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Catalytic One-Step Deoxytrifluoromethylation of Alcohols

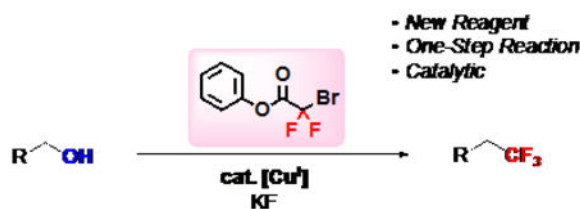
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Abstract

A new bench-stable trifluoromethylation reagent, phenyl bromodifluoroacetate, converts readily available alcohols to trifluoromethanes in a Cu-catalyzed *deoxytrifluoromethylation* reaction. This reaction streamlines access to target biologically active molecules, and should be useful for a variety of medicinal, agricultural, and materials chemists.

Graphical Abstract



Introduction

Methods for directly converting common functional groups to fluorinated motifs enable the rapid and efficient discovery and development of new agrochemicals, materials, and pharmaceuticals.¹ In particular, protocols that employ simple reagents and mild reaction conditions can facilitate both late-stage diversification of lead compounds and large-scale manufacture of chemicals. Given the ubiquity of alcohols in bioactive compounds, materials, and synthetic intermediates, methods that directly convert alcohols to useful fluorinated functional groups that alter physicochemical and biophysical properties of a parent compound are highly valuable.² This powerful strategy has been realized for converting alcohols to monofluorinated analogs, which is an essential strategy to selectively and quickly incorporate fluorine into molecules (Figure 1B, left).^{1a} For these one-step deoxyfluorination reactions of alcohols, many benchmark reagents are commercially available, and new methods are continuously being developed.³ However, analogous one-pot

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ASSOCIATED CONTENT

Supporting Information. Supplementary experiments and copy of NMR spectra.

deoxytrifluoromethylation protocols for transforming alcohols to trifluoromethanes, another useful functional group for medicinal, agricultural and materials chemistries, remain extremely limited.

Considering deoxyfluorination and deoxytrifluoromethylation reactions, intrinsic differences in stability and reactivity of ^-F and $^-CF_3$ render the latter reaction challenging. The deoxyfluorination strategy typically relies on *in situ* activation of alcohols to generate more electrophilic intermediates, and subsequent substitution by nucleophilic ^-F . Fluoride is a stable and small anion that can directly engage in nucleophilic substitutions, such as deoxyfluorination reactions. In contrast, $^-CF_3$ is unstable, bulky, and decomposes quickly in solution in the absence of a competent (usually sp^2 -hybridized) electrophile (Figure 1B, right).⁴ Because of this instability, $^-CF_3$ does not react through pure nucleophilic substitution mechanisms, but instead requires a transition metal to effectively generate a new C– CF_3 bond.⁵ However, conditions for activating alcohols have historically not been compatible with transition metal-catalyzed reactions. As such, deoxytrifluoromethylation reactions of alcohols typically require multi-step transformations that inefficiently manipulate oxidation states, require excess time and labor, generate excess waste, decrease yields of desired products, and limit the use of functional groups that are sensitive to oxidation, reduction, and/or strong nucleophiles.⁶ Herein, we describe the development of a new reagent that, in concert with a Cu-based catalyst, enables the direct conversion of alcohols to trifluoromethanes under mild conditions.

Results and Discussion

To develop a one-step deoxytrifluoromethylation reaction, we aimed to develop a new reagent that would convert an alcohol to a suitable leaving group for reaction with Cu– CF_3 under mild conditions (Figure 1C). Among several alcohol-derived electrophiles, we focused on pioneering work of Chen and co-workers,⁷ who established the Cu-mediated C–O bond activation of bromodifluoroacetates, and the compatibility of this system with Cu-mediated C– CF_3 bond formation. Considering our previous work with bromodifluoroacetates,⁸ we envisioned that a catalytic one-step deoxytrifluoromethylation reaction could be achieved by designing a stable reagent that would convert the starting alcohol to the corresponding bromodifluoroacetate derivative *in situ*, but that would not interfere with catalysis. We initially explored commercially available bromodifluoroacetates (e.g. MeO_2CCF_2Br and NaO_2CCF_2Br) as deoxytrifluoromethylation reagents; however, despite achieving catalytic turnover, thorough evaluation of reaction conditions did not provide a suitable system for deoxytrifluoromethylation (Figure 2A). We reasoned that water or an alcohol, generated from transesterification step, might adversely affect the final Cu-catalyzed decarboxylative trifluoromethylation step. To test this hypothesis, Cu-catalyzed trifluoromethylation of cinnamyl bromodifluoroacetate (**3a**) was conducted in the presence of an alcohol or H_2O (1 equiv.). Compared to the control reaction, addition of MeOH or H_2O decreased the yield of trifluoromethylated product (**4a**) from 75% to 19–24% (Figure 2B), thus confirming the incompatibility of simple H_2O and MeOH leaving groups (LG–H).

Subsequent efforts identified different LG–H that would not interfere with the Cu-catalyzed process (Figure 2C). To identify such leaving groups (LG), we evaluated the effects of

different additives (1.0 equiv.) on the conversion of cinnamyl bromodifluoroacetate **3a** into trifluoromethyl products (Figure 2D).^{8a} In these reactions, succinimide did not decrease the yield of trifluoromethyl product **4a**, while phenol and trifluoroethanol slightly lowered the yields of **4a**. Other N-based additives (e.g. 2-oxazolidinone, *N*-tosylaniline, and N–H heterocycles), thiols, and other alcohols, negatively affected the Cu-catalyzed process. Based on these additives, we prepared several bromodifluoroacetate (BDFA) -derived esters, and tested them as reagents in the deoxytrifluoromethylation reaction of cinnamyl alcohol **2a** using optimized conditions (Table 1). Under these conditions, commercially available NaO₂CCF₂Br (**1a**), MeO₂CCF₂Br (**1b**), and EtO₂CCF₂Br (**1c**) still provided low yields of the desired product. Among the newly prepared reagents, phenyl bromodifluoroacetate (PhBDFA, **1d**) afforded the best compromise between availability, stability, cost and yield of the desired cinnamyl trifluoromethane (**4a**). Substitutions on the phenyl ring of the PhBDFA (**1d**) to perturb electronic character (**1d–1g**) or steric hindrance (**1h**) did not improve the reaction. An exchange of the oxygen for the sulfur in compound **1i** decreased the yield, which is consistent with our additive based screening. Similarly, bromodifluoroacetamide **1j** provided similar yields as compared to the easier to synthesize bromodifluoroacetate esters. Moreover, reactions using **1j** generated significant quantities of side products deriving from the allylation of *N*-tosylaniline. In addition, the bromodifluoroacylated succinimide was insufficiently stable for isolation, thus limiting the use of this presumably useful leaving group. Ultimately, PhBDFA (**1d**) was selected as the most suitable reagent for deoxytrifluoromethylation, given the inexpensive and readily available nature of phenol, and the reasonable stability of the phenyl ester toward storage.⁹

Using phenyl bromodifluoroacetate (PhBDFA, **1d**), representative allylic (**2a–2i**), propargylic (**5a–5f**) and benzylic (**7a–7e**) alcohols were trifluoromethylated in moderate to good yields (Tables 2–4). For allylic^{8a} and propargylic^{8c} substrates, direct deoxytrifluoromethylation typically provided higher yields than two-step protocols involving formation and purification of intermediate bromodifluoroacetic esters and subsequent Cu-catalyzed decarboxylative trifluoromethylation. Notably, many allylic and propargylic bromodifluoroacetates previously explored^{8a, c} were unstable to basic conditions, silica gel, and cold storage (slowly decomposing in the refrigerator for weeks). Therefore, the one-step protocol offered distinct advantages by avoiding isolation of the unstable intermediate bromodifluoroacetic esters. The direct deoxytrifluoromethylation displayed good functional group tolerance, with cinnamyl derivatives **2a–2e** illustrating good compatibility with electron-donating, electron-withdrawing, and halogen functional groups. In addition, the reaction tolerated non-cinnamyl substrates, such as allylic alcohol **2f**. Endocyclic alkenols, a structural unit present in several natural products, served as competent substrates, and delivered **4g–4h** in good yields. As an example of such natural products, perillyl alcohol afforded trifluoromethyl product **4i** in 57% of yield. In addition, selected propargylic alcohols **5a–5f** were also deoxytrifluoromethylated to afford trifluoromethylallenes **6a–6f**, bearing useful ester, amide, and chlorine groups.¹⁰ In contrast to allylic and propargylic alcohols, benzyl alcohols **7a–7e** were more challenging substrates, and required higher temperature to afford synthetically useful yields with electron-rich rings (**7a–7b**). However, the reaction is compatible with a range of drug-like heterocycles, such as indole (**7c**), pyrazole (**7d**), and indazole (**7e**).^{6c} Together, these examples showcase the potential of this

deoxytrifluoromethylation reaction to provide valuable trifluoromethyl drug-like building-blocks from simple alcohols in a single-step.

To further illustrate the potential impact of the catalytic one-step deoxytrifluoromethylation reaction, we prepared trifluoromethylated intermediates **10** and **12** toward the syntheses of the COX-2-inhibitor L-784-512,¹¹ and a fluorinated analog of Tebufenpyrad,¹² respectively. Previously, allyl trifluoromethane **10** was prepared in a one-pot two-step procedure in 74% yield employing chlorodifluoroacetic anhydride [O(O₂CCF₂Cl)₂] as the trifluoromethylating reagent; however, stoichiometric amounts of CuI were required to suppress the formation of the corresponding allyl chloride side-product (Scheme 1A). In contrast, use of PhBDFA (**1d**) as the trifluoromethylating reagent provided a similar yield with only a catalytic amount of copper salt. A more insightful comparison involved the synthesis of trifluoroethyl pyrazole **12** (Scheme 1B). The original route to this compound required four steps, including one final deoxygenation reaction with excess of undesirable Bu₃SnH (Route i).^{12a} In a second preparation of **12**, our previous two-step reaction provided **12** in 60% yield (Route ii).^{8d} Finally, when employing PhBDFA (**1d**), our catalytic conditions afforded the desired product directly from the alcohol in 57% yield (Route iii). This operationally straightforward one-step catalytic deoxytrifluoromethylation reaction provides direct access to a valuable fluorinated product from a simple alcohol precursor, while avoiding inefficient redox manipulations, chromatographic purifications, and generation of stoichiometric metallic byproducts. To further highlight the utility of the reaction, we carried out the deoxytrifluoromethylation of cinnamyl alcohol **2a** in multigram scale, as the scale up of related aromatic trifluoromethylation reactions using a related reagent (MeO₂CCF₂Cl) has proved problematic.¹³ In our case, no loss in the yield was observed relative to the small scales reactions, and 2.7 g of product was obtained in a single-reaction. In perspective, these examples illustrate the streamlined synthetic routes enabled by the catalytic one-step deoxytrifluoromethylation reaction, and its potential to be used in small multigram synthesis.

Several data support a mechanism involving a fast acylation/transesterification step prior to the Cu-catalyzed decarboxylative trifluoromethylation reaction (Scheme 2A). Using time-course analysis, we observed a quick acylation of cinnamyl alcohol **2a** forming the corresponding bromodifluoroacetate **3a** during the first 15 min of the Cu-catalyzed reaction, reaching a maximum concentration at ~2 h, and then converting to product **4a** over the remaining course of the reaction (see SI for details). Further experiments identified KF as the key component in facilitating formation of the thermodynamically favored ester **3a**. In contrast, excess BDFA, serving as a Brønsted acid, did not promote the transesterification step (Scheme 2B). Based on these results, relative to MeO₂CCF₂Br and other commercially available bromodifluoroacetates, the acylating ability of PhBDFA (**1d**) likely shifted the equilibrium of the transesterification step, thus increasing the concentration of the key bromodifluoroacetate **3a**, and subsequently favoring the Cu-catalyzed trifluoromethylation (Scheme 2C). Such a facile acylation step supports an overall deoxytrifluoromethylation mechanism involving conversion of the alcohol to a bromodifluoroacetate ester prior to a Cu-catalyzed decarboxylative trifluoromethylation, as previously suggested (Scheme 2A).^{7, 8e, 14}

The ability of PhBDFA (**1d**) to serve as an effective trifluoromethylating reagent derived from its aforementioned acylating ability in addition to its stability under the reaction conditions (Scheme 2). Reagents previously used for trifluoromethylation of organic halides [RO₂CCF₂X (R = Na, Me, Et; X = Cl, Br)] decompose under mild conditions (>40 °C in the presence of copper)^{14–15} to release difluorocarbene, which polymerizes¹³ or reacts with alkenes or phenols.^{15b, 16} In contrast, minimal decomposition of the PhBDFA (**1d**) was observed (>82% of **1d** recovered) under the reaction conditions (Scheme 2D). Moreover, the stability of PhBDFA (**1d**) discounted mechanisms involving initial outer-sphere thermal decomposition of **1d** to generate difluorocarbene, and subsequent formation of the Cu–CF₃, which has been implicated in trifluoromethylation reactions of organic halides.¹⁷ Overall, this analysis suggests that success of PhBDFA (**1d**), compared to MeO₂CCF₂Br, relies on the inertness of the leaving group (Figure 2D), and from equilibrium (Scheme 2C) and stability factors (Scheme 2D) of the newly designed reagent. Of note, the optimized conditions utilize MeO₂CCF₂Br or HO₂CCF₂Br additives to help generate the active Cu–CF₃ catalyst. Though these species serve as poor reagents for esterifying the alcohol substrate (Figure 2A), they serve to convert the CuI precatalysts into the active Cu–CF₃ species,^{8a} and/or to regenerate Cu–CF₃ that is lost throughout the reaction.^{8d} Further, as previously reported,¹⁴ the CuI/KF-mediated conversion of MeO₂CCF₂Br or HO₂CCF₂Br to afford Cu–CF₃ generates methyl iodide and CO₂ as byproducts, which do not inhibit the catalytic reaction in a similar fashion to H₂O and MeOH, which would be generated by transesterification.

Conclusion

In summary, a catalytic one-step deoxytrifluoromethylation reaction of readily available alcohols was developed using phenyl bromodifluoroacetate (**1d**, PhBDFA) as the key reagent. The new reaction provided diverse trifluoromethyl compounds in good yields and tolerated many useful functional groups. Moreover, its application to rapidly prepare intermediates in the synthesis of biologically active molecules illustrated the potential impact of this reaction. Initial mechanistic analysis suggested that the success of **1d**, in comparison with commercially available bromodifluoroacetates, stems from both equilibrium and stability factors, in addition to its inertness under the catalytic conditions. The deoxytrifluoromethylation reaction complements the well-established deoxyfluorination reaction and opens up new possibilities to obtain fluoroalkylated products from readily available functional groups. Further studies to expand this reaction are undergoing in our lab.

Experimental Section

General Considerations

Unless otherwise noted, reactions were performed under an atmosphere of N₂ using oven-dried glassware. Trifluoromethylation reactions in 1-dram vials sealed with a PTFE-lined screw cap. Reactions were setup inside a N₂-filled glove box. All other reactions were performed in round-bottom flasks that were sealed with rubber septa using oven-dried glassware and standard Schlenk techniques. High-quality laboratory-grade polypropylene and polyethylene syringes bearing stainless steel needles were used to transfer air- and

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, or iodine. Purifications by column chromatography (SiO₂) were conducted using an automated system or following Still's general procedure. ¹⁹F NMR Yields and isolated yields reported in the manuscript represent an average of at least two independent runs. Yields reported in the supporting information refer to a single experiment.

Unless otherwise noted, reagents were purchased from commercial sources, and used as received. Commercial anhydrous potassium fluoride (KF) was further dried in high-vacuum (~1.5 Torr, 185 °C) for 18 h, and stored in the glovebox. *N,N*-dimethylethylenediamine (DMEDA) was distilled under nitrogen and stored in the glovebox. Anhydrous *N,N*-dimethylformamide (DMF), acetonitrile (CH₃CN), methanol (MeOH), dichloromethane (DCM), tetrahydrofuran (THF), and triethylamine (NEt₃) were dispensed from a solvent purification system, in which the solvent was dried by passage through two columns of activated alumina under argon.

Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Bruker AVIIIHD 400 spectrometer (400 and 100 MHz, respectively) or Bruker AVIII 500 with CPDUL cryoprobe spectrometer (500 and 125 MHz, respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to proton resonance of residual CHCl₃ in the NMR solvent (CHCl₃; δ = 7.26 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak (CDCl₃; δ = 77.16 ppm). Fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded on a Bruker AVIIIHD 400 spectrometer (376 MHz). ¹⁹F NMR chemical shifts (δ) are reported in ppm upfield from trichlorofluoromethane (0 ppm). ¹⁹F NMR yields were determined from the crude mixtures using non-deuterated solvents and the relaxation delay time (D1) was set to 4 seconds to ensure reproducible results. NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet), coupling constant in Hertz (Hz), integration.

Exact mass spectra were recorded using (1) electrospray ion source (ESI), positive mode, and time-of-flight (TOF) analyzer on a Waters LCT Premier™ mass spectrometer or (2) an atmospheric-pressure chemical ionization (APCI) ion source and TOF analyzer on a Waters Q-ToF Premier™ mass spectrometer, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were used as the ionization solvent. Mass calibration was carried out directly before the measurement of the sample. Low-resolution mass spectra were recorded using an electron impact (EI) ion source and a tandem quadrupole analyzer on a Waters Quattro Micro GC mass spectrometer, injected via a gas chromatograph Agilent 6890N (GC/MS).

Quantitative gas chromatography (GC) analyses were recorded on an Agilent Technologies 7890A GC-system with Flame Induced Detector (FID) and a HP-5 column (0.32 mm × 30

m, film: 0.25 μm). The method used consisted of 70 $^{\circ}\text{C}$ for 1 min, then 30 $^{\circ}\text{C}/\text{min}$ to 250 $^{\circ}\text{C}$, and holding at 250 $^{\circ}\text{C}$ for 1 min.

Infrared spectra were measured using attenuated total reflection (ATR) at a Fourier Transform Infrared Spectrometer. Uncorrected melting points were measured on Thomas Hoover Capillary Melting Point apparatus.

Preparation of Known Compounds

N-4-toluenesulfonylaniline,¹⁸ (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (**2b**),^{8a} (*E*)-3-(4-fluorophenyl)prop-2-en-1-ol (**2d**),^{8a} (*E*)-3-(3-bromophenyl)prop-2-en-1-ol (**2e**),^{8a} 3-(naphthalen-2-yl)prop-2-yn-1-ol (**5a**),^{8c} 3-(2-methoxy-5-nitrophenyl)prop-2-yn-1-ol (**5b**),^{8c} methyl 3-(3-hydroxyprop-1-yn-1-yl)benzoate (**5c**),^{8c} *tert*-butyl 2-(3-hydroxyprop-1-yn-1-yl)-1H-indole-1-carboxylate (**5d**),^{8c} 2,2,2-trifluoro-*N*-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)acetamide (**5d**),^{8c} 3-(3,4-dichlorophenyl)prop-2-yn-1-ol (**5e**),^{8c} (1-phenyl-1H-pyrazol-4-yl)methanol (**5f**),^{8d} (1-methyl-1H-indazol-3-yl)methanol (**7e**),¹⁹ (*E*)-2-methyl-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-ol¹¹ (**9**) and (5-(furan-2-yl)-1-methyl-1H-pyrazol-3-yl)methanol (**11**),^{12a} were prepared according to previously literature reports. All compounds presented satisfactory analysis coherent with characterization data published previously.

Synthesis of Aryl Bromodifluoroacetates

General Procedure A: An oven-dried two-neck flask equipped with a stirring bar, a gas outlet attached to the Schlenk line and a rubber septum under nitrogen was charged with bromodifluoroacetic acid (12.6 g, 72.0 mmol) and CH_2Cl_2 (150 mL). The resulting solution was cooled using an ice-water bath, and oxalyl chloride (5.7 mL, 66 mmol) was added. Next, DMF (0.23 mL, 3.0 mmol) was added dropwise (caution: rapid evolution of noxious gases). After stirring at low temperature for 10 min, the solution was stirred at room temperature until the gas evolution ceased (~ 3 h). Next, the reaction mixture was cooled using an ice-water bath, and phenol (60.0 mmol) was added in one portion. After 10 min stirring at low temperature, Et_3N (10.0 mL, 72.0 mmol) was added, and the reaction was stirred for 30 min at low temperature, followed by stirring at room temperature for ~ 16 h. The reaction was quenched with $\text{HCl}_{(\text{aq})}$ 1 mol L^{-1} (25 mL) and transferred to a separation funnel. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 \times 25 mL). The combined organic phases were washed with $\text{NaCl}_{(\text{sat})}$ (1 \times 25 mL), dried over anhydrous MgSO_4 , filtered, and concentrated. Purification by flash column chromatography provided the desired product.

Phenyl 2-bromo-2,2-difluoroacetate (**1d**)

General procedure A was followed using phenol (5.64 g, 60.0 mmol), bromodifluoroacetic acid (12.6 g, 72.0 mmol), oxalyl chloride (5.7 mL, 66 mmol), DMF (0.23 mL, 3.0 mmol), CH_2Cl_2 (0.15 L), and Et_3N (10.0 mL, 72.0 mmol). Workup and chromatographic purification (100% hexanes) provided the title compound as a colorless oil (10.7 g, 71%).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.49 – 7.43 (m, 2H), 7.37 – 7.30 (m, 1H), 7.25 – 7.18 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 126 MHz) δ 158.1 (t, $J = 32.3$ Hz), 149.7, 130.0, 127.4, 120.6,

108.6 (t, $J = 314.4$ Hz). **^{19}F NMR** (CDCl_3 , 376 MHz) δ -61.6 (s, 2 F). **IR (ATR)** 3076, 1786, 1589, 1493, 1283, 1186, 1157, 1107, 945, 906, 839, 746, 704, 685 cm^{-1} . **HRMS** (APCI, m/z): calcd for $\text{C}_8\text{H}_5\text{BrF}_2\text{O}_2$ $[\text{M}]^+$ 249.9441, found 249.9433.

4-Methoxyphenyl 2-bromo-2,2-difluoroacetate (1e)

General procedure A was followed using 4-methoxyphenol (1.24 g, 10.0 mmol), bromodifluoroacetic acid (2.10 g, 12.0 mmol), oxalyl chloride (950 μL , 11.0 mmol), DMF (0.31 mL, 4.0 mmol), CH_2Cl_2 (0.030 L), and Et_3N (1.4 mL, 10 mmol). Workup and chromatographic purification (100% hexanes) provided the title compound as a colorless oil (1.57 g, 56%).

^1H NMR (CDCl_3 , 400 MHz) δ 7.17 – 7.10 (m, 2H), 6.98 – 6.91 (m, 2H), 3.82 (s, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR** (CDCl_3 , 126 MHz) δ 158.4 (t, $J = 32.1$ Hz), 158.3, 143.2, 121.4, 114.9, 108.7 (t, $J = 314.8$ Hz), 55.7. **^{19}F NMR** (CDCl_3 , 376 MHz) δ -61.5 (s, 2 F). **IR (ATR)** 3005, 2963, 2839, 1786, 1599, 1504, 1466, 1443, 1286, 1250, 1180, 1109, 1032, 947, 854, 812, 750, 692 cm^{-1} . **HRMS** (APCI, m/z): calcd for $\text{C}_9\text{H}_7\text{BrF}_2\text{O}_3$ $[\text{M}]^+$ 279.9547, found 279.9536.

[1,1'-biphenyl]-4-yl 2-bromo-2,2-difluoroacetate (1f)

General procedure A was followed using 4-phenylphenol (5.10 g, 30.0 mmol), bromodifluoroacetic acid (3.90 g, 20.0 mmol), oxalyl chloride (2.1 mL, 24 mmol), DMF (0.62 mL, 8.0 mmol) CH_2Cl_2 (0.060 L), and Et_3N (5.6 mL, 40 mmol). Instead of the work up described in General Procedure A, the reaction solvent was evaporated, and the crude mixture was washed with hexanes (100 mL). Next, a second filtration in SiO_2 (10% of EtOAc in hexanes) was performed to provide the title compound as a white solid (5.5 g, 84%), contaminated with ~6% of 4-phenylphenol (estimated by ^1H -NMR).

mp: 90 – 92 $^\circ\text{C}$ (decomp.). **^1H NMR** (CDCl_3 , 400 MHz) δ 7.66 (d, $J = 8.7$ Hz, 2H), 7.61 – 7.56 (m, 2H), 7.46 (t, $J = 7.4$ Hz, 2H), 7.38 (t, $J = 7.3$ Hz, 1H), 7.30 (d, $J = 8.7$ Hz, 2H). **$^{13}\text{C}\{^1\text{H}\}$ NMR** (CDCl_3 , 126 MHz) δ 158.1 (t, $J = 32.0$ Hz), 149.1, 140.7, 139.9, 129.1, 128.7, 127.9, 127.3, 120.9, 108.6 (t, $J = 314.3$ Hz). **^{19}F NMR** (CDCl_3 , 376 MHz) δ -61.6 (s, 2 F). **IR (ATR)** 3040, 1794, 1518, 1485, 1217, 1199, 1107, 933, 862, 758, 685 cm^{-1} . **HRMS** (APCI, m/z): calcd for $\text{C}_{14}\text{H}_9\text{BrF}_2\text{O}_2$ $[\text{M}]^+$ 325.9754, found 325.9748.

4-(trifluoromethyl)phenyl 2-bromo-2,2-difluoroacetate (1g)

General procedure A was followed using 4-trifluoromethylphenol (1.62 g, 10.0 mmol), bromodifluoroacetic acid (2.10 g, 12.0 mmol), oxalyl chloride (950 μL , 11.0 mmol), DMF (0.31 mL, 4.0 mmol), CH_2Cl_2 (0.030 L), and Et_3N (1.4 mL, 10 mmol). Workup and a fast filtration in SiO_2 (10% of EtOAc in hexanes) provided the title compound as a colorless oil (1.36 g, 43%).

^1H NMR (CDCl_3 , 400 MHz) δ 7.74 (d, $J = 8.4$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 1H). **$^{13}\text{C}\{^1\text{H}\}$ NMR** (CDCl_3 , 126 MHz) δ 157.6 (t, $J = 32.7$ Hz), 152.0, 129.9 (q, $J = 33.5$ Hz), 127.5 (q, $J = 3.6$ Hz), 123.7 (q, $J = 272.2$ Hz), 121.3, 115.6, 108.3 (t, $J = 314.3$ Hz). **^{19}F NMR** (CDCl_3 , 376 MHz) δ -61.9 (s, 2 F), -63.0 (s, 3 F). **IR (ATR)** 1792, 1612, 1510, 1417, 1323, 1279,

1201, 1165, 1105, 1064, 1018, 941, 866, 812, 704 cm^{-1} . **HRMS** (APCI, m/z): calcd for $\text{C}_9\text{H}_4\text{BrF}_5\text{O}_2$ $[\text{M}]^+$ 317.9315, found 317.9312.

2,6-dimethylphenyl 2-bromo-2,2-difluoroacetate (1h)

General procedure A was followed using 2,6-dimethylphenol (1.83 g, 15.0 mmol), bromodifluoroacetic acid (1.93 g, 11.0 mmol), oxalyl chloride (1.0 mL, 12 mmol), DMF (0.31 mL, 4.0 mmol) CH_2Cl_2 (0.030 L), and Et_3N (2.8 mL, 20 mmol). Workup and chromatographic purification (100% hexanes) provided the title compound as a colorless oil (1.6 g, 52%).

^1H NMR (400 MHz, CDCl_3) δ 7.16 – 7.08 (m, 3H), 2.22 (s, 6H). **$^{13}\text{C}\{^1\text{H}\}$ NMR** (126 MHz, CDCl_3) δ 198.5 (t, J = 31.88 Hz), 188.0, 171.0, 170.3, 168.3, 149.6 (t, J = 314.04 Hz), 57.2. **^{19}F NMR** (CDCl_3 , 376 MHz) δ –60.9 (s, 2 F). **IR (ATR)** 3047, 2927, 1786, 1475, 1286, 1167, 1147, 1111, 945, 841, 770, 700 cm^{-1} . **HRMS** (APCI, m/z): calcd for $\text{C}_{10}\text{H}_9\text{BrF}_2\text{O}_2$ $[\text{M}]^+$ 277.9754, found 277.9743.

S-phenyl 2-bromo-2,2-difluoroethanethioate (1i)

General procedure A was followed using 4-methoxyphenol (1.10 g, 10.0 mmol), bromodifluoroacetic acid (2.10 g, 12.0 mmol), oxalyl chloride (950 μL , 11.0 mmol), DMF (0.31 mL, 4.0 mmol) CH_2Cl_2 (0.030 L), and Et_3N (1.7 mL, 12 mmol). Workup and chromatographic purification (100% hexanes) provided the title compound as a colorless oil (0.4 g, 16%).

^1H NMR (400 MHz, CDCl_3) δ 7.67 – 7.39 (m, 1H). **$^{13}\text{C}\{^1\text{H}\}$ NMR** (126 MHz, CDCl_3) δ 185.6 (t, J = 30.8 Hz), 134.8, 130.9, 130.0, 123.8, 113.2, (t, J = 319.7 Hz). **^{19}F NMR** (CDCl_3 , 376 MHz) δ –59.5 (s, 2 F). **IR (ATR)** 3065, 1712, 1479, 1442, 1192, 1144, 979, 815, 744, 687 cm^{-1} . **HRMS** (APCI, m/z): calcd for $\text{C}_8\text{H}_5\text{BrF}_2\text{OS}$ $[\text{M}]^+$ 265.9213, found 265.9207.

2-bromo-2,2-difluoro-N-phenyl-N-tosylacetamide (1j)

General procedure A was followed using *N-p*-toluenesulfonylaniline¹⁸ (0.54 g, 2.2 mmol), bromodifluoroacetic acid (0.35 g, 2.0 mmol), oxalyl chloride (0.18 mL, 2.1 mmol), DMF (5.0 μL , 0.1 mmol) CH_2Cl_2 (4.0 mL), and Et_3N (0.39 mL, 2.8 mmol). Workup and chromatographic purification (20% EtOAc in hexanes) provided the title compound as a white solid (0.35 g, 43%).

mp: 136 – 138 $^\circ\text{C}$. **^1H NMR** (CDCl_3 , 400 MHz) δ 7.9 (d, J = 8.39 Hz, 2H), 7.6 – 7.5 (m, 1H), 7.5 – 7.4 (m, 2H), 7.4 (d, J = 8.66 Hz, 2H), 7.3 (d, J = 7.65 Hz, 2H), 2.5 (s, 3H). **$^{13}\text{C}\{^1\text{H}\}$ NMR** (CDCl_3 , 126 MHz) δ 157.9 (t, J = 28.19 Hz), 146.4, 134.3, 133.4, 131.1, 131.0, 129.9, 129.9, 129.4, 110.6 (t, J = 319.13 Hz), 22.0. **^{19}F NMR** (CDCl_3 , 376 MHz) δ –54.5 (s, 2 F). **IR (ATR)** 1720, 1361, 1166, 1117, 1084, 883, 398, 671, 572, 543 cm^{-1} . **HRMS** (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{12}\text{BrF}_2\text{NO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 425.9587, found 425.9557.

Initial Screening and Optimization of Reaction Conditions

Additive Screening Experiment

Experimental Procedure: A 1 dram vial sealed with PTFE septum under N₂ was charged with cinnamyl bromodifluoroacetate (**3a**) (58 mg, 0.20 mmol), KF (17 mg, 0.30 mmol), additive (0.20 mmol), DMF (0.10 mL), and a magnetic stir bar. The vial was placed on a pre-heated reaction block at 50 °C, and an aliquot of the “Stock Solution of Activated Catalyst” (*see infra*) (0.10 mL) was transferred to the vial *via* syringe. After heating at 50 °C for 14 h, the vial was removed from the heating block and cooled to room temperature. Next, the reaction mixture was diluted with EtOAc (2 mL), and dodecane (45 µL, 0.20 mmol) was injected as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot was taken from the vial, analyzed by GC-FID, and quantified using a standard curve. Results are reported based on GC-FID yields.

Experimental Procedure for the Preparation of “Stock Solution of Activated Catalyst”: CuI (57 mg, 0.30 mmol), NaO₂CCF₂Br (0.15 g, 0.75 mmol) and KF (87 mg, 1.5 mmol) were added to a 10 mL round bottom flask. The flask was attached to a Schlenk line and evacuated and backfilled with N₂ (3x). DMF (1.5 mL) was injected and the mixture was heated in an oil bath at 50 °C for 10 min.

General Optimization

General Procedure B: A 1 dram vial was charged with CuI (1.9 mg, 0.010 mmol), KF (12 mg, 0.20 mmol), DMEDA (1.2 µL, 0.011 mmol), 0.10 mL of a freshly prepared solution of bromodifluoroacetic acid (8.8 mg, 0.050 mmol) in DMF (0.2 mL, final concentration = 0.25 mol L⁻¹), and a magnetic stir bar. The reaction mixture was stirred for 2–5 min at room temperature until a blue/purple suspension formed, and at 50 °C until the color changed to light yellow (~10 min). Next, the allylic alcohol (0.100 mmol) and phenyl bromodifluoroacetate (50.1 mg, 0.200 mmol) were dissolved in 0.1 mL of the bromodifluoroacetic solution in DMF, and the resulting solution was added to the reaction. Subsequently, the reaction vial was sealed with a PTFE-lined screw cap, and transferred out of the glove box. The sealed vial was placed on a pre-heated reaction block at 25 °C and stirred for 24–48 h. Next, the reaction mixture was diluted with EtOAc (~3.0 mL), and 0.100 mmol naphthalene was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot (130–150 µL) was taken from the vial, analyzed by GC-FID, and quantified using a standard curve. Results are reported based on GC-FID yields. Alternatively (or to double-check results), α,α,α-trifluorotoluene (12.3 µL, 0.100 mmol) was added as an internal standard, and the reaction mixture was stirred at room temperature for 5 minutes to ensure thorough mixing. An aliquot was taken from the vial for ¹⁹F NMR analysis. Results are reported based on ¹⁹F NMR yields.

Experimental Details and Characterization of Trifluoromethyl Compounds

Allyl Trifluoromethanes (Table 2)

General Procedure C: A 1 dram vial was charged with CuI (9.5 mg, 0.050 mmol), KF (58 mg, 1.0 mmol), DMEDA (5.9 µL, 0.055 mmol), 0.30 mL of a freshly prepared solution of

bromodifluoroacetic acid (44 mg, 0.25 mmol) in DMF (1.00 mL, final concentration = 0.25 mol L⁻¹), and a magnetic stir bar. The reaction mixture was stirred for 2–5 min at room temperature until a blue/purple suspension formed, and at 50 °C until the color changed to light yellow (~10 min). Next, the allylic alcohol (0.500 mmol) and phenyl bromodifluoroacetate (251 mg, 1.00 mmol) were dissolved in 0.70 mL of the bromodifluoroacetic acid solution in DMF, and the resulting solution was added to the reaction. Subsequently, the reaction vial was sealed with a PTFE-lined screw cap, and transferred out of the glove box. The sealed vial was placed on a pre-heated reaction block at 25 °C and stirred for 36–48 h. Next, the reaction mixture was diluted with Et₂O (~3.0 mL). α,α,α -Trifluorotoluene (30 μ L, 0.25 mmol) was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot was taken from the vial for ¹⁹F NMR analysis. After determining the ¹⁹F NMR yield, the aliquot was recombined with the reaction mixture. Work up (Method A or B, see Note 1 below) and purification of the crude mixture through flash column chromatography provided the desired product (see Note 2).

Method A: The crude reaction was further diluted with 50 mL of Et₂O, and sequentially washed with H₂O (3 \times 10 mL), 1M NaOH (2 \times 5 mL), H₂O (1 \times 10 mL) and NaCl_(sat) (1 \times 10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure (see Note 2).

Method B: Some non-polar products co-eluted with phenyl bromodifluoroacetate during the chromatographic purification and required an alternative isolation procedure. The crude reaction was diluted with THF (10 mL), 1M NaOH (0.5 mL) was added, and the mixture was stirred for 2 h at room temperature. Next, the crude reaction was further diluted with 50 mL of Et₂O, and sequentially washed with H₂O (3 \times 10 mL) and NaCl_(sat) (1 \times 10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure (see Note 2).

(E)-(4,4,4-trifluorobut-1-en-1-yl)benzene (4a)

General procedure C was followed using (*E*)-3-phenylprop-2-en-1-ol (**2a**) (0.67 g, 5.0 mmol), phenyl bromodifluoroacetate (**1d**) (2.5 g, 10 mmol), CuI (95 mg, 0.50 mmol), DMEDA (59 μ L, 0.55 mmol), bromodifluoroacetic acid (0.44 g, 2.5 mmol), KF (0.58 g, 10 mmol) and DMF (10.0 mL). The reaction was stirred for 38 h. Work up according to Method A, except for the washing with 1M NaOH. Chromatographic purification (pentane) afforded the title compound as a colorless oil (0.70 g, 75%) containing residual CH₂Cl₂ (~0.14 g, estimated by ¹H-NMR). Spectroscopic data agreed with the previous report.²⁰

(E)-1-methoxy-4-(4,4,4-trifluorobut-1-en-1-yl)benzene (4b)

General procedure C was followed using (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (**2b**) (82 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050

Note 1: Two methods for the isolation of the products were used:

Note 2: Extra care was taken to isolate products of lower molecular weight due to volatility. For NMR analysis of the crude reaction mixture, work up and purification using low boiling point solvents was preferred (Et₂O, CH₂Cl₂ or pentane). Solvent evaporation was done under pressure of ~60–100 Torr and water-bath at 15–25 °C.

mmol), DMEDA (5.9 μ L, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 44 h. Work up (Method A) and chromatographic purification (0–5% Et₂O in pentane) afforded the title compound as a colorless oil (85 mg, 78%). Spectroscopic data agreed with the previous report.^{8a}

(E)-1-nitro-4-(4,4,4-trifluorobut-1-en-1-yl)benzene (4c)

General procedure C was followed using (*E*)-3-(4-nitrophenyl)prop-2-en-1-ol (**2c**) (90 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), DMEDA (5.9 μ L, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 39 h. Work up (Method A) and chromatographic purification (0–10% EtOAc in hexanes) afforded the title compound as a yellow solid (83 mg, 72%). Spectroscopic data agreed with the previous report.^{8a}

(E)-1-fluoro-4-(4,4,4-trifluorobut-1-en-1-yl)benzene (4d)

General procedure C was followed using (*E*)-3-(4-fluorophenyl)prop-2-en-1-ol^{8a} (**2d**) (76 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), DMEDA (5.9 μ L, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 44 h. Work up (Method A) and chromatographic purification (pentane) afforded the title compound as a colorless oil (66 mg, 64%). Spectroscopic data agreed with the previous report.^{8a}

(E)-1-bromo-3-(4,4,4-trifluorobut-1-en-1-yl)benzene (4e)

General procedure C was followed using (*E*)-3-(3-bromophenyl)prop-2-en-1-ol^{8a} (**2e**) (106 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), DMEDA (5.9 μ L, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 44 h. Work up according to Method A, except for the washing with 1M NaOH. Chromatographic purification (pentane) afforded the title compound as a colorless oil (81 mg, 61%). Spectroscopic data agreed with the previous report.^{8a}

(E)-(((5,5-trifluoropent-2-en-1-yl)oxy)methyl)benzene (4f)

General procedure C was followed using (*Z*)-4-(benzyloxy)but-2-en-1-ol (**2f**) (89 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), DMEDA (5.9 μ L, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 41 h. Work up (Method A) and chromatographic purification (0–5% Et₂O in pentane or 0–5% EtOAc in hexanes) afforded the title compound as a colorless oil (94 mg, 81%). Spectroscopic data agreed with the previous report.^{8a}

1-(2,2,2-Trifluoroethyl)cyclopent-1-ene (4g)

General procedure C was followed using cyclopent-1-en-1-ylmethanol (**2g**) (49 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), DMEDA (5.9 μ L, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg,

1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 37 h. The product was too volatile for isolation. The yield was determined by ^{19}F -NMR using α,α,α -trifluorotoluene. The identity of the product was confirmed by GC-MS analysis.

^{19}F NMR (CDCl_3 , 376 MHz) δ -65.9 (t, J = 11.5 Hz, 3F). GC-MS 150 (15), 67 (100).

1-(2,2,2-Trifluoroethyl)cyclohex-1-ene

General procedure C was followed using cyclohex-1-en-1-ylmethanol (**2h**) (49 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), DMEDA (5.9 μL , 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 37 h. Product was too volatile for isolation. Yield determined by ^{19}F -NMR using α,α,α -trifluorotoluene. The identity of the product was confirmed by GC-MS analysis.

^{19}F NMR (CDCl_3 , 376 MHz) δ -65.9 (t, J = 11.2 Hz, 3F). GC-MS 164 (50), 149 (45), 136 (35), 81 (100), 67 (65).

4-(prop-1-en-2-yl)-1-(2,2,2-trifluoroethyl)cyclohex-1-ene (4i)

General procedure C was followed using perillyl alcohol (**2i**) (76 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), DMEDA (5.9 μL , 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 42 h. Work up (Method B) and chromatographic purification (pentane) afforded the title compound as a colorless oil (58 mg, 57%). Spectroscopic data agreed with the previous report.²¹

Allenyl Trifluoromethanes (Table 3)

General Procedure D: A 1 dram vial was charged with CuI (9.5 mg, 0.050 mmol), KF (58 mg, 1.0 mmol), 1,10-phenantroline (9.9 mg, 0.055 mmol), 0.30 mL of a freshly prepared solution of bromodifluoroacetic acid (44 mg, 0.25 mmol) in DMF (1.00 mL, final concentration = 0.25 mol L⁻¹), and a magnetic stir bar. The reaction mixture was stirred for 2–5 min at room temperature until a blue/purple suspension formed, and at 50 °C until the color changed to light yellow (~10 min). Next, the propargylic alcohol (0.500 mmol) and phenyl bromodifluoroacetate (251 mg, 1.00 mmol) were dissolved in 0.70 mL of the bromodifluoroacetic acid solution in DMF, and the resulting solution was added to the reaction. Subsequently, the reaction vial was sealed with a PTFE-lined screw cap, and transferred out of the glove box. The sealed vial was placed on a pre-heated reaction block at 50 °C and stirred for 24–38 h. Next, the reaction mixture was diluted with Et₂O (~3.0 mL). α,α,α -Trifluorotoluene (30 μL , 0.25 mmol) was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot was taken from the vial for ^{19}F NMR analysis. After determining the ^{19}F NMR yield, the aliquot was recombined with the reaction mixture. The crude reaction was further diluted with 50 mL of Et₂O, and sequentially washed with H₂O (3 \times 10 mL), 1M NaOH (2 \times 5 mL), H₂O (1 \times 10 mL) and NaCl_(sat) (1 \times 10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the crude mixture through flash column chromatography provided the desired product

2-(1,1,1-trifluorobuta-2,3-dien-2-yl)naphthalene (6a)

General procedure D was followed using 3-(naphthalen-2-yl)prop-2-yn-1-ol^{8c} (**5a**) (91 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), 1,10-phenantroline (9.9 mg, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 37 h at 50 °C. Work up and chromatographic purification (pentane) afforded the title compound as a colorless oil (82 mg, 69%). Spectroscopic data agreed with the previous report.^{8c}

1-Methoxy-4-nitro-2-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (6b)

General procedure D was followed using methyl 3-(3-hydroxyprop-1-yn-1-yl)benzoate^{8c} (**5b**) (104 mg, 0.500 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), 1,10-phenantroline (9.9 mg, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 37 h at 50 °C. Work up and chromatographic purification (0–10% EtOAc in hexanes) afforded the title compound as a yellow oil (85 mg, 66%). Spectroscopic data agreed with the previous report.^{8c}

Methyl 3-(3-hydroxyprop-1-yn-1-yl)benzoate (6c)

General procedure D was followed using methyl 3-(3-hydroxyprop-1-yn-1-yl)benzoate^{8c} (**5c**) (190 mg, 1.00 mmol), phenyl bromodifluoroacetate (**1d**) (0.50 g, 2.0 mmol), CuI (19 mg, 0.10 mmol), 1,10-phenantroline (20 mg, 0.11 mmol), bromodifluoroacetic acid (88 mg, 0.50 mmol), KF (116 mg, 2.0 mmol) and DMF (2.0 mL). The reaction was stirred for 24 h at 50 °C. Work up and chromatographic purification (0–10% EtOAc in hexanes) afforded the title compound as a yellow oil (180 mg, 70%). Spectroscopic data agreed with the previous report.^{8c}

***tert*-Butyl 2-(1,1,1-trifluorobuta-2,3-dien-2-yl)-1H-indole-1-carboxylate (6d)**

General procedure D was followed using *tert*-butyl 2-(3-hydroxyprop-1-yn-1-yl)-1H-indole-1-carboxylate^{8c} (**5d**) (108 mg, 0.40 mmol), phenyl bromodifluoroacetate (**1d**) (0.20 g, 0.80 mmol), CuI (7.7 mg, 0.040 mmol), 1,10-phenantroline (7.9 mg, 0.088 mmol), bromodifluoroacetic acid (35 mg, 0.20 mmol), KF (46 mg, 0.8 mmol) and DMF (0.80 mL). The reaction was stirred for 24 h at 50 °C. Work up and chromatographic purification (0–10% EtOAc in hexanes) afforded the title compound as a yellow oil (53 mg, 41%). Spectroscopic data agreed with the previous report.^{8c}

2,2,2-Trifluoro-N-(4-(1,1,1-trifluorobuta-2,3-dien-2-yl)phenyl)acetamide (6e)

General procedure D was followed using 2,2,2-trifluoro-N-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)acetamide^{8c} (**6e**) (122 mg, 0.500 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), 1,10-phenantroline (9.9 mg, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.50 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 24 h at 50 °C. Work up and chromatographic purification (0–20% EtOAc in hexanes) afforded the title compound still contaminated with ~10% of phenol. After washing with 1M NaOH (3 × 5 mL), the pure product was obtained as an off-white solid (81 mg, 55%). Spectroscopic data agreed with the previous report.^{8c}

1,2-dichloro-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (6f)

General procedure D was followed using 3-(3,4-dichlorophenyl)prop-2-yn-1-ol^{8c} (**5f**) (122 mg, 0.500 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), 1,10-phenantroline (9.9 mg, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.50 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 24 h at 50 °C. Work up and chromatographic purification (0–20% EtOAc in hexanes) afforded the title compound still contaminated with ~10% of phenol. After washing with 1M NaOH (3 × 5 mL), the pure product was obtained as a yellow solid (99 mg, 67%). Spectroscopic data agreed with the previous report.^{8c}

Benzyl Trifluoromethanes (Table 4)

General Procedure E: A 1 dram vial was charged with CuI (19 mg, 0.10 mmol), KF (0.12 mg, 2.0 mmol), KI (21 mg, 0.12 mmol), and a magnetic stir bar. Next, the benzylic alcohol (0.500 mmol) and phenyl bromodifluoroacetate (251 mg, 1.00 mmol) were dissolved in DMF (0.25 mL) and MeCN (0.25 mL), and the resulting solution was added to the reaction. Subsequently, the reaction vial was sealed with a PTFE-lined screw cap, and transferred out of the glove box. The sealed vial was placed on a pre-heated reaction block at 40 °C and stirred for 30 min. Next, it was transferred to a second pre-heated reaction block at 70 °C and stirred for 24 h. Next, the reaction was cooled to room temperature, and diluted with Et₂O (~3.0 mL). α,α,α -Trifluorotoluene (30 μ L, 0.25 mmol) was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot was taken from the vial for ¹⁹F NMR analysis. After determining the ¹⁹F NMR yield, the aliquot was recombined with the reaction mixture. The crude reaction was further diluted with 50 mL of Et₂O, and sequentially washed with H₂O (3 × 10 mL), 1M NaOH (2 × 5 mL) or Na₂CO₃ (3 × 5 mL), H₂O (1 × 10 mL) and NaCl_(sat) (1 × 10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the crude mixture through flash column chromatography provided the desired product

2-(2,2,2-trifluoroethyl)naphthalene (8a)

General procedure E was followed using naphthalen-2-ylmethanol (**7a**) (79 mg, 0.500 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (19 mg, 0.10 mmol), methyl bromodifluoroacetate (38 mg, 0.20 mmol), KI (21 mg, 0.12 mmol), KF (0.12 g, 2.0 mmol) DMF (0.25 mL) and MeCN (0.25 mL). The reaction was stirred for 24 h at 70 °C. Work up and chromatographic purification (pentane) afforded the product as a white solid (78 mg, 74%). Spectroscopic data agreed with the previous report.^{8d}

1-(benzyloxy)-2-methoxy-4-(2,2,2-trifluoroethyl)benzene (8b)

General procedure E was followed using (4-(benzyloxy)-3-methoxyphenyl)methanol (**7b**) (123 mg, 0.500 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (19 mg, 0.10 mmol), methyl bromodifluoroacetate (38 mg, 0.20 mmol), KI (21 mg, 0.12 mmol), KF (0.12 g, 2.0 mmol) DMF (0.25 mL) and MeCN (0.25 mL). The reaction was stirred for 24 h at 70 °C. Work up and chromatographic purification (0–10% EtOAc in hexanes) afforded the product as a white solid (93 mg, 62%). Spectroscopic data agreed with the previous report.²²

1-Tosyl-3-(2,2,2-trifluoroethyl)-1H-indole (8c)

General procedure E was followed using (1-tosyl-1H-indol-3-yl)methanol²³ (**7c**) (301 mg, 1.00 mmol), phenyl bromodifluoroacetate (**1d**) (0.50 g, 2.0 mmol), CuI (38 mg, 0.20 mmol), methyl bromodifluoroacetate (76 mg, 0.40 mmol), KI (42 mg, 0.25 mmol), KF (232 mg, 4.0 mmol), DMF (0.50 mL) and MeCN (0.50 mL). The reaction was stirred for 24 h at 70 °C. Work up and chromatographic purification (0–5% EtOAc in hexanes) afforded the product as a white solid (217 mg, 61%). Spectroscopic data agreed with the previous report.²⁴

(1-phenyl-1H-pyrazol-4-yl)methanol (8d)

General procedure E was followed using (1-phenyl-1H-pyrazol-4-yl)methanol^{8d} (**7d**) (87 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (19 mg, 0.10 mmol), methyl bromodifluoroacetate (38 mg, 0.20 mmol), KI (21 mg, 0.12 mmol), KF (0.12 g, 2.0 mmol), DMF (0.25 mL) and MeCN (0.25 mL). Work up and chromatographic purification (10% EtOAc in hexanes) afforded the title compound as a white solid (43 mg, 39%). Spectroscopic data agreed with the previous report^{8d}

1-Methyl-3-(2,2,2-trifluoroethyl)-1H-indazole (8e)

General procedure E was followed using (1-methyl-1H-indazol-3-yl)methanol¹⁹ (**7e**) (81 mg, 0.50 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (19 mg, 0.10 mmol), methyl bromodifluoroacetate (38 mg, 0.20 mmol), KI (21 mg, 0.12 mmol), KF (0.12 g, 2.0 mmol), DMF (0.25 mL) and MeCN (0.25 mL). Work up and chromatographic purification (10% EtOAc in hexanes) afforded the title compound as a light-yellow solid (43 mg, 39%).

mp: 61 – 63 °C. **¹H NMR** (CDCl₃, 400 MHz) δ 7.71 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.24 – 7.16 (m, 1H), 4.07 (s, 3H), 3.79 (q, *J* = 10.69 Hz, 2H). **¹³C{¹H} NMR** (CDCl₃, 126 MHz) δ 141.1, 134.27 (q, *J* = 3.5 Hz), 126.7, 125.15 (q, *J* = 276.4 Hz), 123.2, 121.0, 120.3, 109.3, 35.6, 32.97 (q, *J* = 31.5 Hz). **¹⁹F NMR** (CDCl₃, 376 MHz) δ –65.4 (t, *J* = 10.6 Hz). **IR (ATR)** 3065, 2978, 2939, 2854, 1618, 1504, 1348, 1256, 1092, 918, 736 cm⁻¹. **HRMS** (ESI, *m/z*): calcd for C₁₀H₁₀F₃N₂ [M+H]⁺ 215.0796, found 215.0793.

Synthetic Applications (Scheme 1)

(E)-1-(methylsulfonyl)-4-(4,4,4-trifluoro-2-methylbut-1-en-1-yl)benzene (10)

General procedure C was followed using (*E*)-2-methyl-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-ol (**9**),¹¹ (113 mg, 0.500 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0 mmol), CuI (9.5 mg, 0.050 mmol), DMEDA (5.9 μL, 0.055 mmol), bromodifluoroacetic acid (44 mg, 0.25 mmol), KF (58 mg, 1.0 mmol) and DMF (1.0 mL). The reaction was stirred for 44 h. Work up and chromatographic purification (0–30% EtOAc in hexanes) afforded the title compound as a colorless oil (105 mg, 75%). Spectroscopic data agreed with the previous report.^{11b}

5-(furan-2-yl)-1-methyl-3-(2,2,2-trifluoroethyl)-1H-pyrazole (12)

General procedure E was followed using (5-(furan-2-yl)-1-methyl-1H-pyrazol-3-yl)methanol^{12a} (**11**) (89 mg, 0.500 mmol), phenyl bromodifluoroacetate (**1d**) (0.25 g, 1.0

mmol), CuI (19 mg, 0.10 mmol), methyl bromodifluoroacetate (38 mg, 0.20 mmol), KI (21 mg, 0.12 mmol), KF (0.12 g, 2.0 mmol), DMF (0.25 mL) and MeCN (0.25 mL). Work up according to General Procedure E was done using Na₂CO₃ (3 × 5 mL), because a decrease in the yield to 43% was observed when 1M NaOH was used. Chromatographic purification (0–30% EtOAc in hexanes) afforded the title compound as a light yellow oil (67 mg, 57%). Spectroscopic data agreed with the previous report.^{8d, 12a}

Stability of the Phenyl Bromodifluoroacetate (1d)

The stability of phenyl bromodifluoroacetate (**1d**) was tested by storing it in 1-dram vials sealed with a PTFE-lined screw cap under three distinct conditions, namely 1) on the bench, 2) in a desiccator, and 3) in the freezer. The stability of the compound was evaluated by ¹H- and ¹⁹F-NMR analysis (Figure S1 and S2), as well as the deoxytrifluoromethylation reaction of cinnamyl alcohol (**2a**) (Scheme S1). The compound was stable in all situations and showed no signs of decomposition by NMR. The reaction yields decreased as the reagent aged. However, the reaction yields were still satisfactory even after 6–8 months. During this work, the only decomposition pathway observed was the hydrolysis of the compound not properly protected against residual moisture. No light sensitivity was observed.

Mechanistic Experiments (Scheme 2)

Stability of Phenyl Bromodifluoroacetate (1d) Under Reaction Conditions

In the absence of alcohol, phenyl bromodifluoroacetate (**1d**) did not decompose when it was submitted to the standard reaction conditions, with either DMEDA or Phen as ligands. Test reactions were setup according to the General Procedure C (or D, if ligand was Phen), but the alcohol was not added. Both reactions were stirred at 50 °C for 24 hours, and then analyzed by ¹⁹F-NMR using α,α,α-trifluorotoluene as standard.

Study of the Formation of Putative “Active Ester Intermediate” *In Situ*

Experimental Procedure for Addition of KF in the Presence of BDFA: Inside the glovebox, a 1 dram vial was charged with the cinnamyl alcohol (**2a**) (67 mg, 0.50 mmol) and phenyl bromodifluoroacetate (**1d**) (251 mg, 1.00 mmol), naphthalene (12.8 mg, 0.100 mmol), 1.00 mL of a freshly prepared solution of bromodifluoroacetic acid (44 mg, 0.25 mmol) in DMF (1.00 mL, final concentration = 0.25 mol L⁻¹), and a magnetic stir bar. The reaction mixture was stirred for 60 min at 25 °C. Next, KF (58 mg, 1.0 mmol) was added, and the reaction mixture was kept stirring at 25 °C. During the whole experiment, 50 μL aliquots were taken every 15–25 min and quenched with a few drops of Et₂O. The samples were analyzed using GC-FID, and standard curves were used to calculate amount of each reaction component as a function of time.

Experimental Procedure for Addition of KF in the Absence of BDFA: Inside the glovebox, a 1 dram vial was charged with the cinnamyl alcohol (**2a**) (67 mg, 0.50 mmol) and phenyl bromodifluoroacetate (**1d**) (251 mg, 1.00 mmol), naphthalene (12.8 mg, 0.100 mmol), 1.00 mL of DMF (1.00 mL, final concentration = 0.25 mol L⁻¹), and a magnetic stir bar. The reaction mixture was stirred for 45 min at 25 °C. Next, KF (58 mg, 1.0 mmol) was added, and the reaction mixture was kept stirring for another 60 min at 25 °C. Next,

bromodifluoroacetic acid (44 mg, 0.25 mmol) was added, and the reaction mixture was kept stirring at 25 °C. During the whole experiment, 50 µL aliquots were taken every 15–25 min and quenched with a few drops of Et₂O. The samples were analyzed using GC-FID, and standard curves were used to calculate amount of each reaction component as a function of time.

Time-Course Analysis of the Reaction

Experimental Procedure: Inside the glovebox, deoxytrifluoromethylation reaction of cinnamyl alcohol **2a** was prepared according General Procedure C. Naphthalene (12.8 mg, 0.100 mmol) was used as the internal standard. During the whole experiment, 50 µL aliquots were taken every 15–60 min and quenched with a few drops of Et₂O. The samples were analyzed using GC-FID, and standard curves were used to calculate the amount of each reaction component as a function of time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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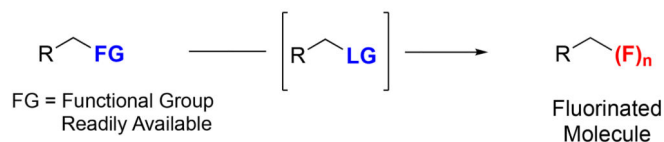
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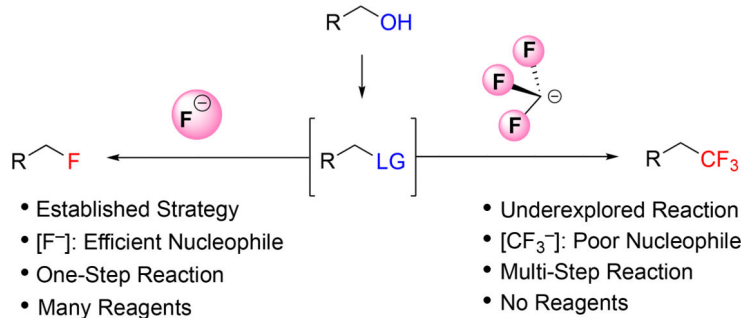
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A) Conceptual Framework: Incorporation of Fluorine through Readily Available Functional Groups



B) Deoxyfluorination vs. Deoxytrifluoromethylation



C) This Work: Catalytic One-Step Deoxytrifluoromethylation

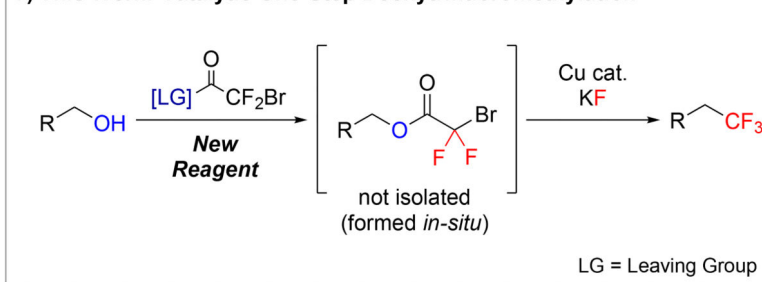
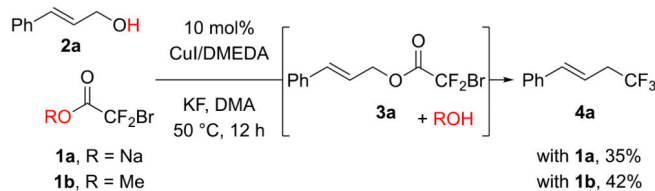


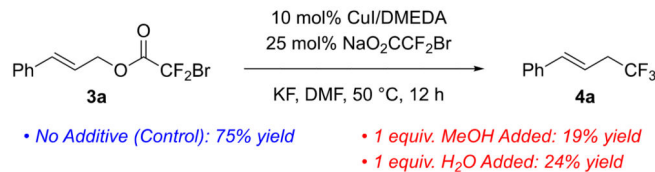
Figure 1:

a) Methods that convert common functional groups to fluorinated motifs are valuable to discovery and process chemists. b) While protocols that directly transform alcohols to alkyl fluorides are widely used, analogous one-pot methods to access trifluoromethanes from alcohols are rare. c) Development of a new reagent enables Cu-catalyzed deoxytrifluoromethylation.

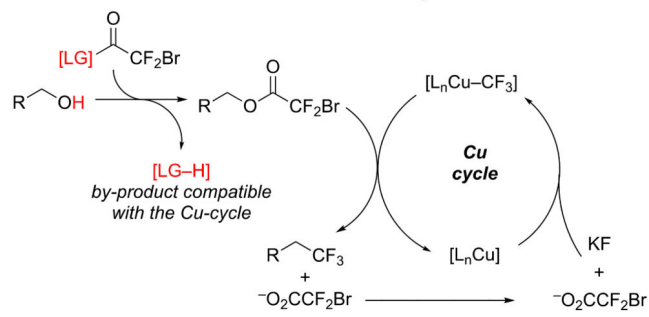
A) Cu-catalyzed Deoxytrifluoromethylation Using Commercially Available Bromodifluoroacetate Provided Low Yields After Optimization



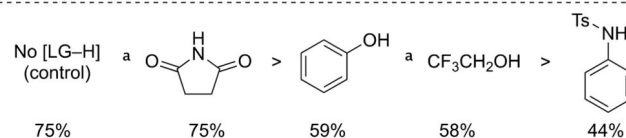
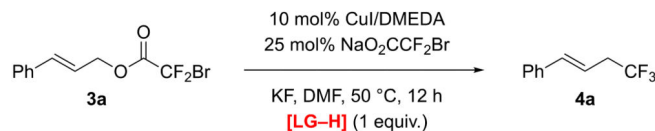
B) MeOH / H₂O Impairs Cu-catalyzed Decarboxylative Trifluoromethylation



C) Ideal Deoxytrifluoromethylation Reagent Releases Leaving Group that Does Not Interfere with Cu-cat. Trifluoromethylation



D) Screen to Identify Benign Leaving Groups



Representative Structures of [LG-H] That Provided Low Yields (typically <40%)

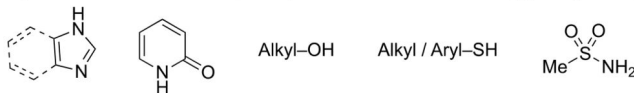
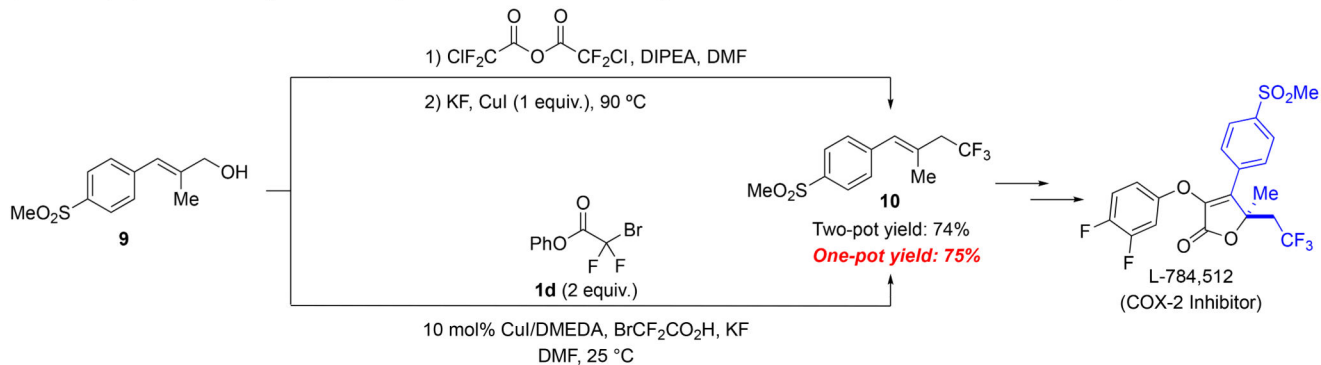
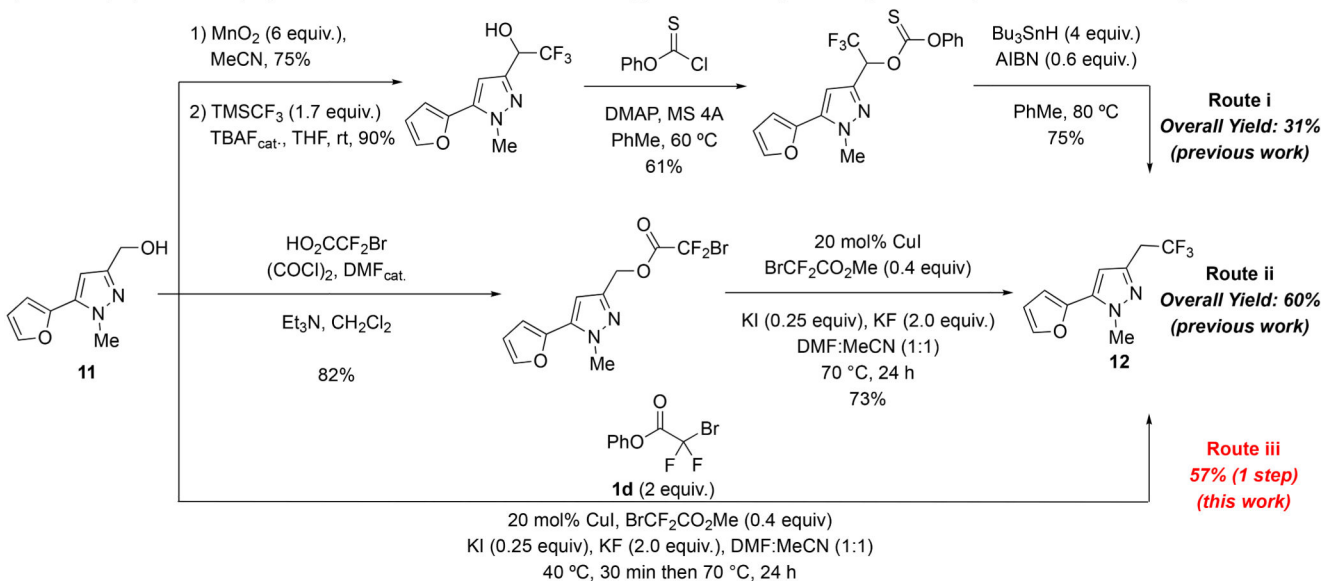


Figure 2:
Design of Deoxytrifluoromethylation Reagent Required Identification of Benign Leaving Group.

A) PhBDFA (1d) Streamlines Synthesis of Key Intermediate 10 Under Catalytic Conditions *en route* to COX-2 Inhibitor in L-784,512



B) PhBDFA (1d) Affords Key Pyrazole 12 *en route* to Acaricidal Tebufenpyrad in One-Step Avoiding Redox Steps and Toxic Metal Reagents



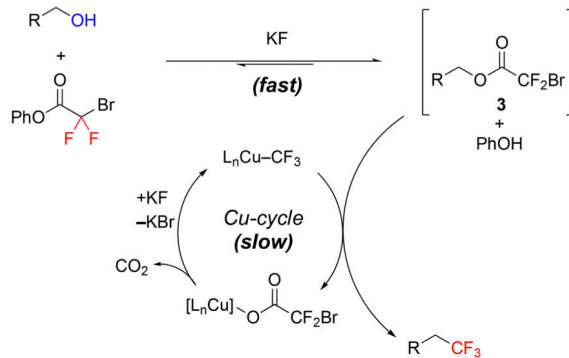
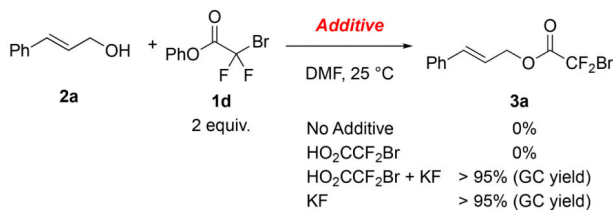
C) One-Step Catalytic Deoxytrifluoromethylation Performs on a Multigram-Scale



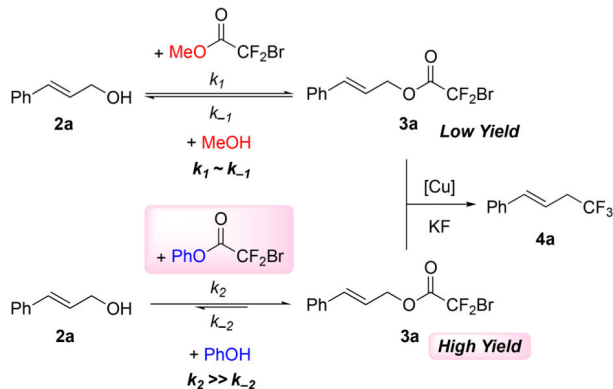
Scheme 1:

Catalytic One-Step Deoxytrifluoromethylation Reaction: (a–b) Shortens the Synthesis of Known Intermediates to the Synthesis of COX-2 Inhibitor L-784,512 and a Fluorinated Analog of Tebufenpyrad; (c) Is Equally Efficient on Multi-Gram Scale.

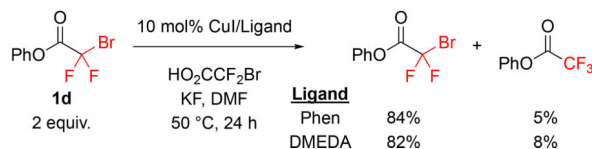
A) Proposed Mechanism

B) KF Facilitates the *In Situ* Formation of the Active Ester 3a

C) PhBDFA (1d) Increases Concentration of Active Ester 3a



D) PhBDFA (1d) Is Stable Under Reaction Conditions



Scheme 2:

Control Experiments Suggest Rapid Formation of Bromodifluoroacetate **3a** Prior to a Slow Cu-catalyzed Decarboxylative Trifluoromethylation Reaction

Table 1:

Phenyl Bromodifluoroacetate (PhBDFa) Provided the Trifluoromethyl Product **4a** in Higher Yield than Other Bromodifluoroacylating Reagents

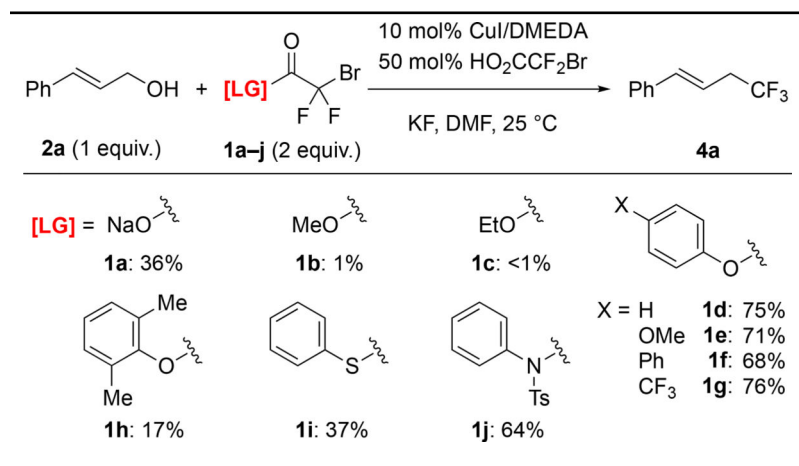
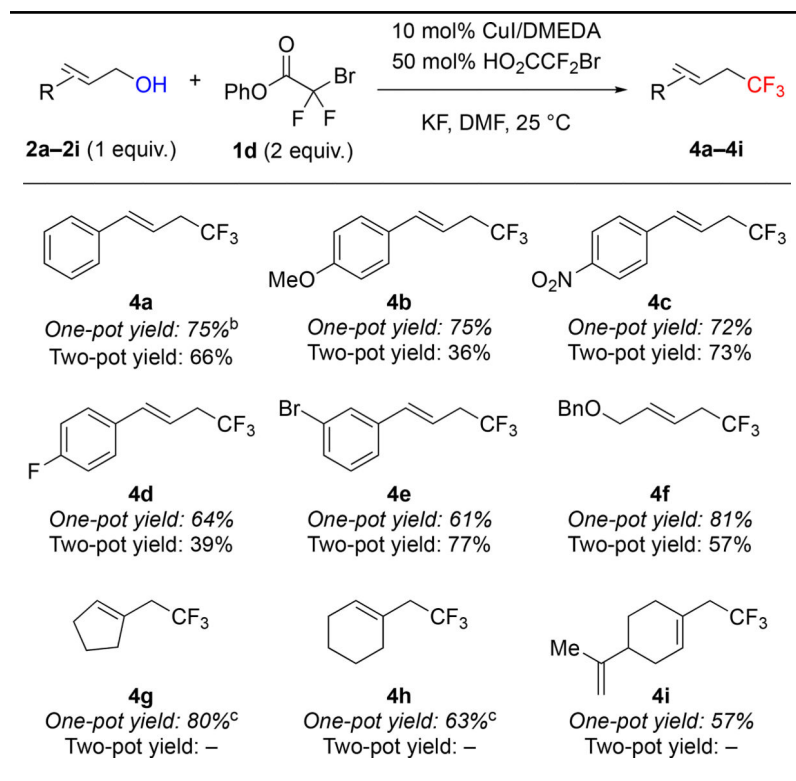


Table 2:Phenyl Bromodifluoroacetate Enables Cu-catalyzed One-pot Deoxytrifluoromethylation of Allylic Alcohols^a

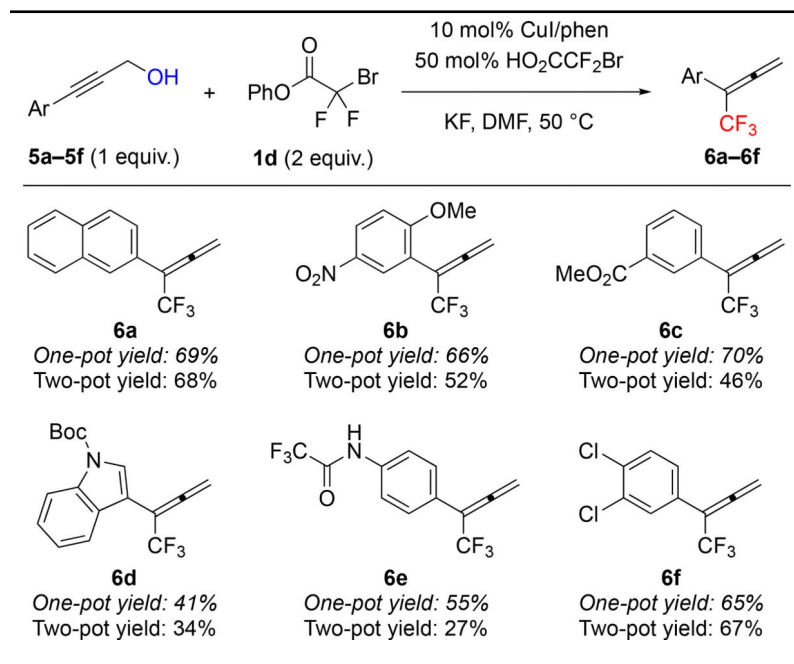
^aStandard reaction conditions: **2a–2i** (0.50 mmol), **1d** (1.0 mmol), CuI (0.050 mmol), DMEDA (0.055 mmol), HO₂CCF₂Br (0.25 mmol), KF (1.0 mmol), DMF (1.0 mL), 25 °C. Yield of material after chromatographic purification. For comparison, two-pot yields reported from reference 8a.

^bReaction conducted on 5.0 mmol scale.

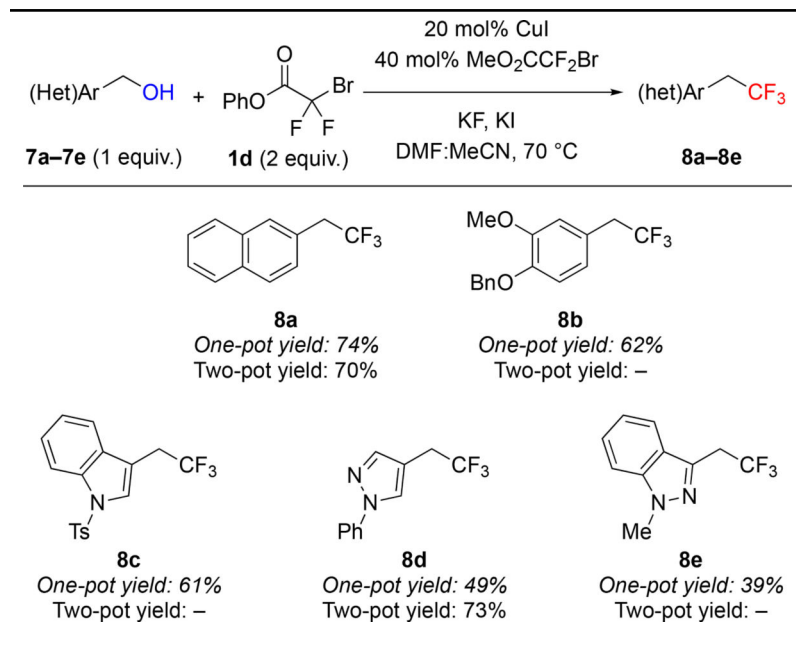
^cYield determined by ¹⁹F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard.

Table 3:

Phenyl Bromodifluoroacetate Enables Cu-catalyzed One-pot Deoxytrifluoromethylation of Propargylic Alcohols^a



^aStandard reaction conditions: **5a–5f** (0.50 mmol), **1d** (1.0 mmol), CuI (0.050 mmol), 1,10-phenanthroline (0.055 mmol), HO₂CCF₂Br (0.25 mmol), KF (1.0 mmol), DMF (1.0 mL), 50 °C. Yield of material after chromatographic purification. For comparison, two-pot yields reported from reference 8c.

Table 4:Phenyl Bromodifluoroacetate Enables Cu-catalyzed One-pot Deoxytrifluoromethylation of Benzylic Alcohols^a

^aStandard reaction conditions: **7a-7e** (0.50 mmol), **1d** (1.0 mmol), CuI (0.10 mmol), MeO₂CCF₂Br (0.20 mmol), KI (0.12 mmol), KF (2.0 mmol), DMF (0.25 mL), MeCN (0.25 mL), 70 °C. For comparison, two-pot yields reported from reference 8d.