C_{12}H_9F_3O$ 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]thiophene (**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)-1H-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%): mp 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 $C_{11}H_{10}F_3NO_2S$ 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]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01343.

Supplementary experiments, including time-course analysis of benzylic trifluoromethylation, as well as NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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