Copper-Catalyzed Decarboxylative Trifluoromethylation Reactions

By

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Abstract

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The University of Kansas

Trifluoromethanes play an important role in medicinal chemistry, and methods that enable the rapid synthesis of trifluoromethanes from common functional groups are essential for the synthesis of bioactive compounds. We describe a series of Cu-catalyzed decarboxylative trifluoromethylation reactions that enable the conversion of alcohols to trifluoromethanes. These reactions rely on the efficient generation of nucleophilic "Cu–CF_3", and Chapter 1 provides background on the synthesis, stability, and reactivity of this organometallic species. In addition, we discuss the use of halodifluoroacetates as common, inexpensive, and green precursors to "Cu–CF_3".

Cu-catalyzed trifluoromethylation of electrophiles was an appealing, but underdeveloped strategy for accessing fluorinated compounds. Chapter 2 describes our entry into Cu-catalyzed decarboxylative trifluoromethylation of bromodifluoroacetates. We discovered that ligand and catalyst activation played critical roles in the development of an efficient Cu-based catalyst system.

Trifluoroethylarenes are commonly found in bioactive compounds, and in Chapter 3, we describe a straightforward Cu-catalyzed strategy to access this motif from benzylic bromodifluoroacetates. A key aspect of this reaction involved the generation of active electrophilic species *in situ*.

In Chapter 4, we describe the ability of ligands to alter the regioselectivity of Cu-catalyzed trifluoromethylation reactions. Propargylic bromodifluoroacetates are converted into a mixture of propargylic trifluoromethanes and trifluoromethylallenes using "Cu–CF_3"; however, the use of 1,10-phenanthroline inverts the typical regioselectivity, and provides trifluoromethylallenes in high yield and selectivity. This is the first example of ligands controlling the regioselectivity of Cu-based trifluoromethylation reactions.

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Chapter 1: Nucleophilic Trifluoromethylation Reactions

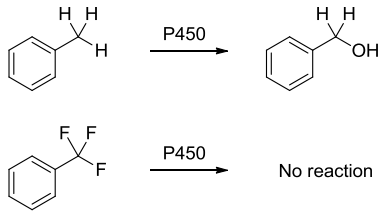
1.1. Trifluoromethanes in medicinal chemistry and chemical biology.

The trifluoromethyl group plays an important role in medicinal chemistry, by modulating the distribution, metabolism, and pharmacokinetic (DMPK) properties of drug candidates. Trifluoromethanes are incorporated in compounds in order to: 1) block metabolic oxidation; 2) alter lipophilicity; 3) adjust pK_a of adjacent functional groups; 4) perturb bond conformation; and 5) reduce electron density of nearby π-systems. Therefore, the development of synthetic methods that convert common functional groups to trifluoromethanes and facilitate the selective addition of CF_3 into drug candidates empowers medicinal chemistry.

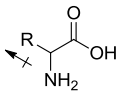
Trifluoromethanes possess unique chemical properties that arise from the strength of C–F bonds, high electronegativity of F, and the small steric footprint of F.[1] C–F bonds are much stronger than C–H bonds; therefore, replacing Me groups that are prone to oxidative metabolism with CF_3 groups increases the biological stability of drug candidates (Scheme 1.1A).[1,2] Trifluoromethanes also modulate the pK_a and H-bonding properties of adjacent functional groups, due to the strong electron-withdrawing nature of F (Scheme 1.1B).[3] In addition, the steric profile of the trifluoromethyl group is similar to Et and ^{i}Pr groups, with an A-value matching the Et group, and a van der Waals radius similar to the ^{i}Pr group (Scheme 1.1C).[2]

Scheme 1.1. Trifluoromethanes perturb properties that are critical in drug design.

A) Incorporation of fluorine blocks oxidative metabolism



B) Inductive effects of fluorine decrease pK_a values of adjacent functional groups



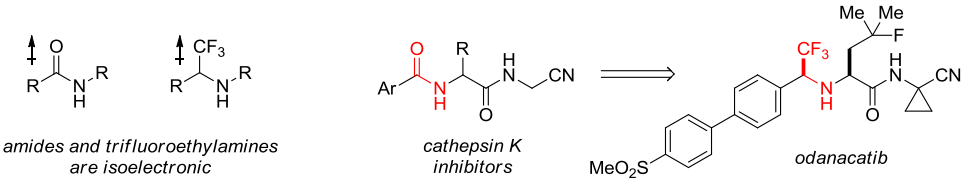
R	Me	CFH_2	CF_2H	CF_3
acid pK_a	2.3	2.4	1.5	1.2
amine pK_a	9.9	9.8	8.4	5.3

C) Steric properties of CF_3 similar to ^{i}Pr and Et

	H	Me	Et	CF_3	^{i}Pr	^{t}Bu
A-value (kcal/mol)	–	1.70	1.70	2.10	2.15	>4.50
van der Waals volume (Å)	1.20	21.6	38.9	39.8	56.2	NA

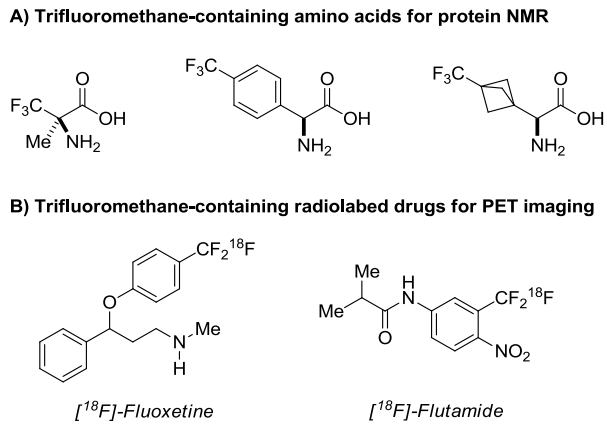
Fluorinated peptidomimetics are important for medicinal chemistry and chemical biology, since fluorinated amide mimics are stable towards metabolic degradation.[1] Trifluoroethylamines are isopolar mimics for amides, since the electron-withdrawing CF_3 group is electronically similar to the carbonyl of an amide (Scheme 1.2).[4] In addition, the CF_3 group increases the H-bond donating ability of the amine to more closely match that of an amide N–H. Trifluoroethylamines have been used as amide mimics in drug candidates, such as odanactib (Scheme 1.2).[4]

Scheme 1.2. Trifluoroethylamines are isoelectronic mimics of amides.



Trifluoromethane-containing compounds are also valuable for biological imaging techniques such as NMR and PET. Since ^{19}F is a NMR active nucleus that is not found in biological systems, fluorinated probes provide high signal to noise ratios, and can be easily monitored by ^{19}F NMR spectroscopy. Since ^{19}F NMR shifts are sensitive to local electronic environment, fluorinated probes have been used to monitor drug-protein binding, and conformational changes in protein and membranes.[1e,5] This approach can utilize either fluorinated ligands, or proteins that incorporate fluorinated amino acids (Scheme 1.3A).[1e] In a second example, [^{18}F] radiolabeled compounds have also been used in PET imaging to monitor the distribution of drugs in animals.[1e]

Scheme 1.3. Fluorinated probes are valuable for biological imaging.

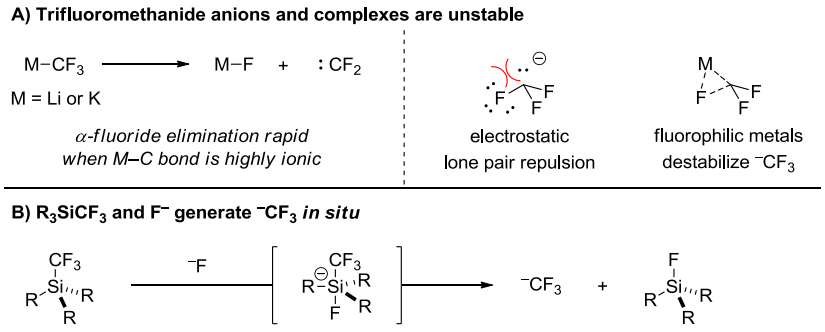


1.2. Nucleophilic trifluoromethylation.

Nucleophilic trifluoromethylation of electrophiles is a robust strategy for accessing many classes of trifluoromethanes. α-Fluoroalkyl nucleophiles possess unique properties compared to standard C-based nucleophiles, and the inherent instability of fluoroalkylanions creates challenges in organofluorine chemistry. M–CF_3 species are unstable (e.g. M = Li or Mg) and undergo α-fluoride elimination to form MF

and singlet difluorocarbene (:CF_2) (Scheme 1.4A).[6,7] Electrostatic lone-pair repulsion between the C-based anion and fluorine 2p electrons destabilize the trifluoromethanide anion, therefore; M–CF_3 species with highly ionic M–C bonds decompose rapidly. In addition, fluorophilic metals (e.g. Li or Mg) interact with fluorine electrons, and further promote decomposition to MF and :CF_2 (Scheme 1.4A).[6,7] Given the instability of many M–CF_3 complexes, the discovery of reagents that generate $^{-}CF_3$ *in situ* enabled the development of nucleophilic trifluoromethylation reactions.

Scheme 1.4. Instability of M–CF_3 species overcome by generation of $^{-}CF_3$ *in situ*.

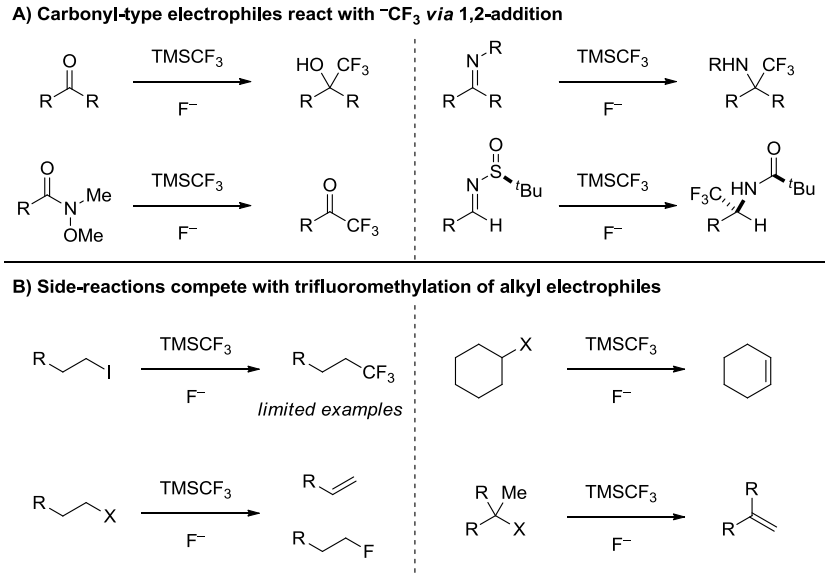


Trifluoromethylsilanes are a widely used class of bench stable reagents that permit the controlled release of $^{-}CF_3$.[8] This family of compounds reacts with Lewis bases (most commonly F^{-}) to generate silicates, which then expel $^{-}CF_3$ (Scheme 1.4B). Since decomposition of $^{-}CF_3$ hinders many reactions, the rate of release, and stabilization of this species is critical for promoting productive C–C bond forming processes. Variables that influence the rate $^{-}CF_3$ release for this reagent system include: steric bulk surrounding the Si atom (R_3SiCF_3: Me, Et, ^{i}Pr), Lewis base of activator (MX: X^{-} = F^{-}, MeO^{-}, $^{t}BuO^{-}$, etc.), solvent, and temperature. In addition, several factors impact the stability of released $^{-}CF_3$, such as Lewis acid of activator (MX: M^{+} =

Na^+, K^+, Cs^+, $^nBu_4^+$, etc.), solvent, and temperature. $^-CF_3$ has been implicated as a discrete intermediate in nucleophilic trifluoromethylation reactions, and was spectroscopically observed at low temperatures {[K(18-crown-6)]$^+CF_3^-$; at –56 to –78 °C}.[7]

C–C bond-forming, transition metal-free nucleophilic trifluoromethylation is generally limited to reactions with carbonyl-type and primary alkyl electrophiles.[8] For example, trimethyl(trifluoromethyl)silane ($TMSCF_3$, Ruppert-Prakash reagent) reacts *via* 1,2-addition with aldehydes, ketones, Weinreb amides, imines, and oxocarbenium species (Scheme 1.5A).[8] Although trifluoromethylation of carbonyl-type electrophiles is robust, reactions with alkyl electrophiles are limited in scope. For example, the trifluoromethylation of 1° alkyl iodides has been described;[9] however, these reactions compete with elimination, and F^- substitution pathways (Scheme 1.5B). In addition, 2° and 3° electrophiles do not form desired trifluoromethanes, and instead eliminate to generate alkenes (Scheme 1.5B).[9]

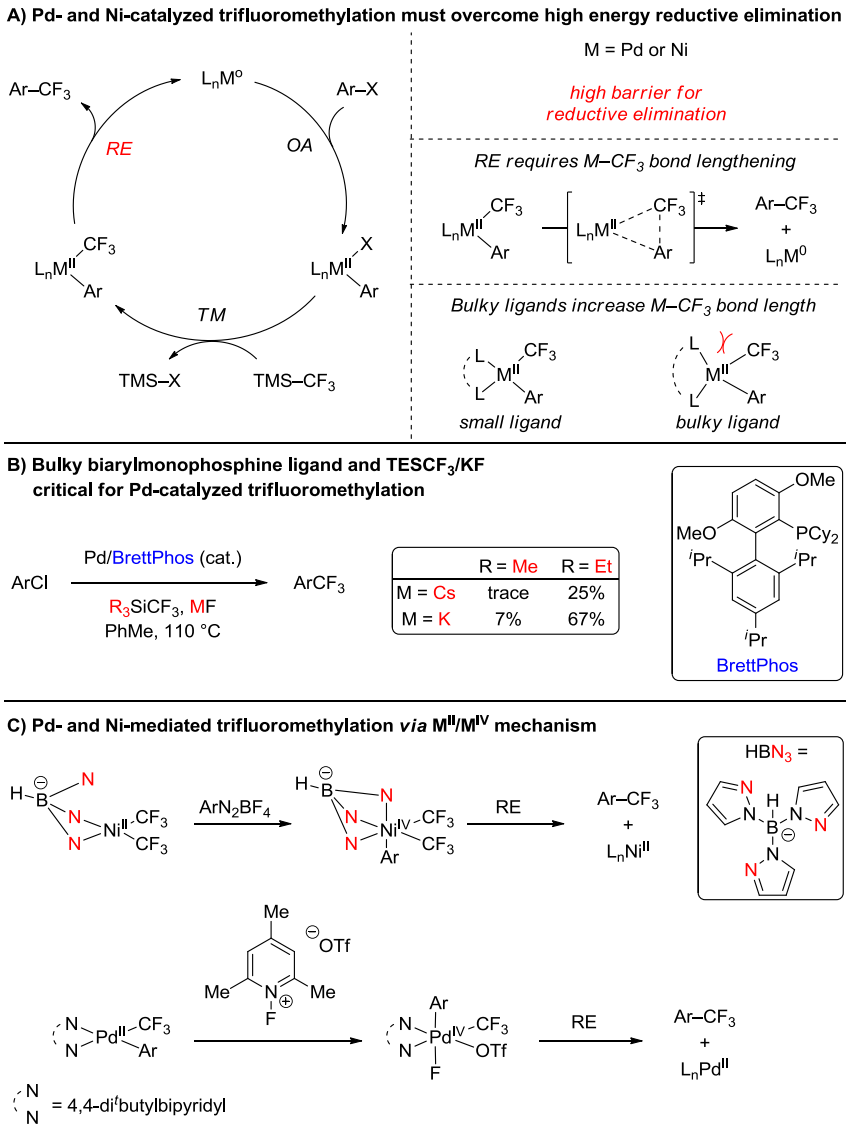
Scheme 1.5. Trifluoromethylation is facile for carbonyl-type electrophiles, and difficult for aliphatic electrophiles.



Transition-metals, such as Pd, Ni, and Cu, enable nucleophilic trifluoromethylation reactions involving C-sp^2 electrophiles.[10] For Pd- and Ni-mediated trifluoromethylation is particularly challenging, due to a high barrier for reductive elimination from $L_nPd^{II}(Ar)(CF_3)$ and $L_nNi^{II}(Ar)(CF_3)$ complexes (Scheme 1.6A).[10] Recently, the development of biarylphosphine ligands facilitated Pd-catalyzed trifluoromethylation of aryl chlorides.[11] Specifically, the steric bulk of the ligand (BrettPhos) caused an elongation and weakening of the Pd–CF_3 bond, and lowered the activation energy for reductive elimination (ca. 22 kcal/mol; Scheme 1.6A). In addition, the combination of triethyl(trifluoromethyl)silane and KF promoted the release of $^-CF_3$ at an appropriate rate (Scheme 1.6B). Despite considerable effort, the development of Ni-catalyzed nucleophilic aromatic trifluoromethylation has not been realized, as reductive elimination is too difficult with all ligands studied to date.[12] An alternative strategy to

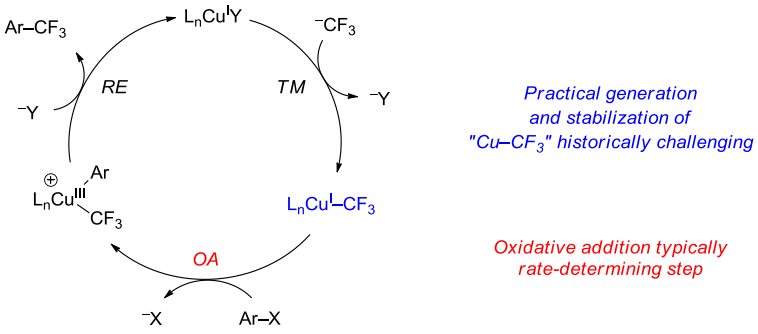
enable reductive elimination from Pd and Ni centers involved M^{II}/M^{IV} mediated mechanisms (Scheme 1.6C).[13] While these studies demonstrated the feasibility of high-valent metal-mediated fluoroalkylation chemistry, they currently require stoichiometric metals, and have lower practical utility.

Scheme 1.6. Ligands and high-valent reaction manifolds permit trifluoromethylation using Pd and Ni.



Cu-promoted trifluoromethylation of aryl electrophiles is facile compared to the Pd- and Ni-promoted processes.[10] The mechanism of Cu-catalyzed trifluoromethylation proceeds *via* a Cu^{I}/Cu^{III} manifold (Scheme 1.7), in which oxidative addition is typically the rate determining step (ca. 18 kcal/mol for ArI), and reductive elimination is rapid (ca. 9 kcal/mol).[14] A major challenge in Cu-promoted trifluoromethylation involves generation and stabilization of "$Cu–CF_3$" from practical and affordable precursors. Continual innovation in reagent strategies to form "$Cu–CF_3$" have improved relative to the first Cu-mediated trifluoromethylations of aryl electrophiles (1969),[15] and eventually enabled Cu-catalyzed trifluoromethylation (2009).[16]

Scheme 1.7. Cu-promoted trifluoromethylation of aryl electrophiles.



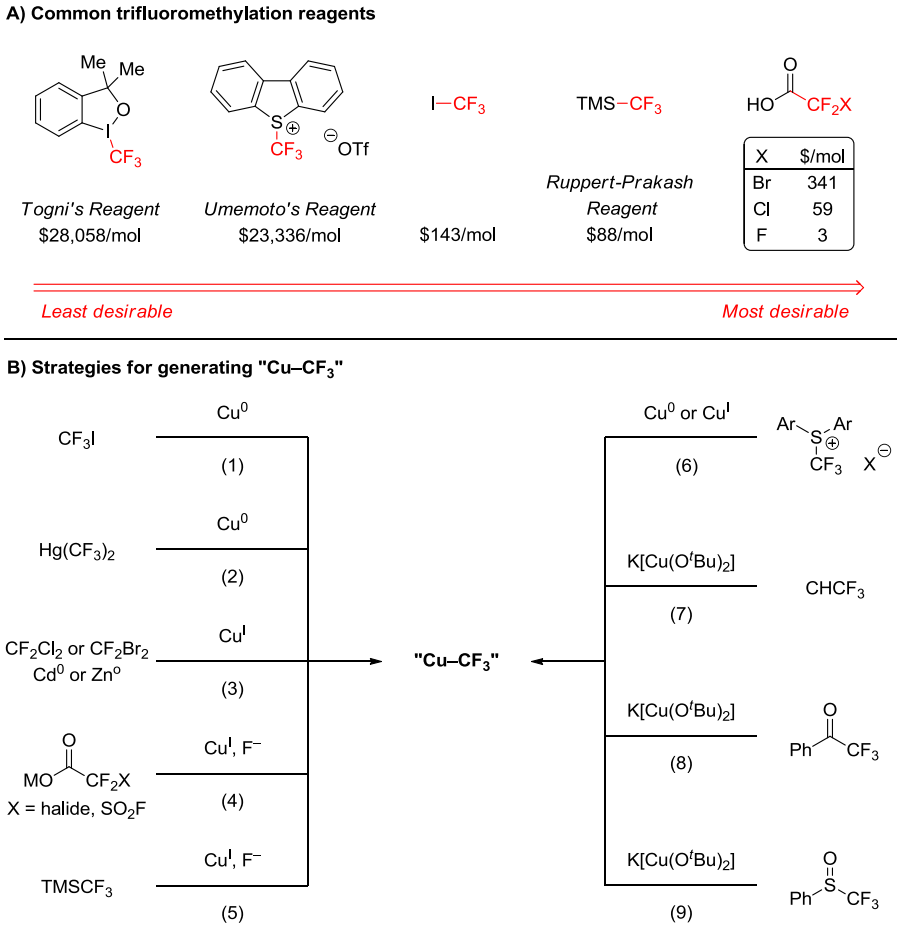
1.3. Formation, stability and reactivity of "Cu–CF_3".

The ideal trifluoromethylation reaction would use reagents that are inexpensive, easy to handle, and environmentally benign. In contrast, many modern strategies for trifluoromethylation require specialty chemicals that are expensive and generate excess waste (e.g. Togni's or Umemoto's reagents, Scheme 1.8A[17]). In order to enable inexpensive and green trifluoromethylation reactions, recent research has focused on using more economical and green reagents, such as $TMSCF_3$ and halodifluoroacetates

(Scheme 1.8A). Historically, many of these reagents have been used in Cu-mediated trifluoromethylation, but modern methods have focused on developing analogous Cu-catalyzed processes.

Early strategies for generating "Cu–CF_3" utilized difficult to handle and/or toxic reagents, and formed ill-defined solution-state complexes. "Cu–CF_3" was first created through the reductive coupling of Cu^0 and gaseous CF_3I (Scheme 1.8B, eq 1).[15,18] An alternative approach involved transmetalation between $Hg(CF_3)_2$ and Cu^0 (eq 2).[19] While this strategy was appealing, since transmetalation can be a highly controlled process, the method was impractical, as dialkylmercury reagents are extremely toxic. Subsequent efforts to promote transmetallation from other $M(CF_3)_n$ species proved successful, and permitted the spectroscopic detection of "Cu–CF_3" for the first time.[20] This strategy formed $Cd(CF_3)_2$ or $Zn(CF_3)_2$ from CF_2X_2 (X = Cl or Br) and M^0, and reacted the trifluoromethylmetal species with Cu^I (eq 3).[20] A more appealing strategy involved decarboxylation of halodifluoroacetates, which are inexpensive, readily available, and easy to handle reagents (eq 4, *vide infra*).[21] Another widely-used method of forming "Cu–CF_3" has been the reaction of trialkyl(trimethyl)silanes, F^-, and Cu^I (eq 5, *vide infra*).[22] Recently, some difficult transformations have been accomplished using Umemoto's reagent with $Cu^{0/I}$ (eq 6).[23] Finally, the use of $K[Cu(O^tBu)_2]$ (generated from CuCl and KO^tBu) permits the generation of "Cu–CF_3" from precursors, such as fluoroform (eq 6),[24] trifluoroacetophenone, (eq 8)[25], and phenyltrifluoromethylsulfoxide (eq 9).[26] The cupration of fluoroform was a notable advance, since this gas is an industrial byproduct from the synthesis of fluoropolymers.[24]

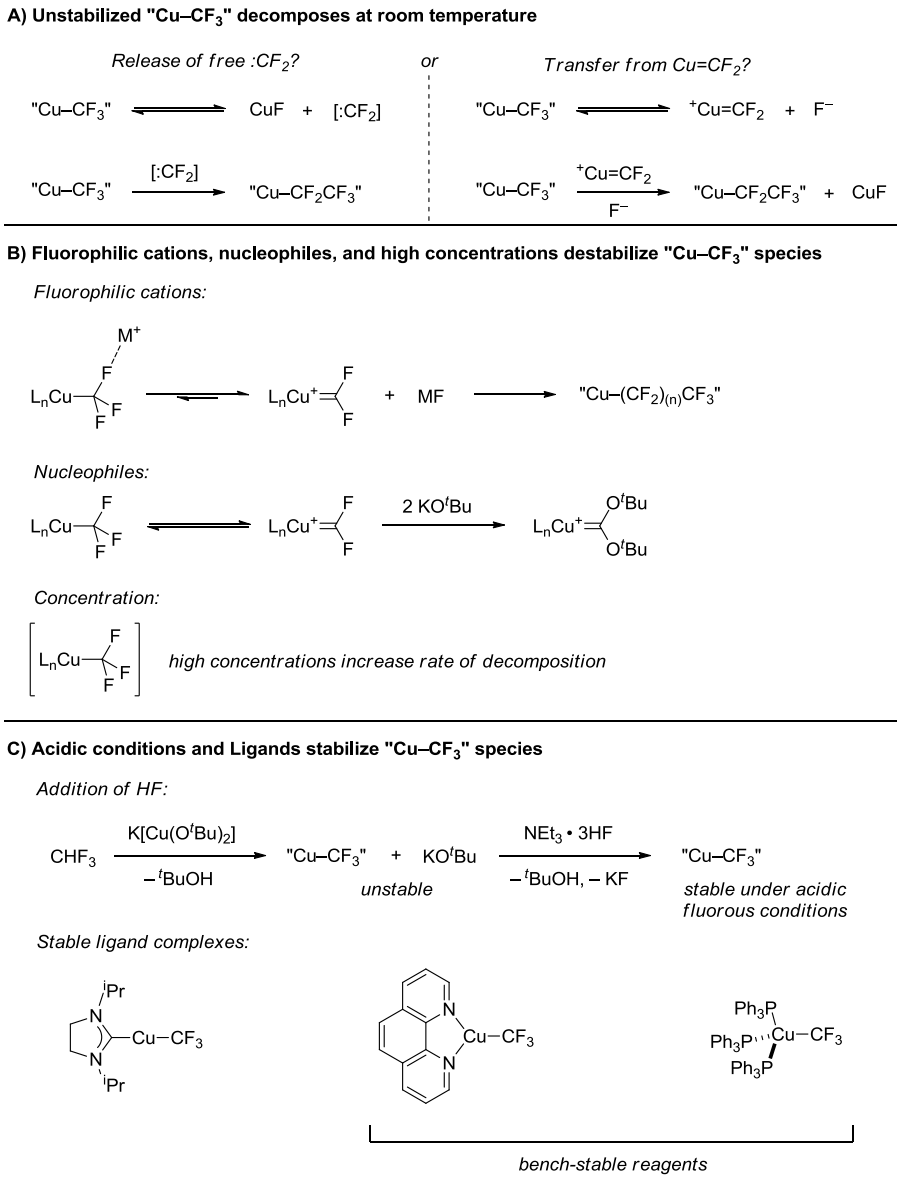
Scheme 1.8. Reagents and strategies for the synthesis of "Cu–CF_3".



"Cu–CF_3" is a notoriously unstable and ill-defined mixture of solution state fluoroalkylmetal species. Initial ^{19}F NMR analysis of "Cu–CF_3" generated from $M(CF_3)_2$ (M = Cd or Zn) and Cu^I (Scheme 1.8B, eq 3) revealed several fluorinated signals, which could be $[L_nCu–CF_3]$ with different ligands (solvent or halides) or at different aggregation states.[20] In addition, trifluoromethylcuprate $[Cu(CF_3)_2^+]$ has been observed in equilibrium with trifluoromethylcopper(I).[24a] Unstabilized "Cu–CF_3" fully decomposes within 11 h at room temperature to generate higher fluoroalkylcopper species $[Cu–(CF_2)_{(n)}CF_3]$.[20b] While the precise mechanism of degradation is not well understood, two pathways have been proposed: 1) "Cu–CF_3" releases free :CF_2, which then inserts into a Cu–CF_3 bond

to generate "Cu–CF_2CF_3"; or 2) "Cu–CF_3" undergoes α-fluoride elimination to form Cu=CF_2, and then reacts with another equivalent of "Cu–CF_3" (Scheme 1.9A). Several factors could further destabilize "Cu–CF_3", including fluorophilic cations, anionic nucleophiles, and concentration (Scheme 1.9B).[20b,24]

Scheme 1.9. "Cu–CF_3" decomposes to form [:CF_2] species.

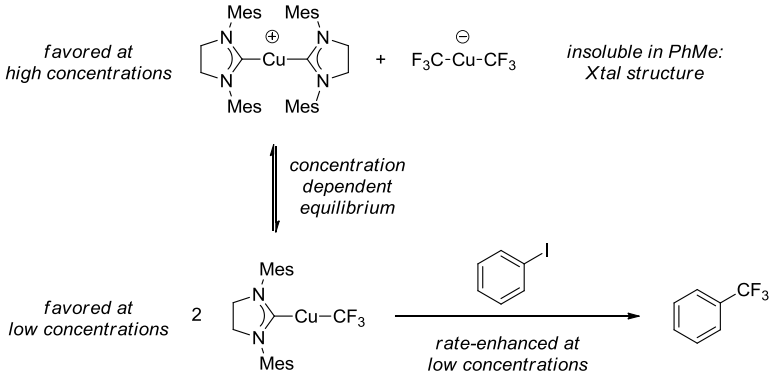


Two strategies have been used to stabilize "Cu–CF_3" species: 1) acidification using NEt_3 • 3HF; and 2) addition of ligands. The first strategy was important for stabilizing "Cu–CF_3" generated from the cupration of fluoroform. In this process, KO^{t}Bu destabilized "Cu–CF_3" through fluorophilic cation interactions (shifted equilibrium from KO^{t}Bu and Cu–CF_3 to $^+$Cu=CF_2, MF, and $^-$O^{t}Bu), and nucleophilic attack of $^-$O^{t}Bu to produce Cu=C(O^{t}Bu)$_2$ (Scheme 1.9B). The addition of NEt_3 • 3HF generated ^{t}BuOH and precipitated KF, and formed a solution of "Cu–CF_3" that was stable for >1 week (Scheme 1.9C).[24a] Another strategy for stabilizing "Cu–CF_3" involved the addition of ligands to create well-defined L_nCuCF_3 species. The first successful example employed a NHC ligand, and generated a complex that was air-sensitive, but could be crystalized under inert conditions (Scheme 1.9C).[27] Later, more stable complexes were synthesized using 1,10-phenanthroline[28] and PPh_3[29] as ligands (Scheme 19C). These bench stable reagents are commercially available, and useful for various trifluoromethylation reactions.

Well-defined $L_nCu–CF_3$ complexes have been used to gather further data on the mechanism of trifluoromethylation reactions. For example, while cuprates are active alkylating reagents in non-fluorous copper chemistry,[30] trifluoromethylcuprates [$Cu^-(CF_3)_2$] are not active species in nucleophilic trifluoromethylation reactions.[31] In solution, "Cu–CF_3" and [$Cu^+(CF_3)_2$] form an equilibrium, which change based on solvent, concentration, ligand, and temperature. In PhMe, the trifluoromethylcuprate complex [$Cu^-(CF_3)_2$][$Cu^+(SIMes)_2$] was insoluble, and could be isolated as a well-defined solid complex (Scheme 1.10).[31] When dissolved in Ph–I, this complex formed an equilibrium with [(SIMes)Cu–CF_3]. The equilibrium shifted towards [(SIMes)Cu–CF_3] at low

concentrations, and the rate of conversion of Ph–I to Ph–CF_3 increased, which implicated [(SIMes)Cu–CF_3], rather than [$Cu^+(CF_3)_2$] as the active species in trifluoromethylation (Scheme 1.10).[31]

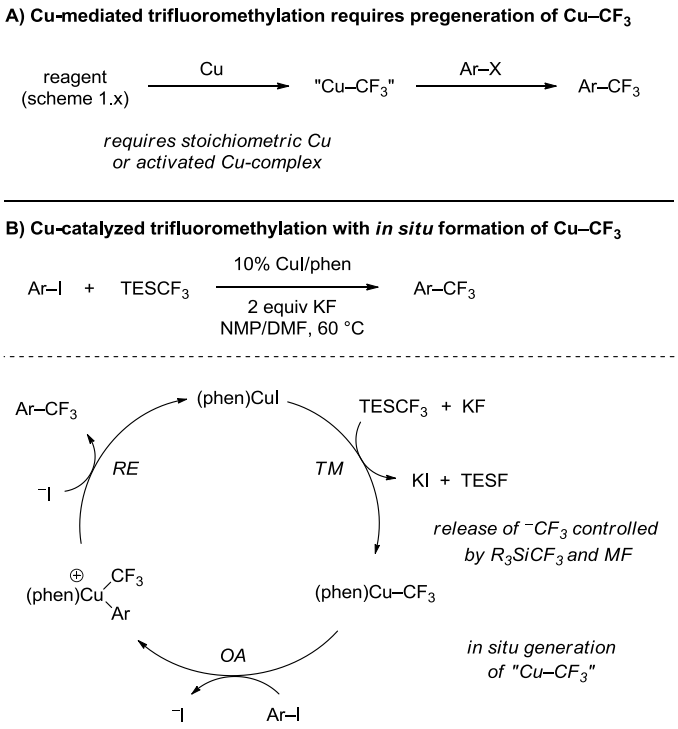
Scheme 1.10. Trifluoromethylcuprate is inactive in nucleophilic trifluoromethylation reactions.



The majority of Cu-promoted nucleophilic trifluoromethylation reactions utilize stoichiometric Cu; however, the development of Cu-catalyzed reactions is desirable for economic and environmental reasons. Many methods that generate "Cu–CF_3" are not suitable for catalytic trifluoromethylation reactions, since they require stoichiometric Cu (Scheme 1.8B; eq 1 and 6) or a preformed Cu-complex (e.g. K[Cu(O^tBu)$_2$]; Scheme 1.8B; eq 7–9). Two reagent classes, trialkyl(trifluoromethyl)silanes and halodifluoroacetates, generate "Cu–CF_3" under mild conditions, and have been successfully employed in catalytic trifluoromethylation reactions. For the catalytic trifluoromethylation of aryl iodides, the combination of $TESCF_3$ and KF effectively promoted the gradual release $^-CF_3$ *in situ*, and form a (phen)Cu–CF_3 complex (Scheme 1.11B).[16] In this reaction, the ligand selection played an important role, as other bidentate N-based ligands provided lower yields of product. The substrate scope for this

transformation was limited, and functional groups that react with free $^{-}CF_3$, such as acidic groups (deprotonation) and carbonyl groups (1,2-addition), would likely be incompatible with the reaction.

Scheme 1.11. Strategy to create "Cu–CF_3" *in situ* critical for Cu-catalyzed trifluoromethylation.



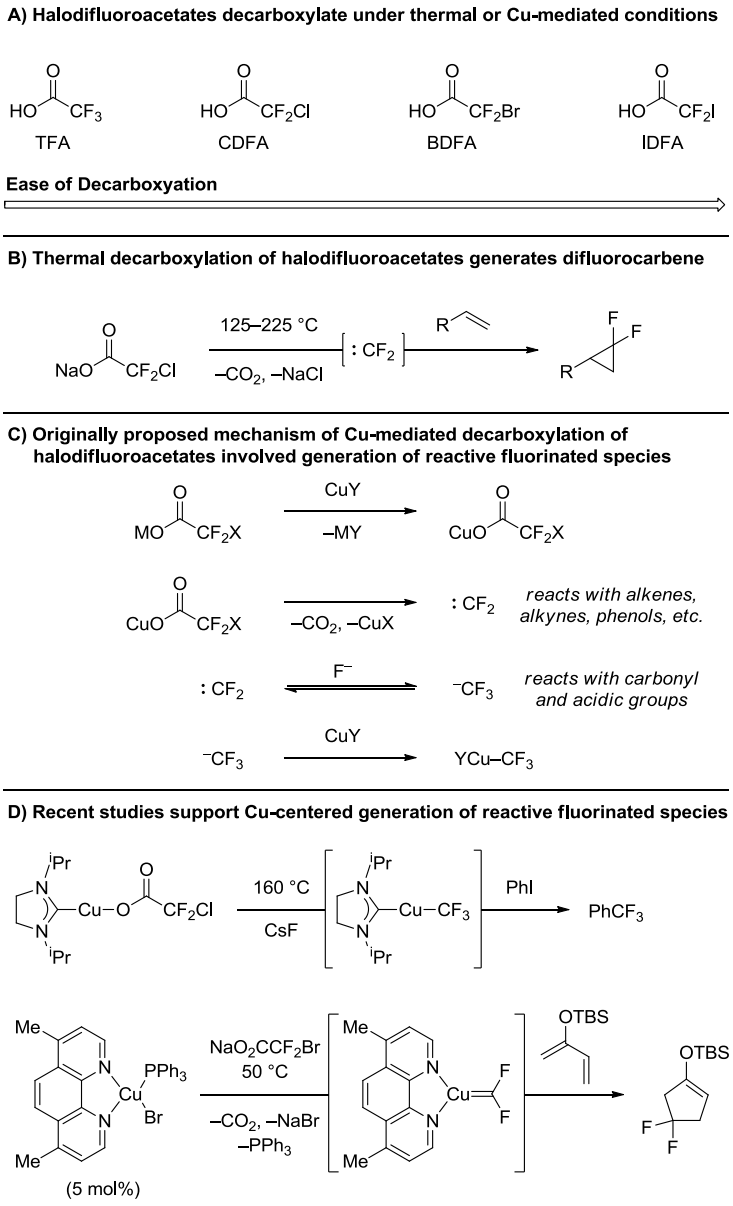
1.4. Halodifluoroacetates as reagents for generation of "Cu–CF_3".

Halodifluoroacetic acids are an attractive class of reagents that undergo decarboxylation to release reactive fluorinated species. While trifluoroacetic acid is the least expensive and most desirable reagent in this class, it decarboxylates slowly, and has an estimated half-life of 40,000 years at 15 °C in aqueous solution.[32] Trifluoroacetates are synthetically useful fluorinating reagents; however, decarboxylation typically requires stoichiometric Cu and reaction temperatures >150

°C.[33] Other halodifluoroacetatic acids decarboxylate more rapidly (Scheme 1.12A); however, metal catalysts, other reagents, and/or high temperatures are required to facilitate synthetically useful transformations.

The mechanism of Cu-promoted decarboxylation of halodifluoroacetates is not well understood; however, the process may involve $:CF_2$ intermediates. In the absence of Cu, halodifluoroacetates decarboxylate at high temperatures to generate $:CF_2$, which reacts with alkenes to form difluorocyclopropanes (Scheme 1.12B).[34] For Cu-mediated decarboxylation, the following mechanism was proposed: 1) formation of a Cu(I)–O_2CCF_2X complex; 2) decarboxylation to generate free $:CF_2$; 3) combination of F^- and $:CF_3$ to create $^-CF_3$; and 4) association of $^-CF_3$ and Cu to form "Cu–CF_3" (Scheme 1.xC).[35] For this process, no evidence of $^-CF_2X$ was observed; therefore, decarboxylation and C–X cleavage were thought to occur in a concerted step.[34] Since the overall mechanism invoked two reactive fluorinated species, $:CF_2$ and $^-CF_3$, many reactive functional groups could potentially be incompatible with the reaction. For example, free $^-CF_3$ could react *via* 1,2-addition with carbonyl groups, and deprotonate acidic groups.

Scheme 1.12. Cu-promoted decarboxylation of halodifluoroacetates generates "Cu–CF_3".

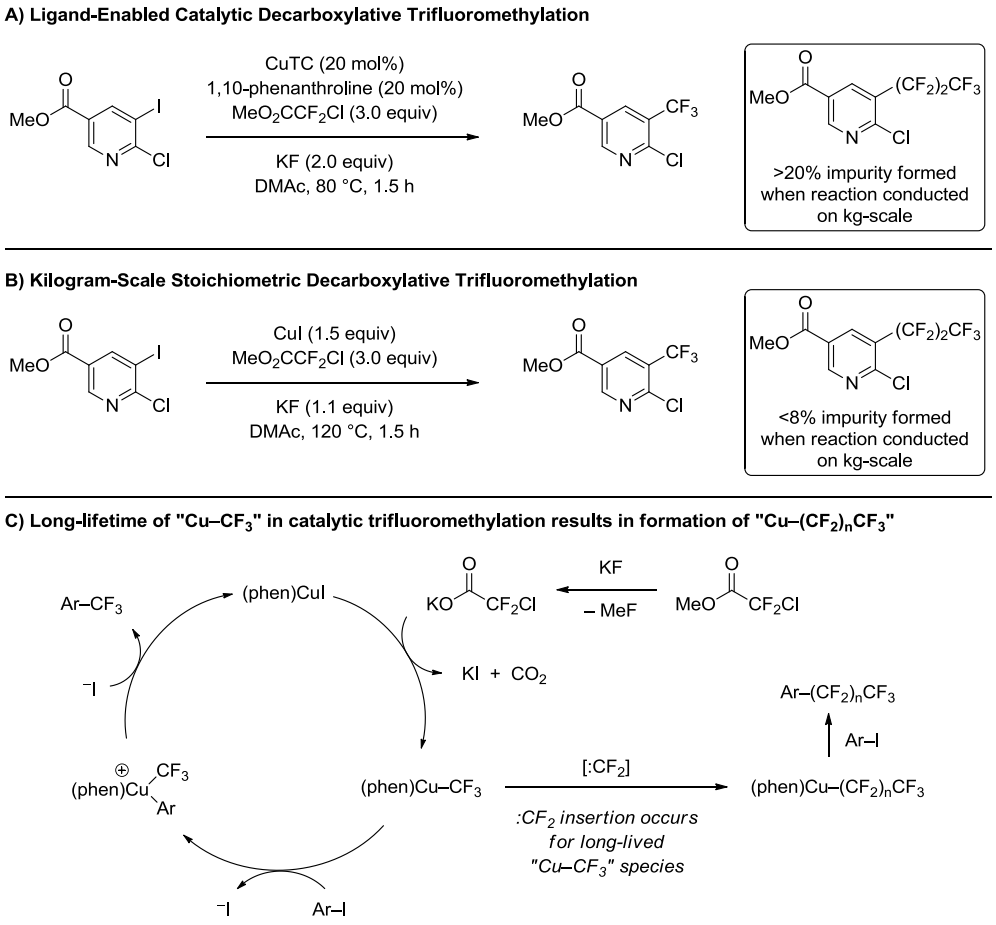


Recent studies support parts of the originally proposed mechanism, but provide evidence that reactive species generated from Cu-mediated decarboxylation of halodifluoroacetates remain bound to Cu, or do not exit the solvent sphere of Cu. The first step of the process likely involves generation of $L_nCu–O_2CCF_2X$, since a well-

defined (NHC)Cu–O_2CCF_2Cl complex was an active trifluoromethylation reagent (Scheme 1.12D).[36] In addition, LCu=CF_2 has been implicated as an intermediate in a formal [4 + 1] cycloaddition (Scheme 1.12D).[37] Further, Cu-catalyzed decarboxylative trifluoromethylation reactions involving bromodifluoroacetates tolerate carbonyl and acidic functional groups (chapters 2-4). Taken together, this data suggested that decarboxylation is a Cu-centered event, and reactive fluorinated species remain in the solvent sphere of Cu.

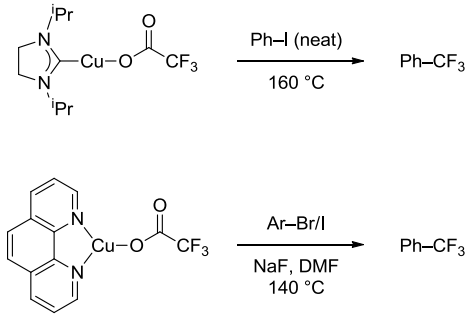
Amongst the various halodifluoroacetate analogs, bromo- and chloro-difluoroacetates are the most commonly used halodifluoroacetates, since they are inexpensive and reactive at low to moderate temperatures (50–120 °C). Traditionally, decarboxylative aromatic trifluoromethylation required stoichiometric CuI; however, limited examples exist that utilize catalytic Cu.[38] For example, the Cu-catalyzed decarboxylative trifluoromethylation of an iodopyridine was explored during the process-scale synthesis of an intermediate in a drug candidate.[38a] On a small to moderate scale, Cu-catalyzed trifluoromethylation was accomplished using MeO_2CCF_2Cl as a reagent, and 20% Cu(I) thiophenes-2-carboxylate with 20% 1,10-phenanthroline as a ligand (Scheme 1.13A). Unfortunately, when this Cu-catalyzed reaction was conducted on a multi-kilogram scale, the formation and separation of $Ar(CF_2)_nCF_3$ side products proved problematic without chromatography. These byproducts resulted from insertion of :CF_2 into "Cu–CF_3", and were suppressed by reverting to the use of stoichiometric CuI (Scheme 1.13B).

Scheme 1.13. Undesired perfluoroalkylation competes with trifluoromethylation in Cu-catalyzed process.



Trifluoroacetic acid (TFA) is the ideal trifluoromethylation reagent, since it is an incredibly inexpensive bulk chemical, and produces CO_2 as the sole byproduct. While considerable effort has been invested in developing Cu-promoted trifluoromethylation reactions using TFA, Cu-catalyzed process have not been discovered, and Cu-mediated methods require high temperatures (140–160 °C).[36,39] Currently, the best reagent system involves heating (phen)Cu–O_2CCF_3 to 140 °C to facilitate trifluoromethylation of aryl bromides and iodides (Scheme 1.14).[39]

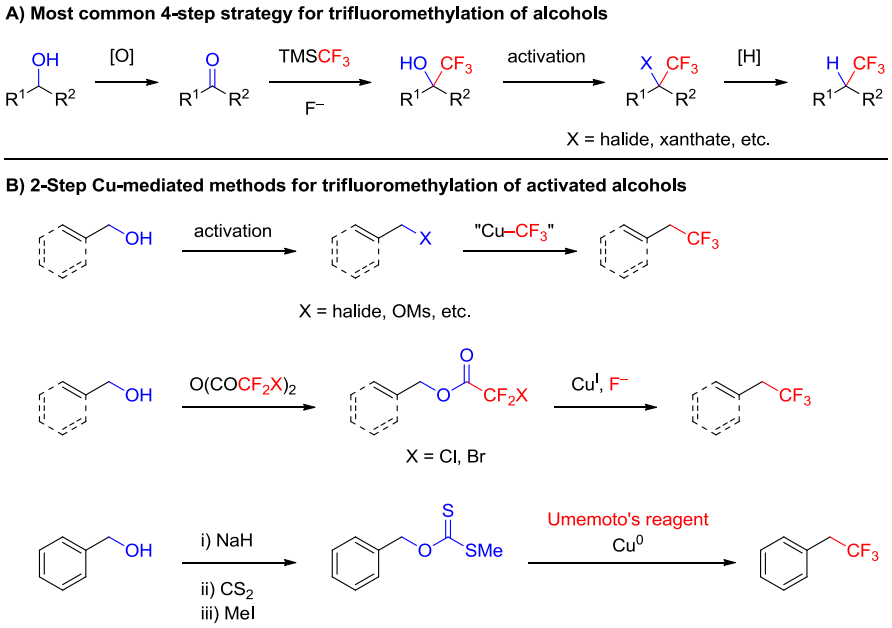
Scheme 1.14. $LCu–O_2CCF_3$ complexes facilitate trifluoromethylation at high temperatures.



1.5. Strategies for converting alcohols to trifluoromethanes.

Methods that convert alcohols to trifluoromethanes are important for medicinal chemistry and chemical biology, since alcohols are a common functional group, and trifluoromethanes can modulate the properties of drugs and probes. Alcohols are found in natural products, bioactive compounds, screening libraries, and can be synthesized from countless organic precursors using well-established chemistry.[40] Given the ubiquity of alcohols in organic compounds, deoxytrifluoromethylation represents a useful approach for accessing trifluoromethanes.

Scheme 1.15. Strategies for converting alcohols to trifluoromethanes.



Several strategies for converting alcohols to trifluoromethanes involve multi-step sequences that require expensive trifluoromethylation reagents and/or stoichiometric metals. The most common approach to deoxytrifluoromethylation involves the following four-step protocol: 1) alcohol oxidation to generate an aldehyde or ketone; 2) 1,2-addition of a trifluoromethyl anion to furnish a 1-substituted-2,2,2-trifluoroethanol; 3) conversion of the alcohol to a halide or xanthate; and 4) reduction using Pd/C and H_2, or Bu_3SnH and AIBN (Scheme 1.15A).[41] While this strategy provides a reliable route to access trifluoromethanes, it has several undesirable features, including: 1) low yields resulting from exponential loss of material during the multi-step process; 2) expense of time and labor for each reaction; 3) generation of excess waste from reactions and purifications; 4) inefficient oxidation and reduction steps during a redox-neutral net transformation; 5) use of stoichiometric metals and/or toxic reagents for redox reactions. In contrast, an alternative approach involves converting activated alcohols (allylic,

benzylic, propargylic, and α-keto alcohols) into electrophiles (acetates, halides, mesylates, xanthates), which undergo trifluoromethylation when treated with stoichiometric "Cu–CF_3" (Scheme 1.15B). While this strategy provides more straightforward access to trifluoromethanes, it has drawbacks, including: 1) use of stoichiometric metal, which is economically and environmentally undesirable; 2) limited substrate scope based on the electronic nature of the electrophile and functional group intolerance with sources of nucleophilic CF_3 (*vide supra*). Recent developments have enabled the conversion of electrophiles to trifluoromethanes using catalytic Cu (chapters 2–4).

1.6. Conclusions.

Nucleophilic trifluoromethylation is an effective strategy for the synthesis of trifluoromethanes. "Cu–CF_3" enables trifluoromethylation of various C–sp^2 and C–sp^3 based electrophiles, and advances in the generation and stabilization of this organometallic species have created more practical and user-friendly trifluoromethylation methods. Halodifluoroacetates serve as attractive reagents for the generation of "Cu–CF_3", and can be used in the two-step conversion of alcohols to trifluoromethanes.

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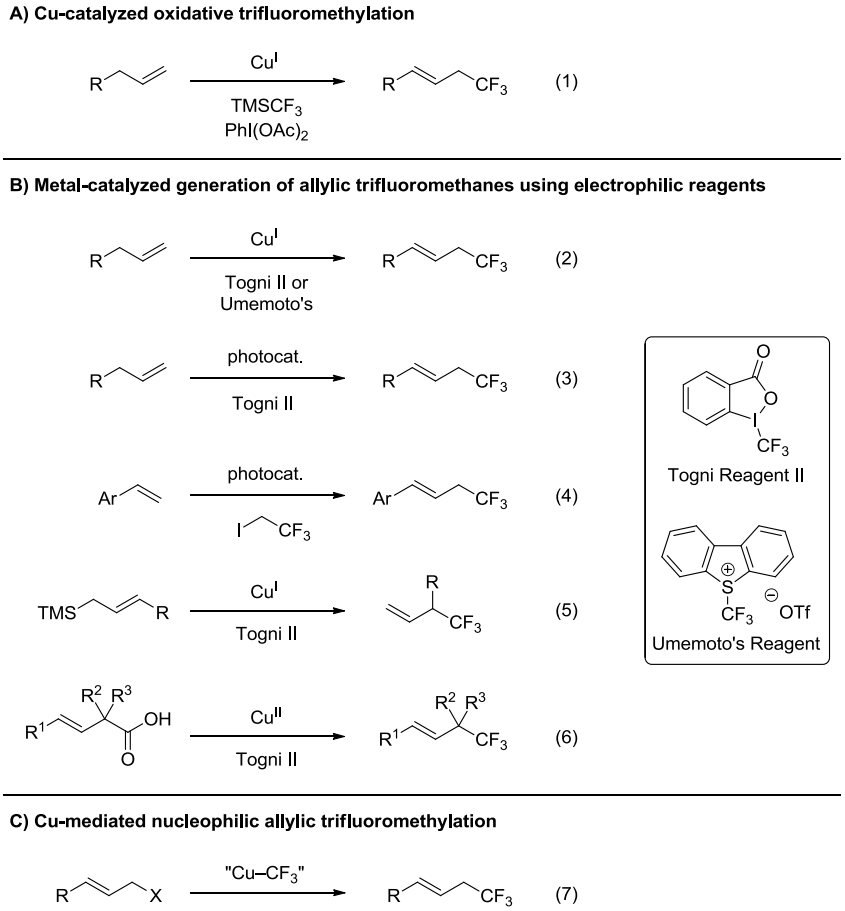
Chapter 2: Copper-Catalyzed Decarboxylative Trifluoromethylation of Allylic Bromodifluoroacetates

2.1. Methods for the preparation of allylic trifluoromethanes.

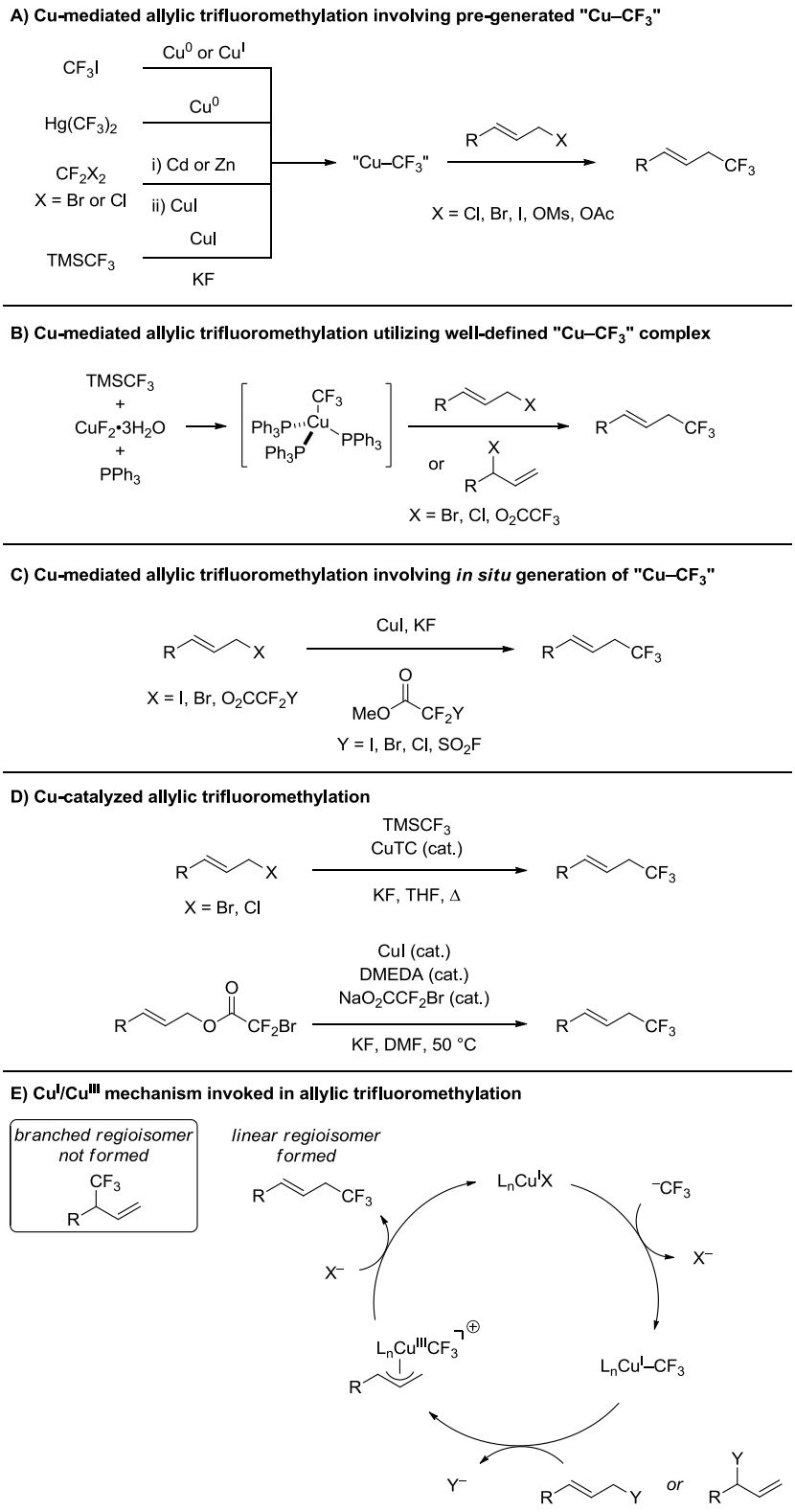
Allylic trifluoromethanes are versatile building blocks, and various strategies have emerged for accessing this fluorinated motif.[1] Recently, several methods that converted alkenes and acids to allylic trifluoromethanes were reported, including: oxidative trifluoromethylation of terminal alkenes using $TMSCF_3$ (Scheme 2.1, eq 1);[2] C–H activation or radical-mediated trifluoromethylation of terminal alkenes using Cu- or photoredox-catalysis and electrophilic trifluoromethylation reagents (eq 2–3);[3,4] radical-mediated trifluoromethylation of styrenes (eq 4);[5] Cu-catalyzed trifluoromethylation of allylsilanes (eq 5);[6] and Cu-catalyzed decarboxylative trifluoromethylation of β,γ-unsaturated carboxylic acids (eq 6).[7] These methods required the use of: 1) stoichiometric oxidants (eq 1), which limited functional group tolerance and increased waste; or 2) specialty trifluoromethylation reagents (eq 2–6), which increased costs of reactions (Togni's and Umemoto's reagents: $28,000–23,000/mol). In contrast, an alternative strategy for synthesizing allylic trifluoromethanes involved Cu-mediated trifluoromethylation of allylic electrophiles (eq 7).[8] This approach was appealing, since allylic electrophiles are readily accessible from simple building blocks, such as allylic alcohols. However, previous methods required use of stoichiometric Cu and/or reagents that were toxic, expensive, and difficult to handle. Therefore, we sought to develop a green, inexpensive, and user-friendly protocol to convert allylic electrophiles to trifluoromethanes using catalytic Cu.

Scheme 2.1. Metal-based construction of allylic trifluoromethanes.



The conversion of allylic electrophiles to trifluoromethanes using "Cu–CF_3" is well established, and was first reported in 1979 by Kobayashi.[8a] Early iterations of this strategy generated solutions of unstabilized "Cu–CF_3" from various fluorinated reagents [CF_3I, CF_2X_2, $Hg(CF_3)_2$], and then added allylic electrophile to the reaction (Scheme 2.2A).[8a,9,10] These reagents were toxic and/or difficult to handle; therefore, subsequent research aimed at developing more efficient and operationally simple methods for generating "Cu–CF_3". One improved method involved mixing the Ruppert-Prakash reagent ($TMSCF_3$), KF, and CuI to generate "Cu–CF_3", and then adding allylic halides to affect trifluoromethylation (Scheme 2.2A).[8g]

Scheme 2.2. Copper-based nucleophilic trifluoromethylation of allylic electrophiles.

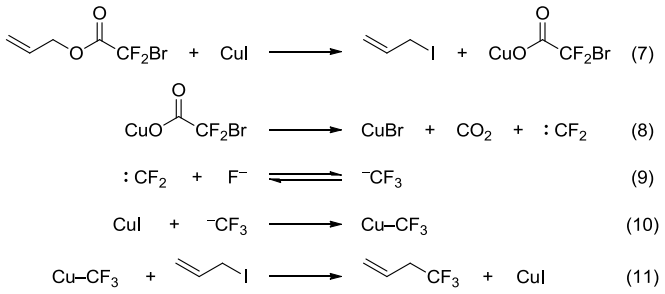


The discovery of solid, isolatable, bench-stable, and well-defined "$L_nCF–CF_3$" complexes improved trifluoromethylation technology.[11] Previous methods required generation of "$Cu–CF_3$" in the absence of electrophile, and the immediate use of this species, since unstabilized "$Cu–CF_3$" degraded within 11 h at 25 °C.[10] Ligand stabilized complexes, such as Grushin's reagent [$(PPh_3)_3Cu–CF_3$],[11b] were air-stable solids that reacted with linear and branched allylic electrophiles to furnish linear allylic trifluoromethanes (Scheme 2.2B).[8f] Since linear product arose from both linear and branched substrates, a mechanism similar to other Cu-mediated allylic substitution reactions[12] was proposed: 1) oxidative addition of $Cu^I–CF_3$ to an allylic electrophile, generating a π-allyl intermediate; 2) reductive elimination to form the thermodynamically stable linear allylic trifluoromethane [Scheme 2.2E (OA and RE steps)].[8f]

An additional advance in allylic trifluoromethylation involved *in situ* formation and reaction of "$Cu–CF_3$" with allylic electrophiles. This was realized by decarboxylation of halodifluoroacetates in the presence of KF and Cu^I to generate "$Cu–CF_3$", which then reacted with allylic electrophiles (Scheme 2.2C).[8c] While this strategy did not require use of highly reactive metals or metal-complexes, it was proposed to generate reactive fluorinated species, including free trifluoromethyl anion ($^-CF_3$) and difluorocarbene [$:CF_2$; (Scheme 2.3)]. Therefore, only simple substrates were compatible with this protocol. We noted that this strategy theoretically turned over CuI; therefore, we reasoned that a catalytic protocol could be realized. In addition, we hypothesized that decarboxylative generation of "$Cu–CF_3$" might occur *via* an inner-sphere process, meaning that the reactive fluorinated species would not be free in solution, and the protocol would tolerate sensitive functional groups. Prior to publishing our results, an

alternative method for Cu-catalyzed allylic trifluoromethylation was reported that used $TMSCF_3$ as a source of nucleophilic CF_3 (Scheme 2.2D). This report demonstrated a limited substrate scope, likely because $TMSCF_3$ and KF generated free $^{-}CF_3$, which would have destroyed carbonyl- and acidic-functional groups.

Scheme 2.3. Chen's Proposed Mechanism of Cu-mediated decarboxylative allylic trifluoromethylation.

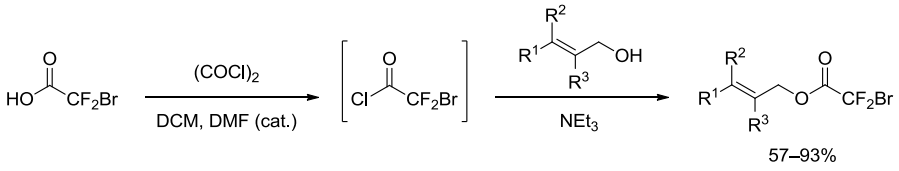


2.2. Conversion of allylic alcohols to trifluoromethanes via Cu-catalyzed decarboxylative trifluoromethylation.

With the goal of converting allylic alcohols to trifluoromethanes, we envisioned an attractive approach might involve the conversion of an alcohol to a halodifluoroacetic ester, followed by a catalytic decarboxylative trifluoromethylation (Scheme 2.2D). Although trifluoromethylation reactions of halodifluoroacetic esters have been conducted using stoichiometric CuI,[8c–e, 13a–b] catalytic reactions have proven elusive over many years. In this project, we developed Cu-catalyzed decarboxylative trifluoromethylation of allyl bromodifluoroacetates, and distinguished this reaction from analogous Cu-mediated reactions with preliminary mechanistic findings.

Initially, we compared the (dis)advantages of using different allylic halodifluoroacetates as substrates for decarboxylative trifluoromethylation. We discarded trifluoroacetates, since decarboxyation occurs at high temperatures (>140 °C), and iododifluoroacetates, since they are expensive and sensitive to light. Therefore, we evaluated allylic chloro- and bromo-difluoroacetates as inexpensive and moderately reactive substrates. During the initial phase of the project, we selected allylic bromo- over chloro-difluoroacetates, since bromodifluoroacetates provided higher yields at lower temperatures (50 vs 70 °C). Next, we confirmed that allylic bromodifluoroacetates are easily accessed *via* coupling of inexpenive and readily available bromdifluoroacetic acid and allylic alcohols (Scheme 2.4). A convenient esterification procedure involved activating bromodifluoroacetic acid with oxalyl chloride to generate bromodifluoroacetyl chloride, and then addition of allylic alcohol to provide desired product. This operation was conducted on a range of allylic alcohols, and generated product esters in moderate to good yields (57–93%). Some allylic bromodifluoroacetates were unstable to column chromatography, which excluded select substrates from this strategy (*vide infra*).

Scheme 2.4. Conversion of allylic alcohols to allylic trifluoromethanes.



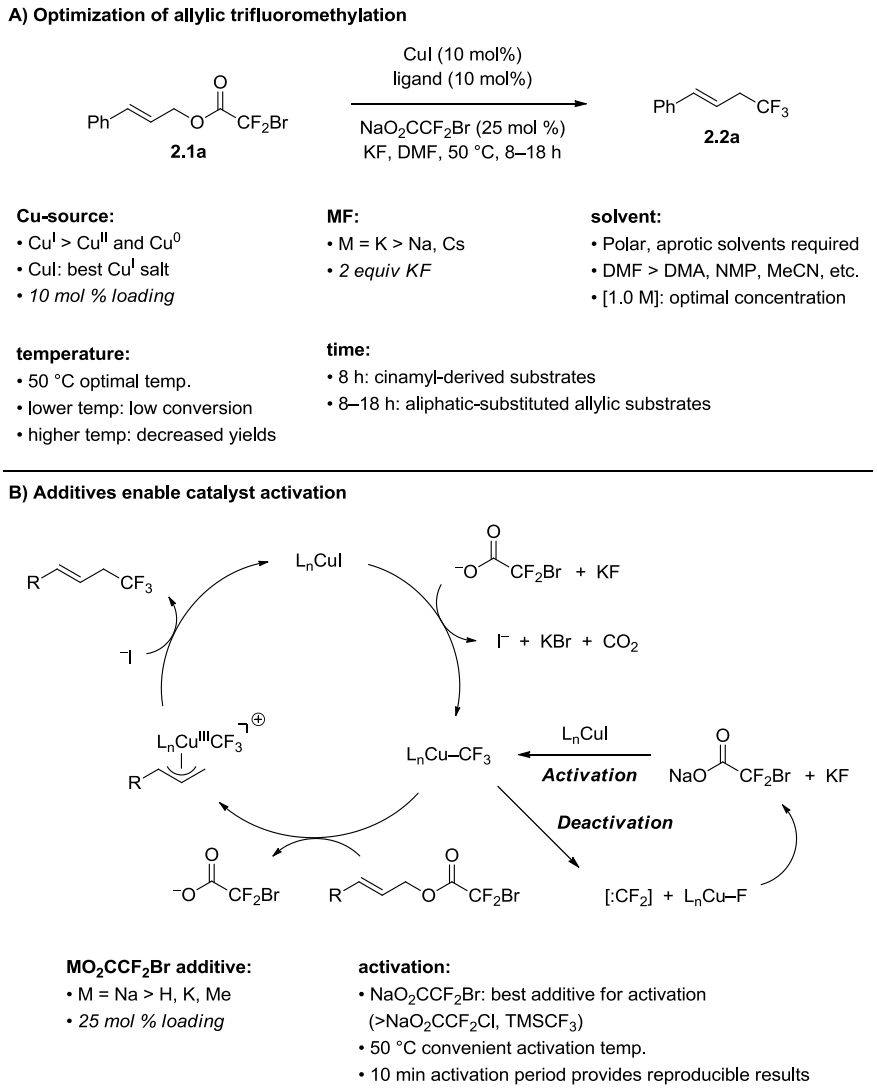
A broad screen of catalysts and conditions revealed the optimal conditions for Cu-catalyzed allylic trifluoromethylation (Scheme 2.5A). The Cu source was an important factor, and Cu^{I} salts provided much higher catalyst turnover than Cu^{II} and Cu^{0}, which supported the proposed $Cu^{I/III}$ mechanistic manifold (Scheme 2.5B). Several $Cu^{I}X$ salts performed similarly (X = I, Br, Cl, thiophene-2-carboxylate, etc.), and CuI was

selected, since it is inexpensive, commonly available, and a free-flowing powder. High yields were obtained using 10% CuI, and decreasing catalyst loading depressed yields. Next, we evaluated F^- sources, and determined that KF provided higher yields than CsF and NaF. KF is a hygroscopic solid, and since water harmed the reaction, we found that using anhydrous KF (flame-dried under vacuum) increased yields. The solvent choice and concentration had dramatic effects, and [1 M] DMF provided optimal yields. Polar aprotic solvents were required to enable decarboxyation at moderate temperature (50 °C), and low conversion of substrate was observed in less polar solvents (1,4-dioxane, PhMe, etc.). The reaction required concentrated conditions, and diluting the mixture resulted in decreased yields. Finally, most cinnamyl-derived substrates fully reacted within 8 h at 50 °C, but less electronically activated substrates required reaction times up 18 h.

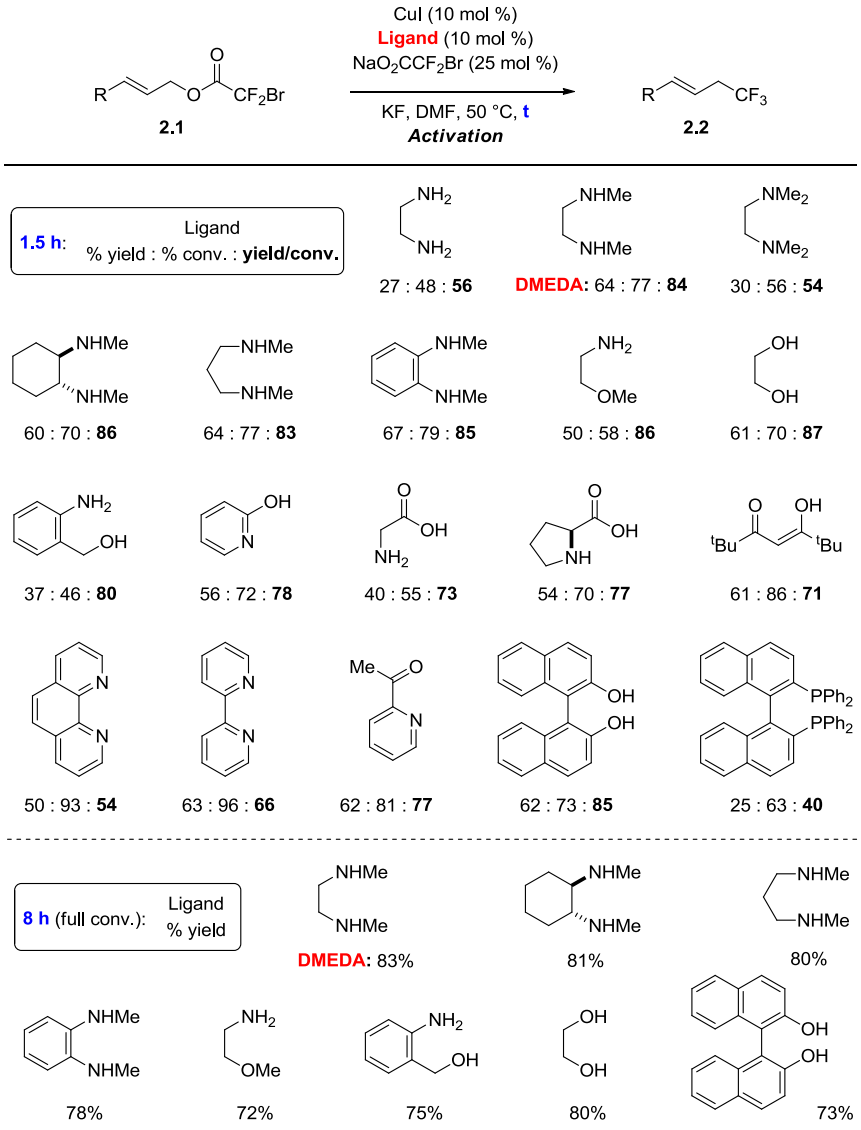
Bromodifluoroacetate additives were screened to enable catalyst activation and overcome "Cu–CF_3" decomposition. When optimizing the reaction, substrate decomposition without productive product formation was observed at the early stages of the reaction. In the absence of additive, we considered the steps required to convert the CuI precatalyst into active "$L_nCu–CF_3$": 1) decomposition of cinnamyl bromodifluoroacetate to release $^-O_2CCF_2Br$; 2) Cu ligand exchange to form "$L_nCu–O_2CCF_2Br$"; and 3) decarboxylation and addition of F^- to generate "$L_nCu–CF_3$" (Scheme 2.5B). We hypothesized that efficient generation of "$L_nCu–CF_3$" was critical for preventing substrate decomposition, so we investigated several additives and protocol to the facilitate conversion of CuI precatalyst into its active state. In practice, we found that heating NaO_2CCF_2Br, CuI, ligand, and KF in DMF for 10 min prior to the addition of

substrate enabled catalyst activation, and prevented unnecessary decomposition of substrate. We also noted that if "$L_nCu–CF_3$" decomposed and exited the catalytic cycle, NaO_2CCF_2Br could enable the reentry of Cu into the cycle (Scheme 2.5B).

Scheme 2.5. Conditions and additives critical for allylic trifluoromethylation.



Scheme 2.6. DMEDA outperformed other ligands.



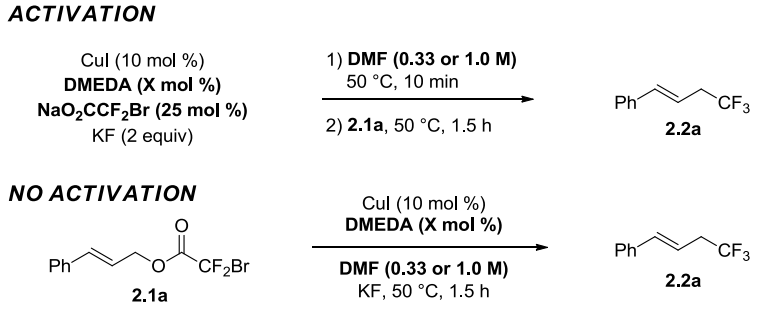
Ligands increase the stability, and alter the reactivity of "Cu–CF_3" species, and we screen various N-, O-, and P-based ligands, in order to improve our allylic trifluoromethylation reactions (Scheme 2.6). We hypothesized that ligands could serve three roles in the present reaction: 1) facilitate the formation of "$L_nCu–CF_3$", and improve the early phase of the reaction; 2) increase the reactivity of "$L_nCu–CF_3$" towards allylic electrophiles; and/or 3) increase the stability of "$L_nCu–CF_3$", and disfavor catalyst decomposition. In order to determine whether ligands assisted with catalyst activation

and reactivity at early time points, we evaluated the impact of ligands on the first 1.5 h of the reaction by comparing % conversion to % yield. During initial reaction optimization, we observed low yield/conversion ratios due to non-productive substrate decomposition; however, the addition of several ligands improved yield/conversion (>80%) after 1.5 h (Scheme 2.6). We discovered that many N- and O-based bidentate ligands positively impacted the reaction, but P-based ligands suppressed product formation. Ethylenediamines were an effective class of ligands, and the alkylation state of the amines significantly impacted ligand performance. *N,N'*-dimethylethylenediamine (DMEDA) was better than ethylenediamine (EDA) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA). This data suggested that unhindered amines could undergo side-reactions with the substrate, while bulky amines did not effectively ligate Cu. The best ligands at the 1.5 h time point were reevaluated at an 8 h time point in order to determine their overall impact on the reaction (Scheme 2.6). While several bidentate ligands improved yields, DMEDA was selected, based on its performance and common availabilty in synthetic chemistry laboratories.[14]

A series of control reactions highlighted three parameters that were most critical for obtaining high product yields: reaction concentration, ligand, and activation of the catalyst (Scheme 2.7). Compared with the optimized reaction conditions (entry 1), reactions run at lower concentration (entry 2), or without employing the activation procedure (entry 3) provided less efficient catalyst systems based on yield/conversion ratios. Employing the activation procedure, the use of CuI/DMEDA provided a less-active catalyst than that derived from CuI alone at the 1.5 h time point (entries 1, 4); however, when the reactions proceed to full conversion, a higher yield of product was

reproducibly obtained using CuI/DMEDA (entries 5–6). Thus, DMEDA could serve to stabilize the active catalyst against decomposition near the end of the reaction.

Scheme 2.7. Sensitivity of Cu-Catalyzed Trifluoromethyation to Concentration, Ligand, and Activation of Catalyst[a]



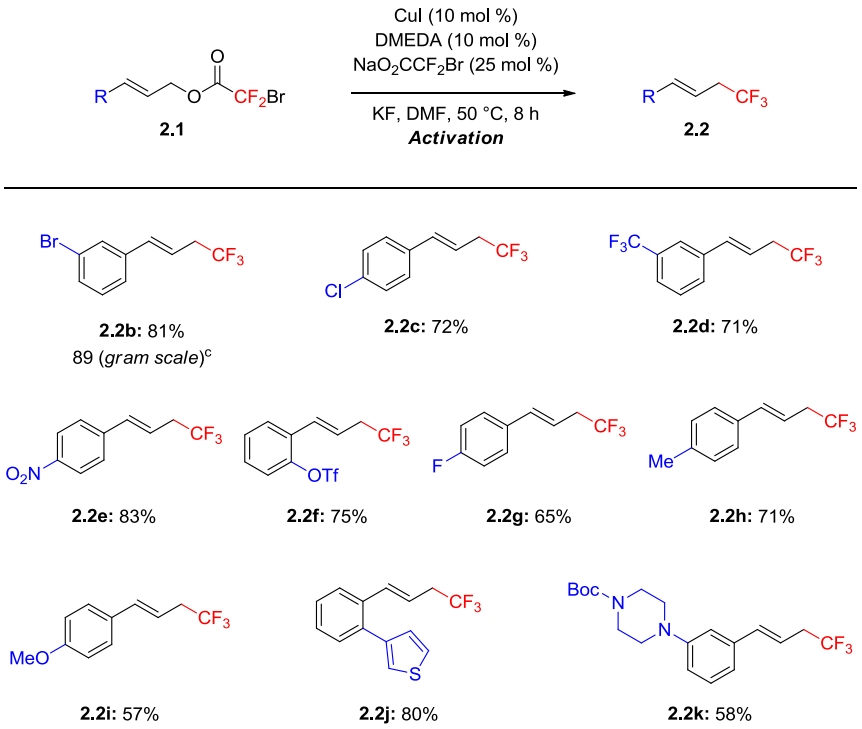
entry	activation	[**1a**] (M)	DMEDA (mol %)	% yield[b]	% conv.[b]	yield/conv.
1	√	1.0	10	52	64	0.82
2	√	0.33	10	63	85	0.74
3	–	1.0	10	26	54	0.49
4	√	1.0	0	66	79	0.83
5[c]	√	1.0	10	83	100	0.83
6[c]	√	1.0	0	72	100	0.72

[a] Reactions were performed with 0.20 mmol **2.1a**, 0.050 mmol NaO_2CCF_2Br, 0.40 mmol KF in 0.20 mL DMF at 50 °C for 1.5 h. [b] Conversion and yield data were determined by GC/FID analysis using dodecane as an internal standard. Each data point represents an average of 2–4 experiments. [c] The reactions were run for 8 h instead of 1.5 h.

A variety of 2-, 3- and 4-substituted cinnamyl bromodifluoroacetates (**2.1b–k**) were compatible with the present reaction (Scheme 2.8). Electron-deficient (**2.2b–e**) and electron-neutral cinnamyl systems (**2.2g–h**) reacted in good yields, although an electron rich substrate provided the product in slightly lower yield (**2.2i**). In general, substrates capable of affording resonance stabilized allyl cations (e.g., 4-NMe_2) were unstable to both acidic and basic conditions, which limited purification and storage of this class of substrates. Aryl (pseudo)halides were well tolerated, and did not undergo aromatic trifluoromethylation (**2.2b–c, f–g**). In addition, compounds bearing

heterocycles were tolerated (**2.2j–k**). Finally, on an 8 mmol scale, over 1.9 g of **2.2b** was obtained in high yield, which suggests that the present reaction could be amenable to larger scale processes.

Scheme 2.8. Substituted Cinnamyl Bromodifluoroacetates Undergo Decarboxylative Trifluoromethylation.[a,b]

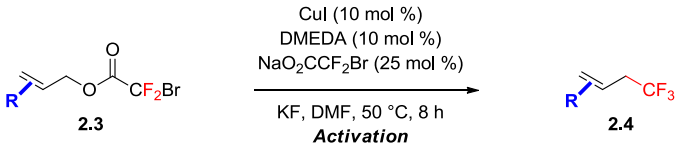


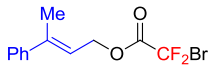
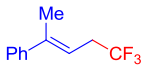
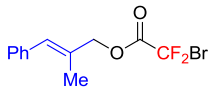
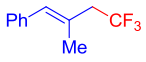
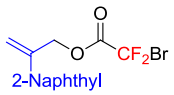
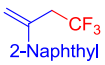
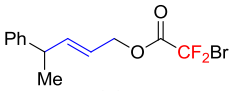
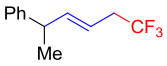
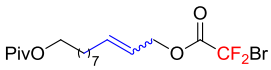
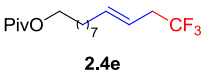
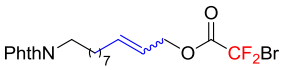
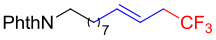
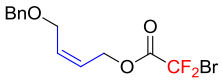
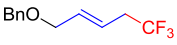
[a] Reactions were performed with 0.20 mmol **2.1**, 0.020 mmol CuI, 0.020 mmol DMEDA, 0.050 mmol NaO_2CCF_2Br, 0.40 mmol KF in 0.20 mL DMF at 50 °C for 8 h following 10 min activation. [b] Isolated yield. [c] Reaction conducted on an 8 mmol scale.

Disubstituted and non-conjugated allylic esters (**2.3**) containing a diverse array of functional groups provided moderate to good yields of *E* alkene products (**2.4**, Scheme 2.9). Substituents at the α and β positions of the styrene were tolerated (**2.4a–c**), and non-conjugated allylic systems displayed good reactivity (**2.4d–g**). Several aliphatic functional groups were compatible with the reaction, including esters, imides, and

benzyl ethers (**2.4e–g**). Substrates that existed as mixtures of gemetrical isomers (**2.3e–f**, *E*/*Z* ca. 4:1) converted to thermodynamically-favored *E*-allyl trifluoromethane products (**2.4e–f**) in excellent selectivities (*E*/*Z* > 19:1). Further, the reaction of a pure *Z*-alkene substrate afforded the *E* product in excellent diastereoselectivity (**2.4g**). When monitoring the reaction by both GC/FID and ^{19}F NMR, slow isomerization of the substrate was observed, while the *E*-product was formed in greater than 15:1 dr throughout the course of the reaction. In control reactions, the *Z*-substrate was stable when treated with KF in DMF at 50 °C. These data could implicate the existence of a π-allyl intermediate that reacts to generate the more stable *E*-product (Scheme 2.5B).[8b] However at present, other explanations for this isomerization phenomenon cannot be excluded.

Scheme 2.9. Disubstituted and Non-Conjugated Allylic Bromodifluoroacetates Undergo Decarboxylative Trifluoromethylation.[a]

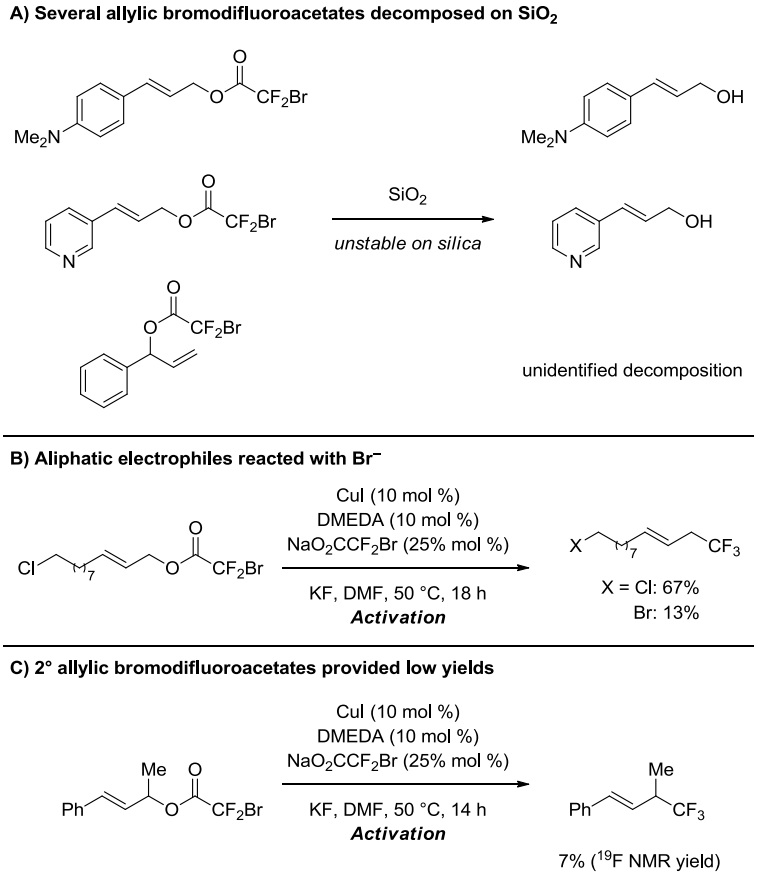


substrate	*E*/*Z*[b]	product	*E*/*Z*[c]	yield[d]
 **2.3a**	>98:2	 **2.4a**	>98:2	55%
 **2.3b**	>98:2	 **2.4b**	>98:2	74%
 **2.3c**	–	 **2.4c**	–	56%
 **2.3d**	>98:2	 **2.4d**	>98:2	78%
 **2.3e**	78:22	 **2.4e**	97:3	76%
 **2.3f**	79:21	 **2.4f**	98:2	85%
 **2.3g**	<2:98	 **2.4g**	96:4	81%

[a] Reactions were performed with 0.20 mmol **2.3**, 0.020 mmol CuI, 0.020 mmol DMEDA, 0.050 mmol NaO_2CCF_2Br, 0.40 mmol KF in 0.20 mL DMF at 50 °C for 8 h following 10 min activation. [b] Determined by ^1H NMR. [c] Determined by ^{19}F NMR. [d] Isolated yield, number in parentheses indicates ^{19}F NMR yield using α,α,α-trifluorotoluene as an internal standard. [e] 18 h.

Several substrates were not compatible with the present strategy, including electron-rich cinnamyl substrates (e.g. 4-NMe_2), compounds containing basic heterocycles, substrates bearing active leaving groups, and 2° allylic bromodifluoroacetates (Scheme 2.10). Electron-rich allylic bromodifluoroacetates that form highly stabilized π-allyl cations decomposed on silica gel, presumably *via* a S_N1 mechanism of hydrolysis. In addition, bromodifluoroacetic esters are highly sensitive to base-mediated hydrolysis, and substrates that contained basic functional groups (e.g. pyridine) in the presence of silica. In the case of a substrate containing a 1° aliphatic chloride, a portion of the material underwent a S_N2 reaction with free Br^- (released after decarboxylation of $^-O_2CCF_2Br$) and generated 1° aliphatic bromide-containg product. In addition, 2° allylic substrates demonstrated poor reactivity under the reaction conditions, and afforded low yields of 2° trifluoromethanes and diene side-product formed *via* elimination.

Scheme 2.10. Classes of substrates incompatible with current trifluoromethylation strategy.

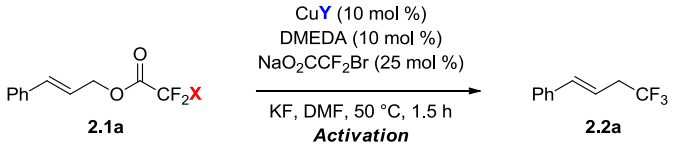


2.3. Mechanistic consideration for Cu-catalyzed decarboxylative trifluoromethylation of allylic bromodifluoroacetates.

Using the Cu/DMEDA-based catalyst system, bromodifluoroacetic esters provided unique reactivity (Scheme 2.11). A trend of increasing reactivity was observed for cinnamyl trifluoroacetate < chlorodifluoroacetate < bromodifluoroacetate (entries 1–3);[15] however, the reaction of cinnamyl difluoroiodoacetate provided a low yield of product (entry 4). We hypothesized that I^-, generated as a byproduct of the reaction, inhibited catalysis. In support of this theory, the addition of exogenous KI to the reaction of cinnamyl bromodifluoroacetate decreased the yield of product (entry 5). Combined,

these two findings suggest that I^- does not participate in the catalytic reaction. In fact, the Cu-catalyzed reaction could be conducted in the complete absence of I^- (entry 6), a key feature that distinguishes the present Cu-catalyzed reaction from previously reported Cu-mediated reactions.[16]

Scheme 2.11. Unique Reactivity of Allyl Bromodifluoroacetates.[a]



2.1a 2.2a

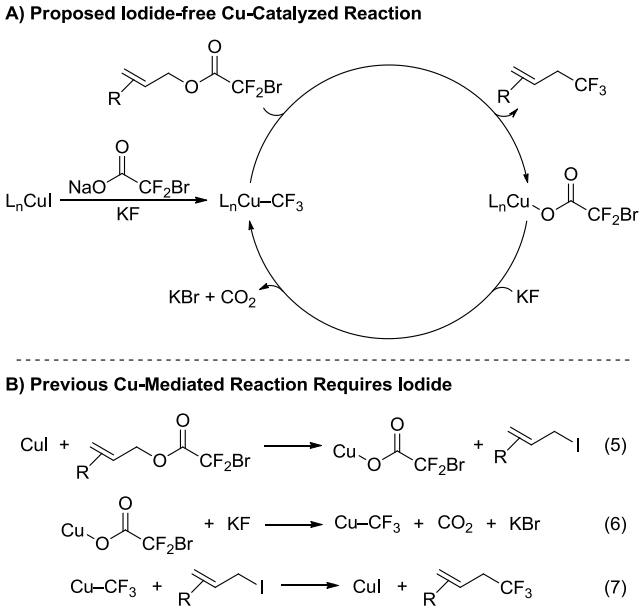
entry	X	Y	total % I	other	conversion (%)[b]	yield (%)[b]	yield/conv.
1	F	I	10	-	26	0	0
2	Cl	I	10	-	31	1	0.03
3	Br	I	10	-	52	46	0.88
4	I	I	10–110	-	53	25	0.47
5	Br	I	110	+100% KI	68	38	0.56
6	Br	$(MeCN)_4PF_6$	0	8 h	>99	79	0.79

[a] Reactions were performed with 0.20 mmol substrate, 0.050 mmol NaO_2CCF_2Br, 0.40 mmol KF in 0.20 mL DMF at 50 °C for 1.5 h. [b] Conversion and yield data were determined by GC/FID analysis using dodecane as an internal standard.

Although thorough mechanistic studies have not been conducted, the present Cu-catalyzed reaction likely involves a mechanism distinct from CuI-mediated reactions of allyl halodifluoroacetates. For the Cu-catalyzed reaction, the activation procedure presumably converts the precatalytic combination of CuI/DMEDA/NaO_2CCF_2Br/KF into the active catalyst, $L_nCu–CF_3$ (Scheme 2.12A). $L_nCu–CF_3$ can then promote direct trifluoromethylation of the substrate without participation of I^-. The substitution reaction potentially involves a π-allyl intermediate, which has been proposed in other allylic substitution reactions using $L_nCu–CF_3$ in both stoichiometric[8b] and catalytic[17] systems. In contrast, the Cu-mediated reaction invokes I^- as a key feature of the mechanism

(Scheme 2.12B).[16] In this case, I^- participated by converting the bromodifluoroacetic ester to an allyl iodide, which then reacted with $Cu–CF_3$.

Scheme 2.11. Proposed Catalytic Cycle Involving a Reactive $Cu–CF_3$ Species.



2.4. Conclusions.

In conclusion, a catalytic method for the conversion of allylic alcohols to trifluoromethanes via bromodifluoroacetic esters has been developed. Conjugated and non-conjugated substrates bearing a variety of functional groups afford α-substituted trifluoromethylated products in moderate to good yield and excellent diastereoselectivity for the *E*-stereoisomer. Beneficial aspects of this transformation include: the 1) employment of a mild, inexpensive and atom-economical source of CF_3 in near-stoichiometric quantity; 2) development of a shortened strategy for converting readily available allylic alcohols into trifluoromethyl analogs; 3) ability to conduct trifluoromethylation reactions using only a catalytic quantity of metal. Finally, functionalization of the allyl trifluoromethane-based product should be useful for accessing more complex fluorinated compounds.[18]

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Chapter 2 Appendix

Experimental procedures and spectra for compounds in Chapter 2

Table of Contents

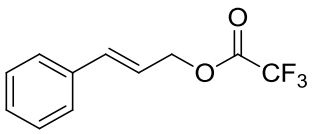
General Considerations:

All reactions were performed under an atmosphere of dry N_2 using oven-dried glassware. Decarboxylative trifluoromethylation reactions were performed in resealable 15 mL test tubes with PTFE septa. Copper (I) Iodide (98%) and *N,N'*-dimethylethylenediamine (DMEDA, 95%) were purchased from commercial sources and used without purification. Potassium fluoride was dried in a vacuum oven (180 °C) for a minimum of 24 h prior to use. Anhydrous DMF was purchased from commercial sources in a sure-seal bottle. All other reagents were purchased from commercial sources and used without further purification. All other solvents were used directly from a solvent purification system in which solvent was dried by passage through two columns of activated alumina under argon. The solvents were transferred *via* syringe from the solvent purification system to the reaction vessel. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing with fluorescence quenching or *p*-anisaldehyde solution. Flash column chromatography was performed using a Combi*Flash*® RF–4x purification system. Silica gel was purchased from Sorbent Technologies (cat. # 30930M-25, 60 Å, 40–63 μm).

Unless otherwise noted, yields reported are of the isolated material. Gas Chromatography (GC) yields in Table 1 were obtained via analysis using an Agilent Technologies 7890A GC system with a FID detector and an Agilent Technologies 30 m x 0.320 mm i.d. HP–5 capillary column using dodecane as an internal standard. Compounds described in the literature were characterized by comparing their ^{1}H NMR and ^{13}C NMR spectra, and melting points (m.p.) to the previously reported data. Previously unknown compounds were characterized by ^{1}H NMR, ^{13}C NMR, m.p.,

infrared (IR) spectroscopy, and high-resolution mass spectrometry (HRMS). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 AVANCE spectrometer (400 and 100 respectively) or Bruker 500 AVANCE spectrometer (500 and 125 MHz, respectively). ^{19}F NMR spectra were recorded on a Bruker 400 AVANCE spectrometer (376 MHz). Chemical shifts (δ) for protons are reported in parts per million downfield from tetramethylsilane and are referenced to proton resonance of residual $CHCl_3$ in the NMR solvent ($CHCl_3$ = 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 residual peak ($CDCl_3$ = 77.16 ppm). Chemical shifts (δ) for fluorine are reported in parts per millions, and are referenced to α,α,α-trifluorotoluene (δ = –63.72 ppm) or fluorobenzene (δ = –113.15 ppm). High-resolution mass data were recorded on a high-resolution mass spectrometer in the ESI mode. Infrared spectra were obtained using a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Melting points (uncorrected) were measured on a Thomas Hoover Capillary Melting Point apparatus.

Experimental procedure for the reactions described in Schemes 2.5–7 and 2.11:



2.1a–CF_3

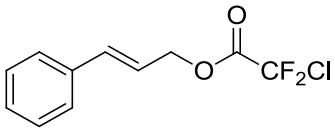
Cinnamyl 2,2,2-trifluoroacetate[1]

A 50 mL round bottom flask was oven dried and cooled under N_2. Cinnamyl alcohol (268 mg, 2.00 mmol) was added, then the system was evacuated and backfilled with N_2 three times. DCM (0.010 L) and NEt_3 (0.56 mL, 4.0 mmol) were added and the solution

was cooled to 0 °C. Trifluoroacetic anhydride (0.36 mL, 2.6 mmol) was injected dropwise, then the reaction was warmed to 21 °C and stirred for 2 h. The mixture was poured over 1 N HCl (10 mL), washed with water (2 x 10 mL) and then brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 1:0 → 50:1) afforded the title compound as a colorless oil (366 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.40 (m, 2 H), 7.39–7.29 (m, 3 H), 6.78 (d, *J* = 15.8 Hz, 1 H), 6.31 (dt, *J* = 15.8, 6.8 Hz, 1 H), 5.00 (d, *J* = 6.9 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –75.95 (s, 3 F).



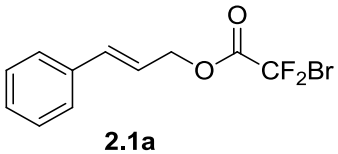
2.1a–CF_2Cl

Cinnamyl 2-chloro-2,2-difluoroacetate[2]

Cinnamyl alcohol (2.6 mL, 0.020 mol) was added to an oven-dried 100 mL round-bottom flask. The system was evacuated and backfilled with N_2 three times. DMF (0.040 L) and NEt_3 (2.8 mL, 0.020 mol) were injected into the flask, and then chlorodifluoroacetic anhydride (3.5 mL, 0.020 mol) was added dropwise. The mixture was stirred for 3 h, then the reaction was diluted with Et_2O (50 mL). The solution was washed with $NaHCO_{3\ (aq)}$ (4 x 50 mL). The organic layer solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes : EtOAc 1:0 → 4:1) afforded the title compound as a colorless oil (3.6 g, 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47–7.40 (m, 2 H), 7.39–7.34 (m, 2 H), 7.34–7.29 (m, 1 H), 6.78 (d, *J* = 15.8 Hz, 1 H), 6.32 (dt, *J* = 15.9, 6.7 Hz, 1 H), 5.00 (dd, *J* = 6.7, 1.3 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.62 (s, 2 F).

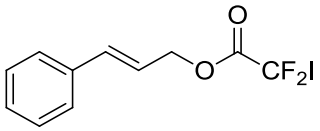


2.1a

Cinnamyl 2-bromo-2,2-difluoroacetate[2]

A one-neck round-bottom flask (flask 1) and a two-neck round-bottom flask (flask 2) were oven-dried and cooled under N_2. Bromodifluoroacetic acid (3.41 g, 19.5 mmol) was added to flask 1 and the system was attached to a bubbler. DCM (0.020 L) was added as solvent, then DMF (0.35 mL, 4.5 mmol) was injected. Oxalyl chloride (1.52 mL, 18.0 mmol) was added dropwise such that steady evolution of gas was maintained (2 h). The solution was stirred at 21 °C until the evolution of gas ceased. Cinnamyl alcohol (2.01 g, 15.0 mmol) was added to flask 2 and the system was attached to a bubbler via a glass adaptor (small-gauge needles clog during acid chloride transfer). DCM (0.030 L) and NEt_3 (4.18 mL, 30.0 mmol) were added and the solution was cooled to 0 °C. The contents of flask 1 were transferred to flask 2 via cannula. Stirring was continued for 30 min at 0 °C, then the mixture was poured over 1 N HCl (50 mL). The phases were separated, then the organic layer was washed with H_2O (50 mL) and brine (50 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 49:1) afforded the title compound as a faint yellow oil (3.47 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.40 (m, 2 H), 7.40–7.29 (m, 3 H), 6.79 (dt, *J* = 15.8, 1.2 Hz, 1 H), 6.32 (dt, *J* = 15.8, 6.7 Hz, 1 H), 5.00 (dd, *J* = 6.7, 1.2 Hz, 2 H).



2.1–CF_2I

Cinnamyl 2,2-difluoro-2-iodoacetate

A one-neck round-bottom flask (flask 1) and a two-neck round-bottom flask (flask 2) were oven-dried and cooled under N_2. Iododifluoroacetic acid (466 mg, 2.10 mmol) was added to flask 1 and the system was attached to a bubbler. DCM (5.0 mL) was added as solvent, then DMF (35 µL, 0.45 mmol) was injected. Oxalyl chloride (0.17 mL, 2.0 mmol) was added dropwise such that steady evolution of gas was maintained (0.5 h). The solution was stirred at 21 °C until the evolution of gas ceased. Cinnamyl alcohol (201 mg, 1.50 mmol) was added to flask 2 and the system was attached to a bubbler. DCM (5.0 mL) and NEt_3 (0.42 mL, 3.0 mmol) were added and the solution was cooled to 0 °C. The contents of flask 1 were transferred to flask 2 via cannula. Stirring was continued for 30 min at 0 °C, then the mixture was poured over 1 N HCl (10 mL). The phases were separated, then the organic layer was washed with H_2O (10 mL) and brine (10 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 49:1) afforded the title compound as a colorless oil (438 mg, 86%).

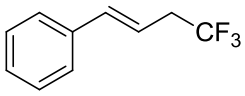
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48–7.42 (m, 2 H), 7.41–7.35 (m, 2 H), 7.35–7.30 (m, 1 H), 6.81 (d, *J* = 15.8 Hz, 1 H), 6.33 (dt, *J* = 15.9, 6.7 Hz, 1 H), 5.01 (dd, *J* = 6.7, 1.2 Hz, 2 H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 160.3 (t, *J* = 28.3 Hz), 136.9, 135.7, 128.9, 128.8, 127.0, 120.4, 86.6 (t, *J* = 321.9 Hz), 68.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –58.34 (s, 2 F).

IR (film): 3032, 1765, 1647, 1495, 1448, 1381, 1283, 1148, 1119, 928, 744, 690 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_9F_2IO_2$) requires m/z 338.0, found m/z 338.0.



2.2a

(*E*)-(4,4,4-Trifluorobut-1-en-1-yl)benzene[3]

Screening Reactions Using Activation Procedure (Scheme 2.5–7 and 2.10): Potassium fluoride (23 mg, 0.40 mmol) was added to a 15 mL screw-top vial. The vial was placed in a vacuum oven (180 °C) and dried for a minimum of 24 h. The vial was removed from the vacuum oven, capped, and cooled under N2. CuI (3.8 mg, 0.020 mmol) and sodium bromodifluoroacetate (9.8 mg, 0.050 mmol) were added. The vial was evacuated and backfilled with N2 three times. DMEDA (2.2 µL, 0.020 mmol), and DMF (0.20 mL) were sequentially injected. The mixture was stirred 10 min at 21 °C resulting in a blue/purple mixture. The vial was placed in a 50 °C heating block and stirred for 10 min. During this time, the color changed to light yellow and bubbling was observed. Cinnamyl halodifluoroacetate (0.200 mmol) was injected and the reaction was heated at 50 °C for 1.5 or 8 h. The vial was allowed to cool to 21 °C, and the mixture was diluted with EtOAc (3 mL). Dodecane (45.4 µL, 0.200 mmol) was injected as a standard, and the solution was stirred to ensure thorough mixing. A small aliquot was removed from the vial, placed on a plug of silica gel and eluted with EtOAc (1 mL).

The sample was analyzed using GC/FID, and the quantity of substrate and product were determined using dodecane as a standard.

Screening Reactions Without Activation Procedure (Scheme 2.7): Potassium fluoride (23 mg, 0.40 mmol) was added to a 15 mL screw-top vial. The vial was placed in a vacuum oven (180 °C) and dried for a minimum of 24 h. The vial was removed from the vacuum oven, capped, and cooled under N2. CuI (3.8 mg, 0.020 mmol) was added, then the vial was evacuated and backfilled with N2 three times. DMEDA (2.2 µL, 0.020 mmol), DMF (0.20 mL), and **1A** (58 mg, 0.20 mmol) were sequentially injected. The vial was placed in a 50 °C heating block and stirred for 1.5 or 8 h. The vial was allowed to cool to 21 °C, and the mixture was diluted with EtOAc (3 mL). Dodecane (45.4 µL, 0.200 mmol) was injected as a standard, and the solution was stirred to ensure thorough mixing. A small aliquot was removed from the vial, placed on a plug of silica gel and eluted with EtOAc (1 mL). The sample was analyzed using GC/FID, and the quantity of substrate and product were determined using dodecane as a standard.

Experimental procedure for compounds in Scheme 2.8:

General Procedure A: A round bottom flask and reflux condenser were oven-dried and cooled under N_2. The acrylic acid derivative (0.010 mol) and anhydrous MeOH (0.050 L) were added followed by drop-wise addition of concentrated sulfuric acid (11 mmol). The system was placed under a balloon of argon and refluxed overnight. The reaction mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. EtOAc (50 mL) and H_2O (20 mL) were added and the phases were separated.

The aqueous layer was extracted with EtOAc (2 x 20 mL) then the combined organic layers were washed with H_2O (20 mL), $Na_2CO_{3\ (aq)}$ (20 mL), and brine (20 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to afford the desired methyl acrylate.

General Procedure B: A two-neck round-bottom flask and liquid addition funnel were oven-dried and cooled under N_2. α,β-Unsaturated ester (0.010 mol) was added, then the system was evacuated and backfilled with N_2 three times. DCM (0.10 L) was added as solvent, then the solution was cooled to –78 °C. DIBAL (1.0 M in PhMe, 21 mL, 21 mmol) was added dropwise over a 60 min period. The solution was warmed to 0 °C over a 30 min period, then MeOH (5 mL) was added to quench the reaction. The mixture was warmed to 21 °C and stirring continued for 30 min. Rochelle's salt $_{(aq)}$ (75 mL) was added to the cloudy mixture and the reaction was vigorously stirred for 12 h. The phases were separated and the aqueous phase was extracted with DCM (2 x 75 mL). The combined organic phases were washed with $Na_2SO_{4\ (aq)}$ (100 mL) and brine (100 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Filtration through a pad of silica (Et_2O) and removal of solvent afforded the desired allylic alcohol.

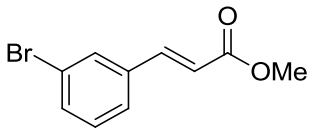
General Procedure C: A one-neck round-bottom flask (flask 1) and a two-neck round-bottom flask (flask 2) were oven-dried and cooled under N_2. Bromodifluoroacetic acid (1.4 mmol) was added to flask 1 and the system was attached to a bubbler. DCM (5 mL) was added as solvent, then DMF (0.30 mmol) was injected. Oxalyl chloride (1.3 mmol)

was added dropwise such that steady evolution of gas was maintained (0.5–2 h). The solution was stirred at 21 °C until the evolution of gas ceased. Allylic alcohol (1.0 mmol) was added to flask 2 and the system was attached to a bubbler via a glass adaptor (small-gauge needles clog during acid chloride transfer). DCM (5 mL) and NEt_3 (2.0 mmol) were added and the solution was cooled to 0 °C. The contents of flask 1 were transferred to flask 2 via cannula. Stirring was continued for 30 min at 0 °C, then the mixture was poured over 1 N HCl (10 mL). The phases were separated, then the organic layer was washed with H_2O (10 mL) and brine (10 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (minimal amount of silica) afforded the desired allylic bromodifluoroacetate.

General Procedure D: Potassium fluoride (23 mg, 0.40 mmol) was added to a 15 mL screw-top vial. The vial was placed in a vacuum oven (180 °C) and dried for a minimum of 24 h. The vial was removed from the vacuum oven, capped, and cooled under N_2. CuI (3.8 mg, 0.020 mmol) and sodium bromodifluoroacetate (9.8 mg, 0.050 mmol) were added. The vial was evacuated and backfilled with N_2 three times. DMEDA (2.2 μL, 0.020 mmol), and DMF (0.20 mL) were sequentially injected. The mixture was stirred 10 min at 21 °C resulting in a blue/purple mixture. The vial was placed in a 50 °C heating block and stirred for 10 min. During this time, the color changed to light yellow and bubbling was observed. Allylic bromodifluoroacetate (0.200 mmol) was injected and the reaction was heated at 50 °C for 8 or 18 h. The vial was allowed to cool to 21 °C, and the mixture was diluted with EtOAc (3 mL). α,α,α-Trifluorotoluene (24.6 μL, 0.200 mmol) was injected as a standard, and an aliquot was removed for ^{19}F NMR analysis. After

determination of the ^{19}F yield, the aliquot was recombined with the reaction mixture. The mixture was further diluted with EtOAc (15 mL) and then washed with H_2O (15 mL) and brine (15 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo.* Chromatographic purification and removal of solvent (care was taken with lower MW compounds) afforded the desired allylic trifluoromethane.

General Procedure E: Potassium fluoride (16 mmol) was added to a 50 mL round-bottom flask. The flask was placed in a vacuum oven (180 °C) and dried for a minimum of 24 h. The flask was removed from the vacuum oven, equipped with a flushing adapter, and cooled under N_2. CuI (0.80 mmol) and sodium bromodifluoroacetate (2.0 mmol) were added. The flask was evacuated and backfilled with N_2 three times. DMEDA (0.80 mmol), and DMF (8.0 mL) were injected. The mixture was stirred 10 min at 21 °C resulting in a blue/purple mixture. The flask was placed in a 50 °C oil bath and stirred for 10 min. During this time, the color changed to brown and bubbling was observed. Allylic bromodifluoroacetate (8.0 mmol) was injected and the reaction was heated at 50 °C for 12 h. The flask was allowed to cool to 21 °C, and the mixture was diluted with EtOAc (25 mL). α,α,α-Trifluorotoluene (98.4 μL, 0.800 mmol) was injected as a standard, and an aliquot was removed for ^{19}F NMR analysis. After determination of the ^{19}F yield, the aliquot was recombined with the reaction mixture. The mixture was further diluted with EtOAc (50 mL) and then washed with H_2O (50 mL) and brine (50 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo.* Chromatographic purification and removal of solvent afforded the desired allylic trifluoromethane.



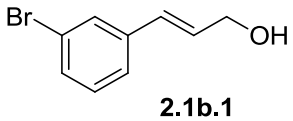
2.1b.2

(*E*)-Methyl 3-(3-bromophenyl)acrylate[4]

General Procedure A was followed using 3-bromocinnamic acid (3.05 g, 13.4 mmol), sulfuric acid (0.79 mL, 15 mmol), and MeOH as solvent (0.050 L). Workup afforded the title compound as a colorless solid (3.01 g, 93%).

m.p.: 54–55 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (t, *J* = 1.8 Hz, 1 H), 7.62 (d, *J* = 16.0 Hz, 1 H), 7.54–7.49 (m, 1 H), 7.46–7.43 (m, 1 H), 7.27 (m, 1 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 3.82 (s, 3 H).

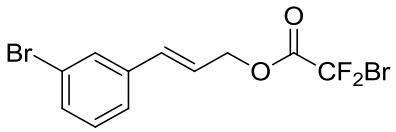


2.1b.1

(*E*)-3-(3-Bromophenyl)prop-2-en-1-ol[5]

General Procedure B was followed using **2.1b.2** (2.91 g, 12.1 mmol), DIBAL (1.0 M in PhMe, 25.3 mL, 25.3 mmol), with DCM (50 mL) as solvent. Workup and filtration through a pad of silica (EtOAc) afforded the title compound as a light yellow oil (2.47 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (t, *J* = 1.8 Hz, 1 H), 7.38 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1 H), 7.31 (dt, *J* = 7.8, 1.3 Hz, 1 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 6.57 (dt, *J* = 15.9, 1.6 Hz, 1 H), 6.38 (dt, *J* = 15.9, 5.5 Hz, 1 H), 4.35 (td, *J* = 5.7, 1.6 Hz, 2 H), 1.50 (t, *J* = 5.9 Hz, 1 H).



2.1b

(*E*)-3-(3-Bromophenyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.1b.1** (259 mg, 1.22 mmol), bromodifluoroacetic acid (299 mg, 1.71 mmol), oxalyl chloride (134 µL, 1.59 mmol), DMF (28 µL, 0.37 mmol), triethylamine (0.340 mL, 2.44 mmol), with DCM (15 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a colorless oil (392 mg, 87%).

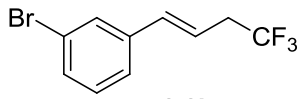
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59–7.56 (m, 1 H), 7.46–7.42 (m, 1 H), 7.36–7.32 (m, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 6.71 (dd, *J* = 15.9, 1.4 Hz, 1 H), 6.31 (dt, *J* = 15.9, 6.5 Hz, 1 H), 5.00 (dd, *J* = 6.5, 1.3 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.5 (t, *J* = 31.5 Hz), 137.7, 135.2, 131.7, 130.4, 129.8, 125.7, 123.0, 122.0, 108.8 (t, *J* = 314.3 Hz), 68.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.89 (s, 2 F).

IR (film): 3063, 2951, 1774, 1591, 1560, 1474, 1377, 1300, 1286, 1167, 1128, 947, 773, 712 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_8Br_2F_2O_2$) requires *m/z* 367.9, found *m/z* 368.0.



2.2b

(*E*)-1-Bromo-3-(4,4,4-trifluorobut-1-en-1-yl)benzene

Entry 1: General Procedure D was followed using **2.2b** (74.0 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane / Et_2O 1:0 → 49:1) afforded the title compound as a colorless oil (43.0 mg, 81%).

Entry 2: General Procedure E was followed using **2.2b** (2.96 g, 8.00 mmol), CuI (152 mg, 0.800 mmol), DMEDA (86 µL, 0.020 mmol), sodium bromodifluoroacetate (394 mg, 2.00 mmol), KF (0.93 g, 16 mmol), and DMF (8.0 mL) as solvent. After activation, the reaction was heated at 50 °C for 12 h. Workup and chromatographic purification (hexanes / EtOAc 49:1) afforded the title compound as a colorless oil (1.89 g, 89%).

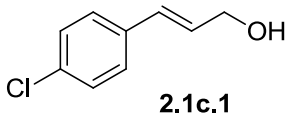
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (t, *J* = 1.9 Hz, 1 H), 7.41 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1 H), 7.30 (dt, *J* = 7.7, 1.3 Hz, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 6.55 (d, *J* = 15.8 Hz, 1 H), 6.13 (dt, *J* = 15.9, 7.2 Hz, 1 H), 3.01 (qdd, *J* = 10.6, 7.3, 1.4 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.4, 135.9, 131.1, 130.3, 129.5, 128.1 (q, *J* = 276.7 Hz), 125.3, 123.0, 119.0 (q, *J* = 3.6 Hz), 37.8 (q, *J* = 30.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.18 (t, *J* = 10.7 Hz, 3 F).

IR (film): 3061, 2928, 2854, 1591, 1564, 1477, 1425, 1366, 1306, 1256, 1140, 1049, 964, 928, 868, 771, 685, 650 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{10}H_8BrF_3$) requires *m/z* 264.0, found *m/z* 264.0.



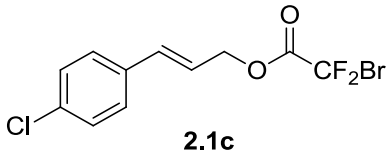
2.1c.1

(E)-3-(4-Chlorophenyl)prop-2-en-1-ol[6]

General Procedure B was followed using 4-chlorocinnamaldehyde (624 mg, 3.75 mmol), DIBAL (1.0 M in PhMe, 4.1 mL, 4.1 mmol), with DCM (0.040 L) as solvent. Workup and filtration through a pad of silica (Et_2O) afforded the title compound as a colorless solid (594 mg, 94%).

m.p.: 54–56 °C (lit.[14] 52–54 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 4 H), 6.59 (dd, *J* = 15.9, 1.7 Hz, 1 H), 6.35 (dt, *J* = 15.9, 5.6 Hz, 1 H), 4.34 (d, *J* = 5.7 Hz, 2 H), 1.44 (s, 1 H).



2.1c

(*E*)-3-(4-Chlorophenyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.1c.1** (396 mg, 2.35 mmol), bromodifluoroacetic acid (575 mg, 3.29 mmol), oxalyl chloride (258 µL, 3.05 mmol), DMF (54 µL, 0.70 mmol), triethylamine (654 µL, 4.69 mmol), with DCM (12 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a colorless oil (707 mg, 93%).

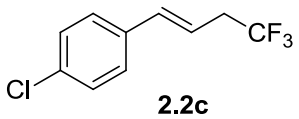
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.30 (m, 4 H), 6.74 (d, *J* = 15.9 Hz, 1 H), 6.29 (dt, *J* = 15.9, 6.6 Hz, 1 H), 4.99 (dd, *J* = 6.6, 1.3 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.6 (t, *J* = 31.5 Hz), 135.6, 134.6, 134.1, 129.1, 128.2, 121.0, 108.8 (t, *J* = 314.4 Hz), 68.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.68 (s, 2 F).

IR (film): 3030, 2951, 1774, 1491, 1304, 1288, 1169, 1126, 1092, 947, 849, 712 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_8BrClF_2O_2$) requires *m/z* 323.9, found *m/z* 324.0.



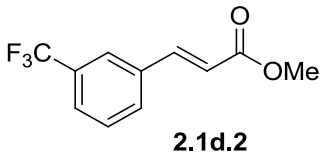
2.2c

(*E*)-1-Chloro-4-(4,4,4-trifluorobut-1-en-1-yl)benzene[7]

General Procedure D was followed using **2.1c** (65.1 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 μL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (31.6 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (s, 4 H), 6.57 (dt, *J* = 15.9, 1.2 Hz, 1 H), 6.10 (dt, *J* = 16.0, 7.3 Hz, 1 H), 3.00 (qdd, *J* = 10.7, 7.2, 1.4 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.18 (t, *J* = 10.6 Hz, 3 F).



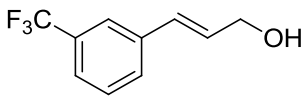
2.1d.2

(*E*)-Methyl 3-(3-(trifluoromethyl)phenyl)acrylate[8]

General Procedure A was followed using 3-(trifluoromethyl)cinnamic acid (649 mg, 3.00 mmol), sulfuric acid (0.18 mL, 3.3 mmol), and MeOH as solvent (15 mL). Workup afforded the title compound as a colorless oil (658 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.76 (m, 1 H), 7.75–7.68 (m, 2 H), 7.67–7.62 (m, 1 H), 7.53 (t, *J* = 7.8 Hz, 1 H), 6.52 (d, *J* = 16.0 Hz, 1 H), 3.84 (s, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.99 (s, 3 F).



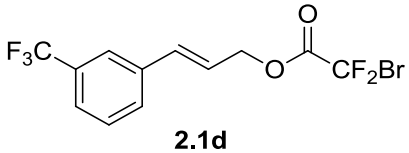
2.1d.1

(*E*)-3-(3-(Trifluoromethyl)phenyl)prop-2-en-1-ol[9]

General Procedure B was followed using **2.1d.2** (655 mg, 2.85 mmol), DIBAL (1.0 M in PhMe, 6.0 mL, 6.0 mmol), with DCM (0.030 L) as solvent. Workup and filtration through a pad of silica (Et_2O) afforded the title compound as a tan oil (530 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.61 (m, 1 H), 7.59–7.53 (m, 1 H), 7.53–7.48 (m, 1 H), 7.47–7.41 (m, 1 H), 6.71–6.62 (m, 1 H), 6.45 (dt, *J* = 15.9, 5.4 Hz, 1 H), 4.38 (dd, *J* = 5.4, 1.7 Hz, 2 H), 1.57–1.52 (m, 1 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.85 (s, 3 F).



2.1d

(*E*)-3-(3-(Trifluoromethyl)phenyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.1d.1** (202 mg, 1.00 mmol), bromodifluoroacetic acid (245 mg, 1.40 mmol), oxalyl chloride (0.110 mL, 1.30 mmol), DMF (23 µL, 0.030 mmol), triethylamine (279 µL, 2.00 mmol), with DCM (0.010 L) as

solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a colorless oil (291 mg, 81%).

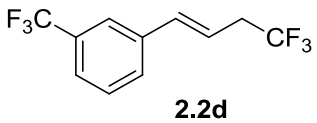
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.65 (m, 1 H), 7.62–7.55 (m, 2 H), 7.52–7.45 (m, 1 H), 6.81 (d, *J* = 15.9 Hz, 1 H), 6.39 (dt, *J* = 15.9, 6.5 Hz, 1 H), 5.02 (dd, *J* = 6.5, 1.3 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.5 (t, *J* = 31.6 Hz), 136.4, 135.1, 131.4 (q, *J* = 32.4 Hz), 130.1, 129.4, 125.3 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.4 Hz), 123.6 (q, *J* = 3.8 Hz), 122.5, 108.8 (t, *J* = 314.4 Hz), 68.23.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.57 (s, 2 F), (–113.93)–(–114.03) (m, 1 F).

IR (film): 3045, 2959, 1778, 1443, 1337, 1306, 1290, 1167, 1126, 1072, 949, 824, 793, 712, 696, 662, 602 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_8BrF_5O_2$) requires *m/z* 358.0, found *m/z* 358.0.



2.2d

(*E*)-1-(4,4,4-Trifluorobut-1-en-1-yl)-3-(trifluoromethyl)benzene

General Procedure D was followed using **2.1d** (71.8 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 μL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a pale yellow oil (36.2 mg, 71%).

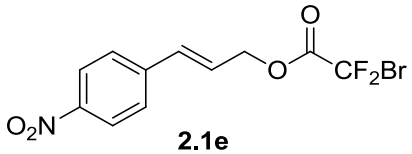
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1 H), 7.59–7.52 (m, 2 H), 7.49–7.44 (m, 1 H), 6.66 (d, *J* = 15.9 Hz, 1 H), 6.21 (dt, *J* = 15.9, 7.2 Hz, 1 H), 3.03 (qdd, *J* = 10.6, 7.3, 1.4 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 137.0, 135.5, 131.3 (q, *J* = 32.2 Hz), 129.7, 129.3, 125.9 (q, *J* = 277.16 Hz), 124.8 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 272.6 Hz), 123.3 (q, *J* = 3.9 Hz), 119.5 (q, *J* = 3.6 Hz), 37.8 (q, *J* = 30.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.62 (s, 3 F), –67.00 (t, *J* = 10.5 Hz, 3 F).

IR (film): 3047, 3015, 2961, 2932, 1431, 1369, 1333, 1283, 1259, 1204, 1130, 1074, 966, 932, 814, 789, 696 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_8F_6$) requires *m/z* 254.1, found *m/z* 254.1.



2.1e

(*E*)-3-(4-Nitrophenyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using 4-nitrocinnamyl alcohol (179 mg, 1.00 mmol), bromodifluoroacetic acid (245 mg, 1.40 mmol), oxalyl chloride (0.110 mL, 1.30 mmol), DMF (23 µL, 0.30 mmol), NEt_3 (279 µL, 2.00 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 19:1) afforded the title compound as a viscous yellow oil (294 mg, 88%).

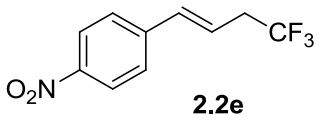
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24–8.21 (m, 2 H), 7.59–7.55 (m, 2 H), 6.84 (dt, *J* = 15.9, 1.4 Hz, 1 H), 6.48 (dt, *J* = 15.9, 6.3 Hz, 1 H), 5.05 (dd, *J* = 6.3, 1.4 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.5 (t, *J* = 31.7 Hz), 147.7, 141.9, 133.8, 127.6, 125.2, 124.3, 108.7 (t, *J* = 314.3 Hz), 67.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.72 (s, 2 F).

IR (film): 3109, 3080, 2941, 2851, 1772, 1597, 1518, 1448, 1344, 1304, 1167, 1126, 949, 860, 822, 743, 710 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_8BrF_2NO_4$) requires *m/z* 335.0, found *m/z* 335.0.



2.2e

(*E*)-1-Nitro-4-(4,4,4-trifluorobut-1-en-1-yl)benzene

General Procedure D was followed using **2.1e** (67.2 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 μL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane / Et_2O 1:0 → 9:1) afforded the title compound as a yellow oil (38.5 mg, 83%).

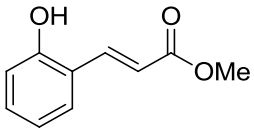
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 6.71 (d, *J* = 15.9 Hz, 1 H), 6.33 (dt, *J* = 15.9, 7.2 Hz, 1 H), 3.08 (qdd, *J* = 10.5, 7.2, 1.4 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.5, 142.5, 134.8, 127.2, 125.7 (q, *J* = 276.8 Hz), 124.2, 122.3 (q, *J* = 3.7 Hz), 37.9 (q, *J* = 30.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –66.94 (t, *J* = 10.9 Hz, 3 F).

IR (film): 3047, 2937, 1659, 1599, 1518, 1429, 1344, 1306, 1250, 1138, 1109, 1051, 970, 924, 849, 808, 743 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{10}H_8F_3NO_2$) requires *m/z* 231.1, found *m/z* 231.1.



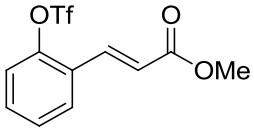
2.1f.3

(*E*)-Methyl 3-(2-hydroxyphenyl)acrylate[10]

General Procedure A was followed using 2-hydroxycinnamic acid (1.64 g, 10.0 mmol), H_2SO_4 (0.59 mL, 11 mmol), and MeOH as solvent (0.050 L). Workup afforded the title compound as a colorless solid (1.66 g, 93%).

m.p.: 132–136 °C (lit.[11] 136–137 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 16.1 Hz, 1 H), 7.48 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.27 – 7.23 (m, 1 H), 6.94 (td, *J* = 7.6, 1.1 Hz, 1 H), 6.85 (dd, *J* = 8.1, 1.1 Hz, 1 H), 6.64 (d, *J* = 16.2 Hz, 1 H), 6.27–6.17 (m, 1 H), 3.84 (s, 3 H).



2.1f.2

(*E*)-Methyl 3-(2-(((trifluoromethyl)sulfonyl)oxy)phenyl)acrylate

A 100 mL round bottom flask was oven-dried and cooled under N_2. Compound **2.1f.3** (0.96 g, 5.4 mmol) was added then the flask was equipped with a rubber septum. The flask was then evacuated and backfilled with N_2 three times. DCM (0.020 L) and 2,6-lutidine (1.26 mL, 10.8 mmol) were injected, and the solution was cooled to –78 °C. Trifluoromethanesulfonic anhydride (1.1 mL, 6.5 mmol) was added dropwise, and the solution was stirred for 15 min. The flask was allowed to warm to 21 °C, and then stirred for 3 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (10 mL), then diluted with DCM (40 mL). The organic phase was washed with H_2O (30 mL), brine (30 mL), dried over

$MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 1:0 → 9:1) afforded the title compound as a pale tan liquid (1.24 g, 74%).

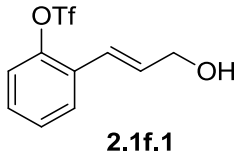
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 16.0 Hz, 1 H), 7.71 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.49 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1 H), 7.45 – 7.41 (m, 1 H), 7.38 (dd, *J* = 8.2, 1.3 Hz, 1 H), 6.52 (d, *J* = 16.1 Hz, 1 H), 3.84 (s, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.5, 147.7, 136.2, 131.8, 128.8, 128.4, 128.1, 122.4, 122.3, 118.7 (q, *J* = 320.3 Hz), 52.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ –74.19 (s, 3 F).

IR (film): 3070, 3003, 2955, 1724, 1637, 1423, 1213, 1140, 1078, 895, 827, 768 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{11}H_9F_3O_5SNa$) requires *m/z* 333.0021, found *m/z* 333.0024 (0.9 ppm).



2.1f.1

(*E*)-2-(3-Hydroxyprop-1-en-1-yl)phenyl trifluoromethanesulfonate

General Procedure B was followed using **2.1f.2** (0.82 g, 2.6 mmol), DIBAL (1.0 M in PhMe, 5.6 mL, 5.6 mmol), and DCM (0.020 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 2:1) afforded the title compound as a colorless oil (0.68 g, 90%).

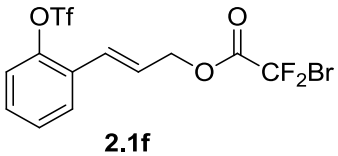
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 7.3, 2.2 Hz, 1 H), 7.39–7.31 (m, 2 H), 7.30–7.28 (m, 1 H), 6.85 (dt, *J* = 15.9, 1.8 Hz, 1 H), 6.47 (dt, *J* = 15.9, 5.3 Hz, 1 H), 4.39 (td, *J* = 5.7, 1.8 Hz, 2 H), 1.62–1.58 (m, 1 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 147.0, 133.8, 130.5, 129.2, 128.6, 127.8, 122.6, 121.9, 118.7 (q, *J* = 321.3 Hz), 63.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –74.61 (s, 3 F).

IR (film): 3416, 2960, 1643, 1483, 1450, 1418, 1138, 1072, 891 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{10}H_9F_3O_4S$) requires *m/z* 282.0, found *m/z* 282.1.



2.1f

(*E*)-3-(2-(((Trifluoromethyl)sulfonyl)oxy)phenyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2A-6-1** (282 mg, 1.00 mmol), bromodifluoroacetic acid (245 mg, 1.40 mmol), oxalyl chloride (0.110 mL, 1.30 mmol), DMF (23 µL, 0.030 mmol), triethylamine (279 µL, 2.00 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 19:1) afforded the title compound as a colorless oil (378 mg, 86%).

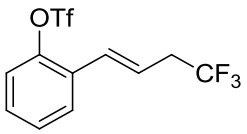
^1H NMR (500 MHz, $CDCl_3$): δ 7.67–7.61 (m, 1 H), 7.43–7.37 (m, 2 H), 7.34–7.29 (m, 1 H), 6.98 (dt, *J* = 16.0, 1.5 Hz, 1 H), 6.40 (dt, *J* = 15.9, 6.2 Hz, 1 H), 5.04 (dd, *J* = 6.2, 1.5 Hz, 2 H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 159.5 (t, *J* = 31.7 Hz), 147.1, 130.2, 129.3, 128.7, 128.0, 127.8, 125.4, 122.1, 118.7 (q, *J* = 320.6 Hz), 108.7 (t, *J* = 314.2 Hz), 67.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.76 (s, 2 F), –74.46 (s, 3 F).

IR (film): 3067, 3036, 2957, 1780, 1485, 1421, 1294, 1248, 1217, 1138, 951, 891, 825, 766, 710, 606 cm^{-1}.

MS (CI): mass calculated for $[M–Br]^+$ ($C_{12}H_8F_5O_5S$) requires *m/z* 359.0, found *m/z* 359.1.



2.2f

(*E*)-2-(4,4,4-Trifluorobut-1-en-1-yl)phenyl trifluoromethanesulfonate

General procedure D was followed using **2.1f** (87.8 mg, 0.200 mmol). Workup and chromatographic purification (pentane) yielded the title compound as a colorless oil (49.9 mg, 75%).

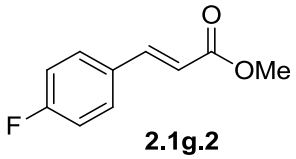
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.59 (m, 1 H), 7.41–7.35 (m, 2 H), 7.33–7.28 (m, 1 H), 6.83 (d, *J* = 15.9 Hz, 1 H), 6.22 (dt, *J* = 15.9, 7.3 Hz, 1 H), 3.07 (qdd, *J* = 10.6, 7.2, 1.5 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 146.9, 129.9, 129.8, 128.9, 128.7, 127.8, 125.7 (q, *J* = 277.0 Hz), 122.5 (q, *J* = 3.6 Hz), 122.0, 118.7 (q, *J* = 320.7 Hz), 38.0 (q, *J* = 30.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.04 (t, *J* = 10.4 Hz, 3 F), –75.08 (s, 3 F).

IR (film): 3065, 2934, 2858, 1485, 1452, 1423, 1371, 1250, 1217, 1138, 1080, 1049, 968, 893, 814, 766, 608 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_8F_6O_3S$) requires *m/z* 334.0, found *m/z* 334.0.



2.1g.2

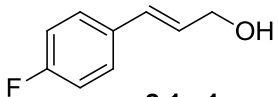
(*E*)-methyl 3-(4-Fluorophenyl)acrylate[12]

General Procedure A was followed using 4-fluorocinnamic acid (1.66 g, 10.0 mmol), H_2SO_4 (0.59 mL, 11 mmol), and MeOH as solvent (0.050 L). Workup afforded the title compound as a colorless solid (1.75 g, 97%).

m.p.: 44–45 °C (lit.[13] 45–47 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 16.0 Hz, 1 H), 7.56–7.49 (m, 2 H), 7.12–7.05 (m, 2 H), 6.37 (dd, *J* = 16.0, 0.6 Hz, 1 H), 3.82 (s, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ (–110.55)–(–110.65) (m, 1 F).



2.1g.1

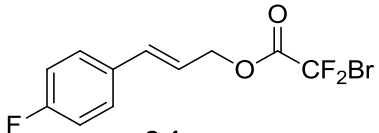
(*E*)-3-(4-Fluorophenyl)prop-2-en-1-ol[14]

General Procedure B was followed using **2.1g.2** (1.70 g, 9.44 mmol), DIBAL (1.0 M in PhMe, 19.8 mL, 19.8 mmol), with DCM (100 mL) as solvent. Workup and filtration through a pad of silica (Et_2O) afforded the title compound as a colorless solid (1.35 g, 94%).

m.p.: 58–60 °C (lit.[14] 57–58 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 2 H), 7.06–6.97 (m, 2 H), 6.64–6.54 (m, 1 H), 6.29 (dt, *J* = 15.9, 5.7 Hz, 1 H), 4.33 (dd, *J* = 5.5, 1.7 Hz, 2 H), 1.48 (s, 1 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –116.96 (ddd, *J* = 14.2, 8.8, 5.5 Hz, 1 F).



2.1g

(*E*)-3-(4-Fluorophenyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.1g.1** (152 mg, 1.00 mmol), bromodifluoroacetic acid (245 mg, 1.40 mmol), oxalyl chloride (0.110 mL, 1.30 mmol), DMF (23 µL, 0.030 mmol), triethylamine (279 µL, 2.00 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a colorless oil (187 mg, 60%).

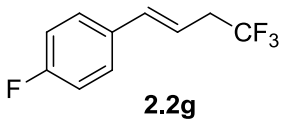
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.37 (m, 2 H), 7.09–7.01 (m, 2 H), 6.75 (d, *J* = 15.8 Hz, 1 H), 6.23 (dt, *J* = 15.8, 6.7 Hz, 1 H), 4.99 (dd, *J* = 6.7, 1.2 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 163.1 (d, *J* = 248.5 Hz), 159.6 (t, *J* = 31.4 Hz), 135.9, 131.8 (d, *J* = 3.3 Hz), 128.7 (d, *J* = 8.2 Hz), 120.1 (d, *J* = 2.3 Hz), 115.9 (d, *J* = 21.7 Hz), 108.8 (t, *J* = 314.4 Hz), 68.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.64 (s, 2 F), –113.58 (ddd, *J* = 13.8, 8.7, 5.4 Hz, 1 F).

IR (film): 3045, 2957, 2924, 1774, 1655, 1603, 1508, 1450, 1416, 1379, 1290, 1234, 1169, 1128, 947, 851, 712, 604 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_8BrF_3O_2$) requires *m/z* 308.0, found *m/z* 308.0.



2.2g

(*E*)-1-Fluoro-4-(4,4,4-trifluorobut-1-en-1-yl)benzene

General Procedure D was followed using **2.1g** (61.8 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg,

0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (26.4 mg, 65%).

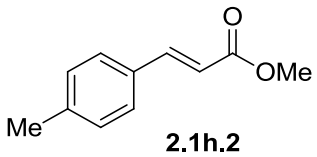
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.34 (m, 2 H), 7.07–7.00 (m, 2 H), 6.58 (d, *J* = 15.9 Hz, 1 H), 6.04 (dt, *J* = 15.8, 7.2 Hz, 1 H), 2.99 (qdd, *J* = 10.7, 7.2, 1.4 Hz, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.7 (d, *J* = 247.6 Hz), 135.6, 132.5 (d, *J* = 3.3 Hz), 128.2 (d, *J* = 8.1 Hz), 126.0 (q, *J* = 276.6 Hz), 117.2–117.0 (m), 115.7 (d, *J* = 21.7 Hz), 37.8 (q, *J* = 30.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.30 (t, *J* = 10.9 Hz, 3 F), (–115.03)–(–115.14) (m, 1 F).

IR (film): 3045, 3007, 2968, 2932, 1601, 1510, 1429, 1369, 1308, 1258, 1252, 1140, 1115, 1049, 968, 922, 837, 797, 770 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{10}H_8F_4$) requires *m/z* 204.1, found *m/z* 204.1.



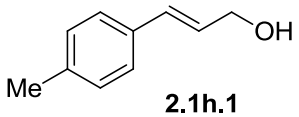
2.1h.2

(*E*)-Methyl 3-(p-tolyl)acrylate[13]

General Procedure A was followed using 4-methylcinnamic acid (1.62 g, 10.0 mmol), sulfuric acid (0.59 mL, 11 mmol), and MeOH as solvent (0.050 L). Workup afforded the title compound as a colorless solid (1.68 g, 95%).

m.p.: 55–56 °C (lit.[13] 50–52 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 16.0 Hz, 1 H), 7.44 (d, *J* = 8.1 Hz, 2 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 6.41 (d, *J* = 16.0 Hz, 1 H), 3.81 (s, 3 H), 2.39 (s, 3 H).



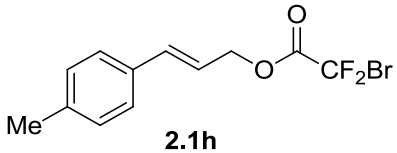
2.1h.1

(*E*)-3-(p-Tolyl)prop-2-en-1-ol[6]

General Procedure B was followed using **2.1h.2** (1.68 g, 9.5 mmol), DIBAL (1.0 M in PhMe, 20.0 mL, 20.0 mmol), with DCM (0.10 L) as solvent. Workup and filtration through a pad of silica (Et_2O) afforded the title compound as a colorless solid (1.37 g, 97%).

m.p.: 49–52 °C (lit.[13] 60–61 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.1 Hz, 2 H), 7.16–7.13 (m, 2 H), 6.60 (dt, *J* = 15.9, 1.5 Hz, 1 H), 6.33 (dt, *J* = 15.8, 5.9 Hz, 1 H), 4.33 (td, *J* = 5.9, 1.5 Hz, 2 H), 2.35 (s, 3 H), 1.40 (t, *J* = 5.9 Hz, 1 H).



2.1h

(*E*)-3-(p-Tolyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.1h.1** (148 mg, 1.00 mmol), bromodifluoroacetic acid (245 mg, 1.40 mmol), oxalyl chloride (0.110 mL, 1.30 mmol), DMF (23 µL, 0.030 mmol), triethylamine (279 µL, 2.00 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a colorless oil (204 mg, 67%).

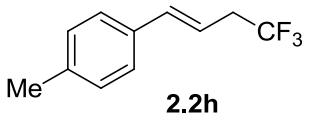
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.30 (m, 2 H), 7.19–7.15 (m, 2 H), 6.75 (d, *J* = 15.8 Hz, 1 H), 6.26 (dt, *J* = 15.8, 6.8 Hz, 1 H), 4.99 (dd, *J* = 6.8, 1.1 Hz, 2 H), 2.36 (s, 3 H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 159.6 (t, *J* = 31.3 Hz), 138.9, 137.1, 132.8, 129.6, 126.9, 119.2, 108.9 (t, *J* = 314.4 Hz), 69.1, 21.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.64 (s, 2 F).

IR (film): 3047, 3024, 2951, 2921, 1774, 1655, 1514, 1448, 1379, 1304, 1288, 1169, 1128, 968, 947, 845, 827, 793, 712, 604 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_{11}BrF_2O_2$) requires *m/z* 304.0, found *m/z* 304.0.



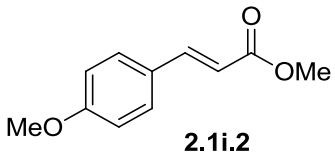
2.2h

(*E*)-1-Methyl-4-(4,4,4-trifluorobut-1-en-1-yl)benzene[7]

General Procedure D was followed using **2.1h** (61.0 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 μL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (28.2 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.1 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.58 (d, *J* = 15.9 Hz, 1 H), 6.07 (dt, *J* = 15.8, 7.2 Hz, 1 H), 2.99 (qdd, *J* = 10.7, 7.2, 1.4 Hz, 2 H), 2.36 (s, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.37 (t, *J* = 9.9 Hz, 3 F).



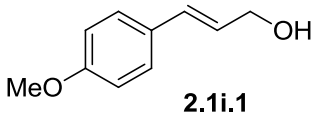
2.1i.2

(*E*)-Methyl 3-(4-methoxyphenyl)acrylate[8]

General Procedure A was followed using 4-methoxycinnamic acid (891 mg, 5.00 mmol), sulfuric acid (0.29 mL, 5.5 mmol), and methanol as solvent (25 mL). Workup afforded the title compound as a colorless solid (946 mg, 98%).

m.p.: 85–87 °C (lit.[15] 85–87 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 16.0 Hz, 1 H), 7.54–7.43 (m, 2 H), 6.97–6.86 (m, 2 H), 6.32 (d, *J* = 16.0 Hz, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H).



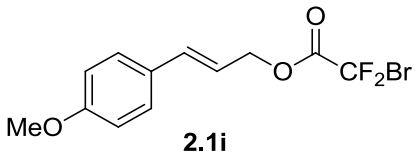
2.1i.1

(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol[6]

General Procedure B was followed using **2.1i.2** (941 mg, 4.90 mmol), DIBAL (1.0 M in PhMe, 10.3 mL, 10.3 mmol), with DCM (0.050 L) as solvent. Workup and filtration through a pad of silica (Et_2O) afforded the title compound as a colorless solid (765 mg, 95%).

m.p.: 72–75 °C (lit.[15] 79–81 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.31 (m, 2 H), 6.90–6.84 (m, 2 H), 6.57 (d, *J* = 15.9 Hz, 1 H), 6.25 (dt, *J* = 15.8, 6.0 Hz, 1 H), 4.31 (td, *J* = 5.9, 1.5 Hz, 2 H), 3.82 (s, 3 H), 1.46–1.41 (m, 1 H).



2.1i

(*E*)-3-(4-Methoxyphenyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.1i.1** (164 mg, 1.00 mmol), bromodifluoroacetic acid (245 mg, 1.40 mmol), oxalyl chloride (0.110 mL, 1.30 mmol), DMF (23 µL, 0.30 mmol), NEt_3 (279 µL, 2.00 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 19:1) afforded the title compound as a yellow oil (179 mg, 63%).

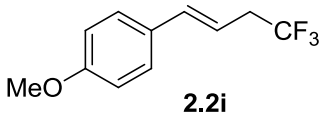
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.33 (m, 2 H), 6.93–6.84 (m, 2 H), 6.73 (d, *J* = 15.8 Hz, 1 H), 6.18 (dt, *J* = 15.8, 6.9 Hz, 1 H), 4.98 (dd, *J* = 6.9, 1.1 Hz, 2 H), 3.83 (s, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.2, 159.6 (t, *J* = 31.4 Hz), 137.0, 128.3, 127.9, 117.9, 114.3, 108.9 (t, *J* = 314.5 Hz), 69.3, 55.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.76 (s, 2 F).

IR (film): 3034, 3003, 2957, 1772, 1607, 1512, 1294, 1250, 1175, 1126, 1034, 945, 829 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_{11}BrF_2O_3$) requires *m/z* 320.0, found *m/z* 320.0.



2.2i

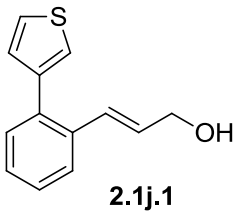
(*E*)-1-Methoxy-4-(4,4,4-trifluorobut-1-en-1-yl)benzene[7]

General Procedure D was followed using **2.1i** (64.2 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation,

the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane / Et_2O 1:0 → 49:1) afforded the title compound as a tan oil (24.8 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.30 (m, 2 H), 6.91–6.84 (m, 2 H), 6.55 (d, *J* = 15.8 Hz, 1 H), 5.98 (dt, *J* = 15.9, 7.2 Hz, 1 H), 3.83 (s, 3 H), 2.97 (qdd, *J* = 10.7, 7.3, 1.4 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –66.35 (t, *J* = 10.7 Hz, 3 F).



2.1j.1

(*E*)-3-(2-(Thiophen-3-yl)phenyl)prop-2-en-1-ol

Two resealable 15 mL test tubes were oven-dried, capped with PTFE septa, and cooled under N_2. $Pd(OAc)_2$ (4.5 mg, 0.020 mmol) and X-Phos (19.1 mg, 0.0400 mmol) were added to tube 1. The tube was evacuated and backfilled with N_2 three times. Degassed H_2O (1.4 µL, 0.080 mmol) and THF (1.0 mL) were injected. The tube was placed in a 60 °C oil bath for 3 min resulting in a color change of the reaction from deep red to dark green. The tube was removed from the oil bath and allowed to cool to 21 °C. Compound **2.1f.1** (282 mg, 1.00 mmol) and 3-thiopheneboronic acid (192 mg, 1.50 mmol) were added to tube 2. The tube was evacuated and backfilled with N_2 three time. THF (1 mL) and degassed 0.5 M $K_3PO_{4\ (aq)}$ were injected. The solution in tube 1 was transferred to tube 2 via cannula. The reaction was placed in a 40 °C oil bath and vigorously stirred for 2 h. The tube was removed from the oil bath and cooled to 21 °C. The reaction was diluted with Et_2O (10 mL) and H_2O (5 mL). The phases were separated then the

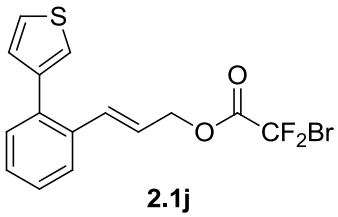
aqueous phase was extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (25 mL). The organic solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 1:0 → 3:1) afforded the title compound as a viscous brown oil (154 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 7.1, 2.0 Hz, 1 H), 7.41–7.28 (m, 4 H), 7.25 (dd, *J* = 3.0, 1.3 Hz, 1 H), 7.16 (dd, *J* = 4.9, 1.3 Hz, 1 H), 6.75 (dt, *J* = 15.9, 1.6 Hz, 1 H), 6.32 (dt, *J* = 15.8, 5.9 Hz, 1 H), 4.32–4.26 (m, 2 H), 1.40 (bs, 1 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 141.4, 135.7, 135.2, 130.4, 130.1, 129.8, 129.4, 127.8, 127.7, 126.5, 125.3, 123.6, 64.1.

IR (film): 3375, 3103, 3057, 3026, 2926, 2856, 1474, 1443, 1364, 1109, 1082, 1009, 970, 858, 791, 754 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{13}H_{12}OS$) requires *m/z* 216.1, found *m/z* 216.1.



2.1j

(*E*)-3-(2-(Thiophen-3-yl)phenyl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.1j.1** (132 mg, 0.610 mmol), bromodifluoroacetic acid (0.15 g, 0.85 mmol), oxalyl chloride (67 µL, 0.79 mmol), DMF (14 µL, 0.18 mmol), NEt_3 (0.17 mL, 1.2 mmol), with DCM (6.0 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 19:1) afforded the title compound as a colorless oil (129.9 mg, 57%).

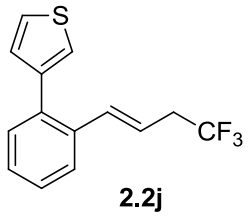
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62–7.58 (m, 1 H), 7.41–7.34 (m, 4 H), 7.24 (dd, *J* = 3.0, 1.3 Hz, 1 H), 7.15 (dd, *J* = 4.9, 1.3 Hz, 1 H), 6.92 (dt, *J* = 15.8, 1.3 Hz, 1 H), 6.25 (dt, *J* = 15.8, 6.6 Hz, 1 H), 4.96 (dd, *J* = 6.5, 1.3 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.6 (t, *J* = 31.4 Hz), 140.9, 136.2, 135.9, 134.1, 130.2, 129.4, 128.6, 127.8, 126.6, 125.6, 123.9, 121.5, 108.9 (t, *J* = 314.5 Hz), 68.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.65 (s, 2 F).

IR (film): 3103, 3059, 3026, 2955, 1774, 1474, 1447, 1379, 1169, 1126, 945, 793, 754, 710 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{15}H_{11}BrF_2O_2S$) requires *m/z* 372.0, found *m/z* 372.0.



2.2j

(E)-3-(2-(4,4,4-trifluorobut-1-en-1-yl)phenyl)thiophene

General Procedure D was followed using **2.1j** (74.6 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 μL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (42.9 mg, 80%).

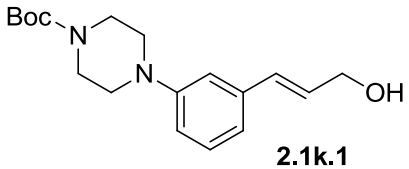
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.53 (m, 1 H), 7.41–7.31 (m, 4 H), 7.24 (dd, J = 3.1, 1.3 Hz, 1 H), 7.16 (dd, J = 4.9, 1.3 Hz, 1 H), 6.74 (d, J = 15.8 Hz, 1 H), 6.05 (dt, J = 15.8, 7.3 Hz, 1 H), 2.96 (qdd, J = 10.7, 7.3, 1.4 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.1, 136.3, 135.6, 134.9, 130.0, 129.4, 128.2, 127.7, 126.6, 126.1 (q, J = 276.7 Hz), 125.4, 123.7, 118.5 (q, J = 3.6 Hz), 37.9 (q, J = 29.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.21 (t, J = 11.0 Hz, 3 F).

IR (film): 3061, 3026, 2926, 1474, 1429, 1364, 1248, 1138, 1053, 970, 858, 791, 754 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{14}H_{11}F_3S$) requires m/z 268.1, found m/z 268.1.



2.1k.1

(*E*)-*tert*-Butyl 4-(3-(3-hydroxyprop-1-en-1-yl)phenyl)piperazine-1-carboxylate

1-Boc-piperazine (224 mg, 1.20 mmol), Pd_2dba_3 (9.2 mg, 0.010 mmol), and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (9.4 mg, 0.024 mmol) were added to an oven dried 15 mL resealable test tube equipped with a PTFE septum. The tube was evacuated and backfilled with dry N_2 three times. THF (1.0 mL) and LHMDS (1.06 M in THF/ethylbenzene, 2.08 mL, 2.20 mmol) were injected and the mixture was stirred for 5 min. **2.1b.1** (213 mg, 1.00 mmol) was injected. The tube was placed in a 65 °C oil bath and the reaction was stirred for 7 h. The tube was removed from the oil bath and allowed to cool to 21 °C. The reaction was diluted with EtOAc (15 mL) and washed with H_2O (15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (DCM / MeOH 1:0 → 19:1) afforded the title compound as a pale yellow solid (213 mg, 67%).

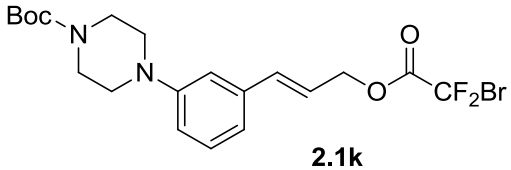
m.p.: 79–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, *J* = 8.2 Hz, 1 H), 6.98–6.92 (m, 2 H), 6.88–6.81 (m, 1 H), 6.64–6.55 (m, 1 H), 6.36 (dt, *J* = 15.8, 5.7 Hz, 1 H), 4.33 (td, *J* = 5.8, 1.5 Hz, 2 H), 3.64–3.54 (m, 4 H), 3.15 (t, *J* = 5.2 Hz, 4H), 1.49 (s, 9 H), 1.47–1.42 (m, 1 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.9, 151.7, 137.8, 131.6, 129.5, 128.7, 118.7, 116.3, 115.0, 80.1, 63.9, 49.6, 44.1 (br s), 43.3 (br s), 28.6.

IR (film): 3391, 2974, 2928, 2858, 2820, 1695, 1597, 1423, 1240, 1167, 1126, 970, 868, 770 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}N_2O_3$) requires *m/z* 319.2022, found *m/z* 319.2030 (2.5 ppm).



2.1k

(*E*)-*tert*-Butyl 4-(3-(3-(2-bromo-2,2-difluoroacetoxy)prop-1-en-1-yl)phenyl)piperazine-1-carboxylate

General Procedure C was followed using **2.1k.1** (187 mg, 0.587 mmol), bromodifluoroacetic acid (144 mg, 0.822 mmol), oxalyl chloride (65 µL, 0.76 mmol), DMF (14 µL, 0.18 mmol), NEt_3 (163 µL, 1.17 mmol), with DCM (6.0 mL) as solvent. Workup and chromatographic purification (hexane / EtOAc 1:0 → 9:1) afforded the title compound as a viscous yellow oil (0.200 g, 72%).

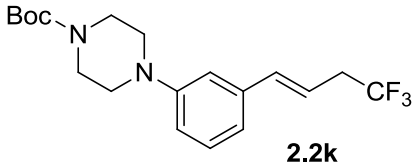
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28–7.23 (m, 1 H), 6.99–6.94 (m, 2 H), 6.91–6.87 (m, 1 H), 6.74 (dd, *J* = 15.8, 1.3 Hz, 1 H), 6.29 (dt, *J* = 15.8, 6.7 Hz, 1 H), 4.99 (dd, *J* = 6.7, 1.2 Hz, 2 H), 3.60 (t, *J* = 5.2 Hz, 4 H), 3.16 (t, *J* = 5.2 Hz, 4 H), 1.50 (s, 9 H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 159.6 (t, *J* = 31.4 Hz), 154.9, 151.8, 137.4, 136.6, 129.7, 120.4, 119.0, 117.2, 115.2, 108.9 (t, *J* = 314.4 Hz), 80.1, 68.9, 49.5, 44.1 (br s), 43.2 (br s), 28.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.62 (s, 2 F).

IR (film): 2976, 2930, 2858, 2822, 1774, 1691, 1597, 1420, 1286, 1240, 1167, 1126, 945 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}BrF_2N_2O_4$) requires *m/z* 475.1044, found *m/z* 475.1060 (3.4 ppm).



2.2k

(*E*)-*tert*-Butyl 4-(3-(4,4,4-trifluorobut-1-en-1-yl)phenyl)piperazine-1-carboxylate

General Procedure D was followed using **2.1k** (95.1 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane / Et_2O 9:1) afforded the title compound as a yellow oil (43.0 mg, 58%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (t, *J* = 8.0 Hz, 1 H), 6.96–6.90 (m, 2 H), 6.86 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1 H), 6.58 (d, *J* = 15.9 Hz, 1 H), 6.09 (dt, *J* = 15.8, 7.3 Hz, 1 H), 3.59 (t, *J* = 5.3 Hz, 4 H), 3.15 (t, *J* = 5.3 Hz, 4 H), 2.99 (qdd, *J* = 10.6, 7.2, 1.4 Hz, 2 H), 1.50 (s, 9 H).

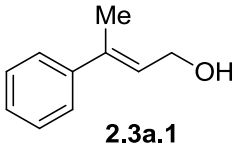
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 154.9, 151.8, 137.3, 137.1, 129.6, 126.0 (q, *J* = 276.7 Hz), 118.7, 117.4 (q, *J* = 3.6 Hz), 116.7, 114.9, 80.1, 49.6, 44.1 (br s), 43.3 (br s), 37.8 (q, *J* = 29.9 Hz), 28.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.20 (t, *J* = 10.6 Hz, 3 F).

IR (film): 2976, 2928, 2858, 2822, 1697, 1597, 1423, 1366, 1248. 1170, 1134, 968, 870, 773 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{19}H_{26}F_3N_2O_2$) requires *m/z* 371.1946, found *m/z* 371.1941 (1.3 ppm).

Experimental procedure for compounds in Scheme 2.9:

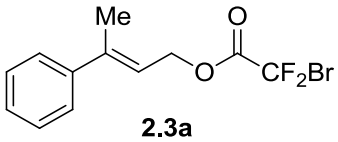


2.3a.1

(*E*)-3-Phenylbut-2-en-1-ol

General Procedure B was followed using ethyl *trans*-β-methylcinnamate (1.83 mL, 10.0 mmol), DIBAL (1.0 M in PhMe, 21.0 mL, 21.0 mmol), with DCM (7.0 mL) as solvent. Workup and filtration through a pad of silica (Et_2O) afforded the title compound as a faint tan oil (1.16 g, 79%).

^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.40 (m, 2 H), 7.37–7.32 (m, 2 H), 7.30–7.26 (m, 1 H), 5.99 (tq, *J* = 6.8, 1.3 Hz, 1 H), 4.38 (d, *J* = 6.7 Hz, 2 H), 2.11–2.10 (m, 3 H), 1.58–1.40 (m, 1 H).



2.3a

(*E*)-3-Phenylbut-2-en-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.3a.1** (0.440 g, 2.97 mmol), bromodifluoroacetic acid (730 mg, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (69 µL, 0.89 mmol), NEt_3 (0.83 mL, 6.0 mmol), with DCM (15 mL) as solvent. Workup and chromatographic purification (hexane / EtOAc 1:0 → 19:1) afforded the title compound as a colorless oil (813 mg, 90%).

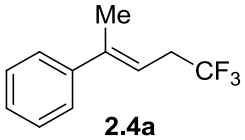
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.42 (m, 2 H), 7.40–7.31 (m, 3 H), 6.00–5.91 (tq, *J* = 7.22, 1.37 Hz, 1 H), 5.08 (d, *J* = 7.2 Hz, 2 H), 2.24–2.18 (m, 3 H).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 160.0, 159.8, 159.5, 143.6, 142.1, 128.6, 128.2, 126.1, 118.6, 111.5, 109.0, 106.5, 65.3, 16.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.89 (s, 2 F).

IR (film): 3034, 2995, 1772, 1643, 1495, 1445, 1381, 1339, 1294, 1169, 1128, 947, 825, 808, 758, 696 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_{11}BrF_2O_2$) requires *m/z* 304.0, found *m/z* 304.1.



2.4a

(*E*)-(5,5,5-Trifluoropent-2-en-2-yl)benzene

General Procedure D was followed using **2.3a** (61.0 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg,

0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (21.9 mg, 55%).

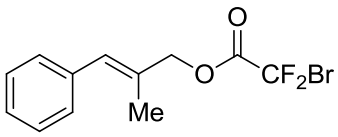
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.28 (m, 5 H), 5.74 (tq, *J* = 7.3, 1.4 Hz, 1 H), 3.08–2.98 (m, 2 H), 2.10 (s, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 142.9, 141.5, 128.5, 127.7, 126.5 (q, *J* = 276.7 Hz), 126.0, 115.2 (q, *J* = 3.4 Hz), 33.8 (q, *J* = 29.6 Hz), 16.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.37 (t, *J* = 9.9 Hz, 3 F).

IR (film): 3082, 3057, 2928, 2858, 1447, 1364, 1339, 1288, 1254, 1136, 1068, 912, 872, 758, 696 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_{11}F_3$) requires *m/z* 200.1, found *m/z* 200.1.



2.3b

(*E*)-2-Methyl-3-phenylallyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using *trans*-2-methyl-3-phenyl-2-propen-1-ol (432 µL, 3.00 mmol), bromodifluoroacetic acid (735 mg, 4.20 mmol), oxalyl chloride (0.330 mL, 3.90 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (836 µL, 6.00 mmol), with DCM (15 mL) as solvent. Workup and chromatographic purification (hexane / EtOAc 1:0 → 49:1) afforded the title compound as a light yellow oil (853 mg, 93%).

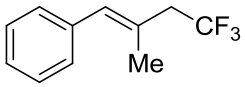
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.36 (m, 2 H), 7.34–7.29 (m, 3 H), 6.68–6.64 (m, 1 H), 4.93 (d, *J* = 1.1 Hz, 2 H), 1.98 (d, *J* = 1.5 Hz, 3 H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 159.6 (t, *J* = 31.3 Hz), 136.5, 130.9, 130.6, 129.1, 128.4, 127.4, 108.9 (t, *J* = 314.5 Hz), 74.0, 15.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.61 (2 F).

IR (film): 1772, 1645, 1491, 1447, 1373, 1296, 1167, 1124, 967, 914 cm^{-1}.

MS (CI): mass calculated for [M] ($C_{12}H_{11}BrF_2O_2$) requires *m/z* 304.0, found *m/z* 304.1.



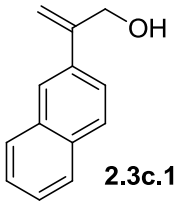
2.4b

(*E*)-(4,4,4-Trifluoro-2-methylbut-1-en-1-yl)benzene[7]

General Procedure D was followed using **2.3b** (61.0 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 μL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (29.4 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.33 (m, 2 H), 7.30–7.23 (m, 3 H), 6.49 (s, 1 H), 2.94 (q, J = 10.9 Hz, 2 H), 1.98 (s, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.64 (t, J = 11.3 Hz, 3 F).



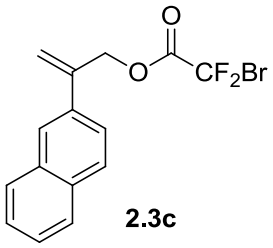
2.3c.1

2-(Naphthalen-2-yl)prop-2-en-1-ol[16]

An oven-dried 3 neck 100 mL round-bottom flask was equipped with a reflux condenser, liquid addition funnel, and a glass stopper. Mg turnings (175 mg, 7.19 mmol) were added to the flask, then the system was evacuated and backfilled with N_2 three times. THF (15 mL) was added as solvent, and then one bead of I_2 was added to the mixture. The mixture was vigorously stirred for 1 h. A solution of 2-bromonaphthalene (1.49 g, 7.19 mmol in 15 mL THF) was added dropwise over 30 min. The reaction was refluxed until 2-bromonaphthalene was determined to be consumed by GC analysis (4 h). The reaction was cooled to 21 °C then CuI (65 mg, 0.34 mmol) was added to the mixture. Propargyl alcohol (0.20 mL, 3.4 mmol) was injected dropwise and the mixture was stirred at 21 °C for 30 min. The reaction was refluxed for 12 h, then cooled to 21 °C. $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was stirred for 30 min. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 25 mL) then the combined organic layers were washed with brine (50 mL). The organic solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (hexanes / EtOAc 1:0 → 4:1) afforded the title compound as a tan solid (248 mg, 39%).

m.p.: 90–92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.88 (m, 1 H), 7.88–7.80 (m, 3 H), 7.63 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.52–7.45 (m, 2 H), 5.66–5.61 (m, 1 H), 5.49–5.45 (m, 1 H), 4.72–4.65 (m, 2 H), 1.66–1.58 (m, 1 H).



2.3c

2-(Naphthalen-2-yl)allyl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.3c.1** (111 mg, 0.603 mmol), bromodifluoroacetic acid (148 mg, 0.84 mmol), oxalyl chloride (66 μL, 0.78 mmol), DMF (14 μL, 0.18 mmol), NEt_3 (0.17 mL, 1.21 mmol), with DCM (6.0 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 19:1) afforded the title compound as a colorless oil (178 mg, 87%).

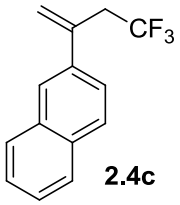
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89–7.82 (m, 4 H), 7.63–7.57 (m, 1 H), 7.54–7.47 (m, 2 H), 5.82 (s, 1 H), 5.62–5.55 (m, 1 H), 5.38–5.34 (m, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.5 (t, *J* = 31.6 Hz), 140.6, 134.5, 133.4, 133.3, 128.5, 128.4, 127.8, 126.7, 126.6, 125.1, 124.0, 117.7, 108.7 (t, *J* = 314.3 Hz), 69.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.01 (s, 2 F).

IR (film): 3057, 2961, 2930, 1776, 1628, 1597, 1506, 1443, 1366, 1292, 1169, 1124, 984, 953, 937, 858, 818, 752, 709, 602 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{15}H_{11}BrF_2O_2$) requires *m/z* 340.0, found *m/z* 340.1.



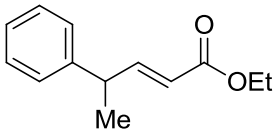
2.4c

2-(4,4,4-Trifluorobut-1-en-2-yl)naphthalene[17]

General Procedure D was followed using **2.3c** (68.2 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (26.6 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90–7.81 (m, 4 H), 7.57 (dd, J = 8.6, 1.8 Hz, 1 H), 7.54–7.46 (m, 2 H), 5.76 (s, 1 H), 5.49 (s, 1 H), 3.42 (qd, J = 10.5, 1.0 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.43 (t, J = 10.5 Hz, 3 F).



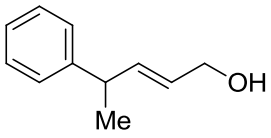
2.3d.2

(*E*)-Ethyl 4-phenylpent-2-enoate[18]

Triethyl phosphonoacetate (1.39 mL, 7.00 mmol) was dissolved in THF (75 mL). The solution was cooled to –78 °C, then ^{n}BuLi (1.8 M in hexanes, 3.9 mL, 7.0 mmol) was added dropwise. The reaction was stirred at –78 °C for 45 min, then 2-phenylpropionaldehyde (1.03 mL, 7.70 mmol) was injected dropwise. The reaction was allowed to warm to RT and stirring continued for 5 h. $NH_4Cl_{(aq)}$ (40 mL) was added and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic extracts

were washed with brine (50 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Column chromatography (hexanes / Et_2O 1:0 → 19:1) afforded the title compound as a colorless oil (137 mg, 10%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.31 (m, 2 H), 7.26–7.19 (m, 3 H), 7.12 (dd, *J* = 15.7, 6.7 Hz, 1 H), 5.81 (dd, *J* = 15.6, 1.6 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.63 (pd, *J* = 6.9, 1.6 Hz, 1 H), 1.44 (d, *J* = 7.1 Hz, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

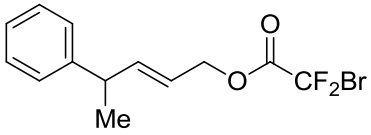


2.3d.1

(*E*)-4-Phenylpent-2-en-1-ol[19]

General Procedure B was followed using **2.3d.2** (140 mg, 0.67 mmol), DIBAL (1.0 M in PhMe, 1.4 mL, 1.4 mmol), with DCM (0.010 L) as solvent. Workup and filtration through a pad of silica (Et_2O) afforded the title compound as a colorless solid (89 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.29 (m, 2 H), 7.25–7.18 (m, 3 H), 5.89 (ddt, *J* = 15.4, 6.7, 1.4 Hz, 1 H), 5.68 (dtd, *J* = 15.4, 5.8, 1.4 Hz, 1 H), 4.18–4.09 (m, 2 H), 3.50 (p, *J* = 6.9 Hz, 1 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.35 – 1.29 (br s, 1 H).



2.3d

(*E*)-4-Phenylpent-2-en-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.3d.1** (60 mg, 0.37 mmol), bromodifluoroacetic acid (91 mg, 0.52 mmol), oxalyl chloride (41 µL, 0.48 mmol), DMF

(8.6 µL, 0.11 mmol), NEt_3 (0.10 mL, 0.74 mmol), with DCM (5.0 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a colorless oil (98 mg, 83%).

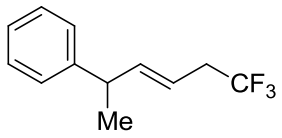
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.3, 6.9 Hz, 2 H), 7.25–7.18 (m, 3 H), 6.11 (ddt, *J* = 15.3, 6.5, 1.2 Hz, 1 H), 5.64 (dtd, *J* = 15.1, 6.6, 1.5 Hz, 1 H), 4.82 (d, *J* = 6.7 Hz, 2 H), 3.54 (p, *J* = 7.0 Hz, 1 H), 1.40 (d, *J* = 7.0 Hz, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.6 (t, *J* = 31.3 Hz), 144.6, 143.5, 128.7, 127.3, 126.6, 120.5, 108.9 (t, *J* = 314.5 Hz), 68.8, 42.1, 20.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.72 (s, 2 F).

IR (film): 3061, 3028, 2968, 2932, 2874, 1774, 1493, 1452, 1375, 1294, 1169, 1126, 947, 825, 804, 760, 700 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{13}H_{13}BrF_2O_2$) requires *m/z* 318.0, found *m/z* 318.0.



2.4d

(*E*)-(6,6,6-Trifluorohex-3-en-2-yl)benzene

General Procedure D was followed using **2.3d** (63.8 mg, 0.200 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 8 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (33.5 mg, 78%).

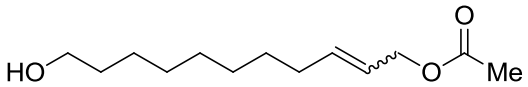
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (m, 2 H), 7.26–7.19 (m, 3 H), 5.90 (dd, *J* = 15.4, 6.6 Hz, 1 H), 5.44 (dtd, *J* = 15.5, 7.1, 1.5 Hz, 1 H), 3.51 (p, *J* = 7.2 Hz, 1 H), 2.81 (qdt, *J* = 10.8, 7.1, 1.0 Hz, 2 H), 1.38 (d, *J* = 7.1 Hz, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.1, 142.8, 128.7, 127.3, 126.5, 126.2 (q, *J* = 276.5 Hz), 116.7 (q, *J* = 3.6 Hz), 42.3, 37.5 (q, *J* = 29.6 Hz), 21.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.57 (t, *J* = 10.7 Hz).

IR (film): 3061, 3028, 2968, 2932, 2876, 1493, 1452, 1431, 1364, 1258, 1138, 1080, 1061, 970, 760, 700 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_{13}F_3$) requires *m/z* 214.1, found *m/z* 214.1.



2.3e.2

11-Hydroxyundec-2-en-1-yl acetate

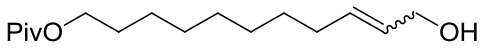
A 2-neck 250 mL round-bottom flask, reflux condenser, and flushing adapter were oven-dried and cooled under N_2. Grubbs 1st generation catalyst (597 mg, 0.725 mmol) was added to the flask. The system was evacuated and backfilled with N_2 three times. DCM (75 mL) was added as solvent. *cis*-1,4-diacetoxy-2-butene (2.31 mL, 14.5 mmol) was injected and the mixture was stirred for 15 min at 21 ° C. 9-decen-1-ol (1.30 mL, 7.29 mmol) was injected then the reaction was refluxed for 12 h. The solvent was removed *in vacuo* and the crude material was loaded onto silica. Column chromatography (hexanes / EtOAc 1:0 → 7:3) afforded the title compound as a brown liquid (1.20 g, 72%). Analysis of the ^{1}H NMR spectrum revealed an *E/Z* ratio of 79:21.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82–5.73 (dtt, *J* = 15.3, 6.7, 1.1 Hz, 1 H), 5.69–5.49 (m, 1 H), 4.65–4.60 (m, 2 H : minor diastereomer), 4.54–4.49 (m, 2 H : major diastereomer), 3.71–3.59 (m, 2 H), 2.07 (m, 5 H), 1.62–1.52 (m, 2 H), 1.44–1.22 (m, 11 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): Major diastereomer: δ 171.1, 136.8, 123.8, 65.5, 63.2, 32.9, 32.4, 29.5, 29.5, 29.2, 29.0, 25.8, 21.2. Minor diastereomer: δ 171.2, 135.6, 123.4, 60.6, 27.6 (remaining peaks overlap with major diastereomer).

IR (film): 3375, 2926, 2854, 1740, 1458, 1379, 1232, 1024, 968 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{24}O_3Na$) requires *m/z* 251.1623, found *m/z* 251.1628 (2.0 ppm).



2.3e.1

11-Hydroxyundec-9-en-1-yl pivalate

Compound **2.e3.2** (217 mg, 0.949 mmol) and 4-(dimethylamino)pyridine (12 mg, 0.10 mmol) were added to a 25 mL round bottom flask. A bubbler was attached and the system was flushed with N_2. DCM (0.010 L) and *N,N*-diisopropylethylamine (0.50 mL, 2.9 mmol) were injected. The flask was placed in a 0 °C ice bath and allowed to cool. Pivaloyl chloride (0.23 mL, 1.9 mmol) was injected and the reaction was stirred for 15 min. The ice bath was removed and stirring continued for 2 h. MeOH was injected and the solution was stirred for 30 min. The solvent was removed *in vacuo*, then the crude oil was dissolved in Et_2O (20 mL). The solution was washed with $NH_4Cl_{(aq)}$ (10 mL), H_2O (10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The resultant oil was dissolved in MeOH (0.010 L), then K_2CO_3 (13 mg, 0.095 mmol) was added to the flask. The reaction was stirred at 21

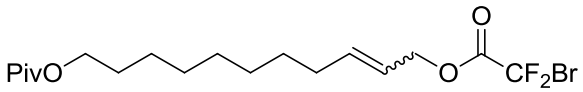
°C for 12 h. EtOAc (30 mL) and H_2O (30 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined and washed with brine (45 mL). The solution was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Column chromatography (hexane / EtOAc 1:0 → 3:1) afforded the title compound as a tan oil (173 mg, 67%). Analysis of the ^{1}H NMR spectrum revealed an *E/Z* ratio of 78:22.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75–5.51 (m, 2 H), 4.22–4.18 (m, 1 H, minor diastereomer), 4.12–4.07 (m, 1 H, major diastereomer), 4.05 (t, *J* = 6.7 Hz, 2 H), 2.11–2.01 (m, 2 H), 1.66–1.59 (m, 2 H), 1.41–1.23 (m, 11 H), 1.20 (s, 9 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): Major diastereomer: δ 178.8, 133.6, 129.0, 64.6, 64.0, 38.9, 32.3, 29.5, 29.3, 29.2, 29.2, 28.7, 27.4, 26.0. Minor diastereomer: δ 133.3, 128.5, 58.8, 29.7, 27.5 (remaining peaks overlap with major diastereomer).

IR (film): 3435, 2928, 2854, 1728, 1479, 1285, 1157, 970 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{30}O_3Na$) requires *m/z* 293.2093, found *m/z* 293.2088 (1.7 ppm).



2.3e

11-(2-Bromo-2,2-difluoroacetoxy)undec-9-en-1-yl pivalate

General Procedure C was followed using **2.e3.1** (153 mg, 0.566 mmol), bromodifluoroacetic acid (139 mg, 0.792 mmol), oxalyl chloride (62 µL, 0.74 mmol), DMF (13 µL, 0.17 mmol), NEt_3 (158 µL, 1.13 mmol), with DCM (6.0 mL) as solvent. Workup and chromatographic purification (hexane / EtOAc 49:1) afforded the title

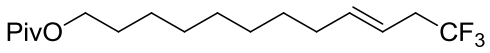
compound as a colorless oil (162 mg, 67%). Analysis of the ^{1}H NMR spectrum revealed an *E/Z* ratio of 78:22.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (dtt, *J* = 14.9, 6.8, 1.1 Hz, 1 H, major diastereomer), 5.80 (dtt, *J* = 10.9, 7.6, 1.1 Hz, 1 H, minor diastereomer), 5.65–5.56 (m, 1 H), 4.89 (dd, *J* = 7.2, 1.1 Hz, 2 H, minor diastereomer), 4.78 (dd, *J* = 6.7, 1.0 Hz, 2 H, major diastereomer), 4.05 (t, *J* = 6.6 Hz, 2 H), 2.15 (qd, *J* = 7.5, 1.6 Hz, 2 H, minor diastereomer), 2.09 (qd, *J* = 7.1, 1.5 Hz, 2 H, major diastereomer), 1.66–1.58 (m, 2 H), 1.45–1.27 (m, 10 H), 1.20 (s, 9 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): Major diastereomer: δ 178.8, 159.6 (t, *J* = 31.3 Hz), 139.9, 121.5, 109.0 (t, *J* = 314.4 Hz), 69.1, 64.6, 38.9, 32.4, 29.4, 29.3, 29.3, 29.1, 28.7, 27.4, 26.0. Minor diastereomer: δ 138.6, 120.8, 64.0, 29.5, 29.4, 29.2, 27.8 (remaining peaks overlap with major diastereomer).

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.60 (s, 2 F). IR (film) 2930, 2856, 1776, 1728, 1479, 1288, 1163, 1126, 947 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{29}BrF_2O_4Na$) requires *m/z* 449.1115, found *m/z* 449.1134 (4.2 ppm).



2.4e

(*E*)-12,12,12-Trifluorododec-9-en-1-yl pivalate

General Procedure D was followed using **2.e3** (85.5 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 μL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 18 h. Workup and chromatographic purification

(pentane / Et_2O 1:0 → 39:1) afforded the title compound as a light yellow oil (49.0 mg, 76%).

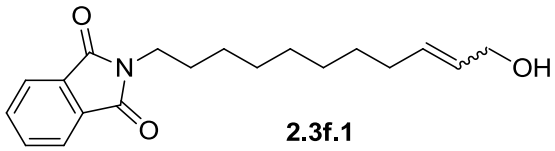
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.70 (dt, *J* = 15.4, 6.8 Hz, 1 H), 5.37 (dtt, *J* = 15.6, 7.1, 1.5 Hz, 1 H), 4.05 (t, *J* = 6.6 Hz, 2 H), 2.77 (qd, *J* = 10.7, 7.6 Hz, 2 H), 2.05 (qd, *J* = 7.3, 1.3 Hz, 2 H), 1.62 (p, *J* = 6.7 Hz, 2 H), 1.42–1.23 (m, 10 H), 1.20 (s, 9 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 178.8, 138.6, 126.2 (q, *J* = 276.5 Hz), 117.6 (q, *J* = 3.5 Hz), 64.6, 38.9, 37.5 (q, *J* = 29.5 Hz), 32.6, 29.4, 29.3, 29.1, 29.0, 28.7, 27.4, 26.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ –66.62 (t, *J* = 11.2 Hz, 3 F : minor diastereomer), –67.11 (t, *J* = 11.1 Hz, 3 F : major diastereomer).

IR (film): 2930, 2856, 1730, 1481, 1460, 1366, 1285, 1271, 1250, 1155, 1138, 970 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{17}H_{29}F_3O_2$) requires *m/z* 322.2, found *m/z* 322.2.



2.3f.1

2-(11-Hydroxyundec-9-en-1-yl)isoindoline-1,3-dione

Compound **2.e3.2** (215 mg, 0.942 mmol), phthalimide (207 mg, 1.41 mmol), and PPh_3 (371 mg, 1.41 mmol) were added to a 25 mL round bottom flask. The system was evacuated and backfilled with N_2 three times. THF (0.010 L) was added as solvent. The flask was placed in a 0 °C ice bath and allowed to cool. Diisopropyl azodicarboxylate (0.28 mL, 1.4 mmol) was injected dropwise and the reaction was stirred for 15 min. The cold bath was removed and the reaction was stirred at 21 °C for 2 h. The solvent was removed *in vacuo*. Column chromatography (hexanes / EtOAc 1:0 → 3:1) afforded a

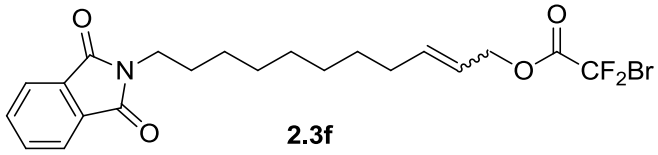
brown oil. The material was dissolved in MeOH, then K_2CO_3 was added. The reaction was stirred for 12 h at 21 °C. EtOAc (30 mL) and H_2O (30 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined and washed with brine (45 mL). The solution was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Column chromatography (hexane / EtOAc 1:0 → 3:2) afforded the title compound as an amorphous tan solid (249 mg, 84%). Analysis of the ^{1}H NMR spectrum revealed an *E/Z* ratio of 80:20.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 2 H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2 H), 5.73–5.49 (m, 2 H), 4.20 (d, *J* = 6.7 Hz, 2 H : minor diastereomer), 4.09 (d, *J* = 5.3 Hz, 2 H : major diastereomer), 3.70–3.66 (m, 2 H), 2.10–1.99 (m, 2 H), 1.71–1.63 (m, 2 H), 1.40–1.25 (m, 11 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): Major diastereomer: δ 168.6, 134.0, 133.6, 132.3, 129.0, 123.3, 64.0, 38.2, 32.3, 29.4, 29.2, 29.2, 29.1, 28.7, 26.9. Minor diastereomer: δ 133.3, 128.5, 58.8, 29.6, 29.2, 27.5 (remaining peaks overlap with major diastereomer).

IR (film): 3437, 2926, 2854, 1772, 1711, 1466, 1437, 1396, 1369, 1057, 1003, 970, 719 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{25}O_3Na$) requires *m/z* 338.1732, found *m/z* 338.1738 (1.8 ppm).



2.3f

11-(1,3-Dioxoisoindolin-2-yl)undec-2-en-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **2.3f.1** (230 mg, 0.73 mmol), bromodifluoroacetic acid (180 mg, 1.0 mmol), oxalyl chloride (81 µL, 0.96 mmol), DMF (17 µL, 0.22 mmol), NEt_3 (0.20 mL, 1.5 mmol), with DCM (7.0 mL) as solvent. Workup and chromatographic purification (hexane / EtOAc 9:1) afforded the title compound as an amorphous tan solid (289 mg, 83%). Analysis of the ^{1}H NMR spectrum revealed an *E/Z* ratio of 79:21.

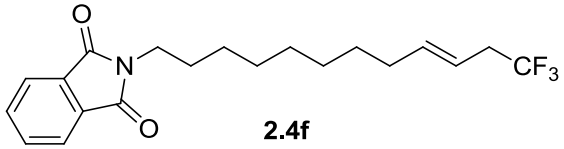
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 5.4, 3.0 Hz, 2 H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2 H), 5.91 (dtt, *J* = 15.3, 6.6, 1.1 Hz, 1 H, major diastereomer), 5.79 (dtt, *J* = 10.9, 7.6, 1.1 Hz, 1 H, minor diastereomer), 5.63–5.55 (m, 1 H), 4.88 (dd, *J* = 7.2, 1.1 Hz, 2 H, minor diastereomer), 4.77 (dd, *J* = 6.7, 1.1 Hz, 2 H, major diastereomer), 3.68 (t, *J* = 7.3 Hz, 2 H), 2.14 (qd, *J* = 7.5, 1.5 Hz, 2 H, minor diastereomer), 2.10–2.05 (m, 2 H, major diastereomer), 1.67 (p, *J* = 7.6 Hz, 2 H), 1.42–1.25 (m, 10 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): Major diastereomer: δ 168.6, 159.6 (t, *J* = 31.2 Hz), 139.9, 134.0, 132.3, 123.3, 121.5, 109.0 (t, *J* = 314.4 Hz), 69.1, 38.2, 32.3, 29.4, 29.21, 29.21, 29.1, 28.7, 26.9. Minor diastereomer: δ 138.6, 120.8, 64.0, 29.4, 29.3, 27.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.62 (s, 2 F).

IR (film): 2930, 2854, 1774, 1713, 1396, 1294, 1169, 1124, 945, 719 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{21\ H24}BrF_2NO_4Na$) requires *m/z* 494.0754, found *m/z* 494.0773 (3.8 ppm).



2.4f

(*E*)-2-(12,12,12-Trifluorododec-9-en-1-yl)isoindoline-1,3-dione

General Procedure D was followed using **2.3f** (94.5 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 18 h. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 9:1) afforded the title compound as a light yellow oil (62.3 mg, 85%). Analysis of the ^{19}F NMR spectrum revealed an *E/Z* ratio of 97:3.

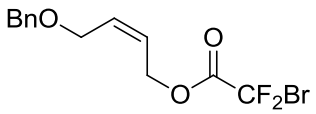
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87–7.82 (m, 2 H), 7.74–7.69 (m, 2 H), 5.68 (dt, *J* = 15.3, 6.8 Hz, 1 H), 5.36 (dtt, *J* = 15.5, 7.1, 1.5 Hz, 1 H), 3.70–3.66 (m, 2 H), 2.76 (qdd, *J* = 10.8, 7.1, 1.2 Hz, 2 H), 2.08–1.99 (m, 2 H), 1.67 (p, *J* = 7.3 Hz, 2 H), 1.41–1.23 (m, 10 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.6, 138.6, 134.0, 132.3, 126.2 (q, *J* = 276.5 Hz), 123.3, 117.6 (q, *J* = 3.6 Hz), 38.2, 37.5 (q, *J* = 29.4 Hz), 32.6, 29.4, 29.2, 29.1, 29.0, 28.7, 26.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.23 (t, *J* = 10.9 Hz, 3 F : minor diastereomer), –67.73 (t, *J* = 10.8 Hz, 3 F : major diastereomer).

IR (film): 2928, 2854, 1772, 1715, 1468, 1437, 1396, 1369, 1250, 1134, 1063, 970, 719 cm^{-1}.

HRMS (ESI^{+}): exact mass calculated for $[M+H]^+$ ($C_{20}H_{25}F_3NO_2$) requires *m/z* 368.1837, found *m/z* 368.1843 (1.6 ppm).



2.3g

(*Z*)-4-(Benzyloxy)but-2-en-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using *cis*-4-benzyloxy-2-buten-1-ol (0.84 mL, 5.0 mmol), bromodifluoroacetic acid (1.22 g, 7.00 mmol), oxalyl chloride (0.55 mL, 6.5 mmol), DMF (0.12 mL, 1.5 mmol), NEt_3 (1.39 mL, 10.0 mmol), with DCM (35 mL) as solvent. Workup and chromatographic purification (hexane / EtOAc 19:1) afforded the title compound as a colorless oil (1.17 g, 70%).

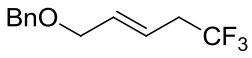
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.29 (m, 5 H), 5.96 (dtt, *J* = 11.2, 6.1, 1.3 Hz, 1 H), 5.80–5.71 (m, 1 H), 4.92 (d, *J* = 6.9 Hz, 2 H), 4.55 (s, 2 H), 4.19–4.16 (m, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.5 (t, *J* = 31.5 Hz), 137.9, 133.4, 128.6, 128.0, 128.0, 124.0, 108.8 (t, *J* = 314.4 Hz), 72.8, 65.8, 64.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.75 (s, 2 F).

IR (film): 3065, 3032, 2924, 2858, 1774, 1497, 1454, 1366, 1296, 1167, 1130, 949, 808, 737, 698, 604 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{13}H_{13}BrF_2O_3$) requires *m/z* 334.0, found *m/z* 334.0.



2.4g

(*E*)-(((5,5,5-Trifluoropent-2-en-1-yl)oxy)methyl)benzene

General Procedure D was followed using **2.3g** (94.5 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), sodium bromodifluoroacetate (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation,

the reaction was heated at 50 °C for 18 h. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 9:1) afforded the title compound as a light yellow oil (62.3 mg, 85%). Analysis of the ^{19}F NMR spectrum revealed an *E/Z* ratio of 97:3.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.28 (m, 5 H), 5.87 (dt, *J* = 15.5, 5.7 Hz, 1 H), 5.70 (dtt, *J* = 15.6, 7.1, 1.5 Hz, 1 H), 4.53 (s, 2 H), 4.05–4.03 (m, 2 H), 2.91–2.81 (m, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.1, 134.2, 128.6, 127.9, 127.9, 125.9 (q, *J* = 276.6 Hz), 120.9 (q, *J* = 3.5 Hz), 72.5, 70.0, 37.3 (q, *J* = 29.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.15 (t, *J* = 10.8 Hz, 3 F : minor diastereomer), –67.38 (t, *J* = 10.7 Hz, 3 F : major diastereomer).

IR (film): 3032, 2934, 2854, 1637, 1456, 1354, 1298, 1252, 1136, 1103, 1059, 970 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_{13}F_3O$) requires *m/z* 230.1, found *m/z* 230.1.

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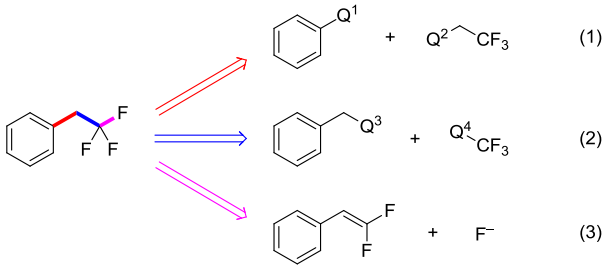
Chapter 3: Copper-Catalyzed Decarboxylative Trifluoromethylation of Benzylic Bromodifluoroacetates

3.1. Introduction to the synthesis of benzylic trifluoromethanes.

The trifluoromethyl group (CF_3) is commonly utilized in medicinal chemistry, agricultural chemistry and materials sciences to modulate the physical and biological properties of molecules.[1,2] Among trifluoromethyl-containing substructures, trifluoroethyl(hetero)arenes represent an important motif, with over 30,000 trifluoroethyl(hetero)arenes possessing documented biological activity or being precursors to bioactive compounds.[3] Thus, general strategies for preparing this substructure are important for accessing biological probes and therapeutics.

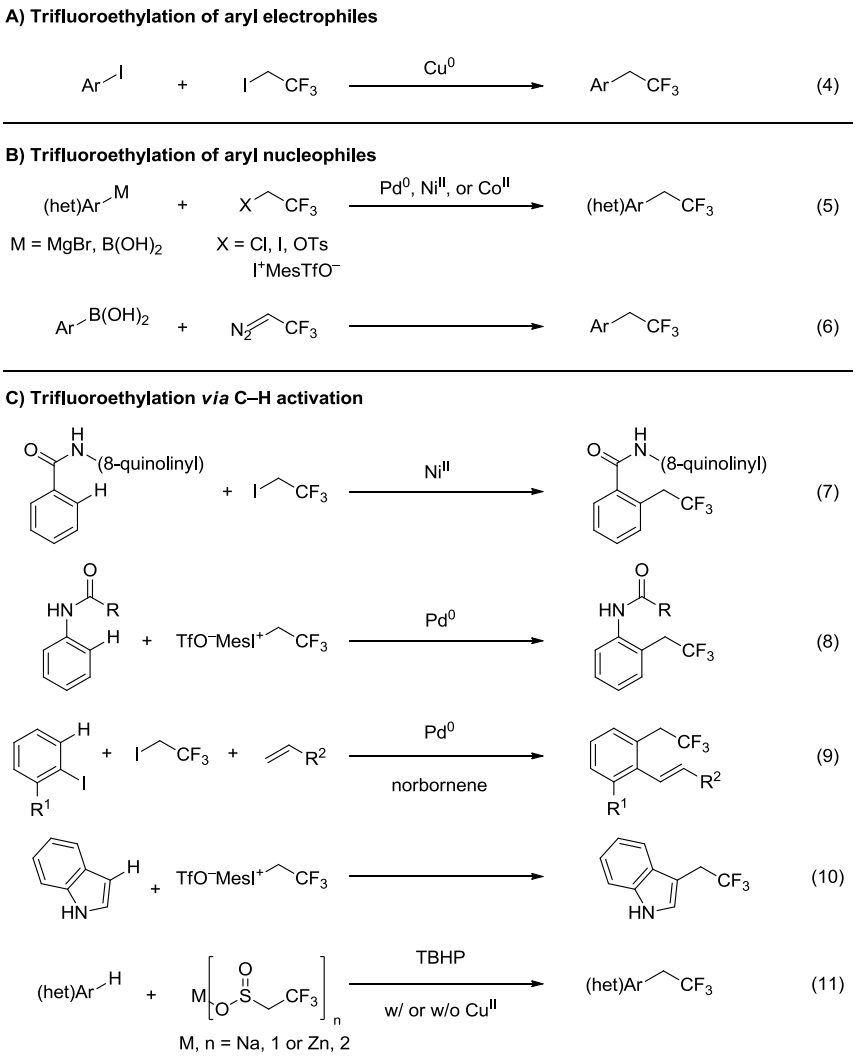
While classic trifluoromethylation methods are suitable for the synthesis of trifluoroethylarenes (e.g. 4-step oxidation/trifluoromethylation/deoxygenation; Chapter 1.5), unique approaches for the creation of this motif have been developed that utilize the proximal aryl group. Specifically, three general strategies for creating trifluoroethylarenes include: 1) trifluoroethylation of arenes (Scheme 3.1, eq 1); 2) trifluoromethylation of benzylic species (eq 2); and 3) hydrofluorination of difluorostyrenes (eq 3).

Scheme 3.1. Unique strategies for the construction of trifluoroethylarenes.



Arenes are convenient precursors to trifluoroethylarene, and approaches to affect this transformation include: 1) trifluoroethylation of aryl electrophiles (Scheme 3.2A); 2) trifluoroethylation of aryl nucleophiles (Scheme 3.2B); and 3) C–H activation/trifluoroethylation (Scheme 3.2C). Many of these reactions involved "M–CH_2CF_3" species, which were previously thought to be unstable, *via* decomposition to generate MF and difluoroethylene. While "M–CH_2CF_3" species with high ionic M–C bond character rapidly undergo β-fluoride elimination, transition metal "M–CH_2CF_3" species with more covalent M–C bond character are stable intermediates that participate in trifluoroethylarylation cross-coupling reactions.[4] For example, "Cu–CH_2CF_3" promoted reductive cross-coupling reaction between aryl iodides and 1,1,1-trifluoro-2-iodoethane (Scheme 3.2, eq 4).[5] In this reaction, a single electron transfer (SET) mechanism may form "Cu–CH_2CF_3", which then reacted with aryl iodides to generate desired trifluoroethylarenes.[5b] Similarly, "M–CH_2CF_3" intermediates also promote trifluoroethylation reactions between aryl nucleophiles and trifluoroethyl electrophiles (eq 5).[6] In contrast, an alternative metal-free approach to trifluoroethylation of aryl nucleophiles has been developed using 2,2,2-trifluorodiazoethane as a trifluoroethylation reagent (eq 6).[7] Trifluoroethylation of arenes has also been accomplished *via* C–H functionalization using metal catalysts. C–H activation/trifluoroethylation was enabled by amide-based directing groups (eq 7–8)[8,9] and transient directing groups during tandem vinylation/trifluoroethylation of aryl iodides (eq 9).[10] In addition, other substrate-controlled C–H trifluoroethylations include trifluoroethylation of indoles (eq 10)[11] and radical C–H trifluoroethylation of (hetero)arenes (eq 11).[12]

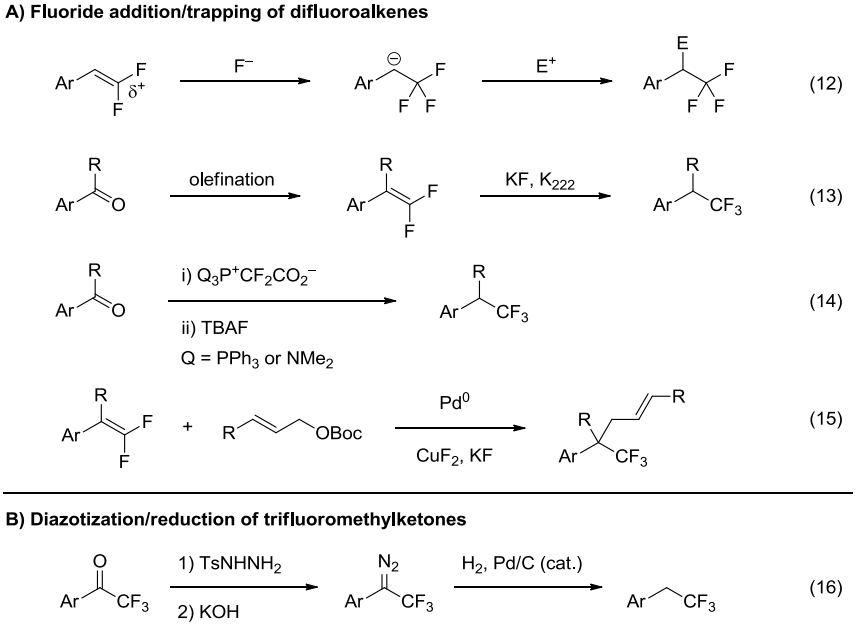
Scheme 3.2. Methods for the direct conversion of arenes to trifluoroethylarenes.



Aryl aldehydes and ketones have been used as precursors to trifluoroethylarenes (Scheme 3.3). One strategy for this transformation involved converting carbonyl groups to difluoroalkenes, which have unusual reactivity compared to typical olefins. Specifically, the fluorine atoms of difluoroalkenes were highly electron-withdrawing, and made the terminal position of the olefin electrophilic (eq 12). Difluorostyrenes were particularly reactive, since after nucleophilic attack, they generated benzylically-stabilized carbanions (eq 12). Finally, trapping of carbanions with electrophiles formed trifluoroethylarenes (eq 12). Initially, this concept was realized in a two-step

difluoroolefination[13]/hydrofluorination[14] sequence (eq 13). Later, this strategy was employed in a one-pot conversion of carbonyls to trifluoroethylarenes (eq 14).[15] More complex trifluoroethylarenes were generated by Pd-catalyzed fluorination/allylation of difluoroalkenes (eq 15).[16] An alternative approach for converting carbonyl compounds to trifluoroethylarenes involved generation of trifluoroacetophenones, conversion to α-diazotrifluoromethanes, and Pd-catalyzed reduction to create fluorinated final products (eq 16).[17]

Scheme 3.3. Conversion of aryl carbonyl compounds to trifluoroethylarenes.

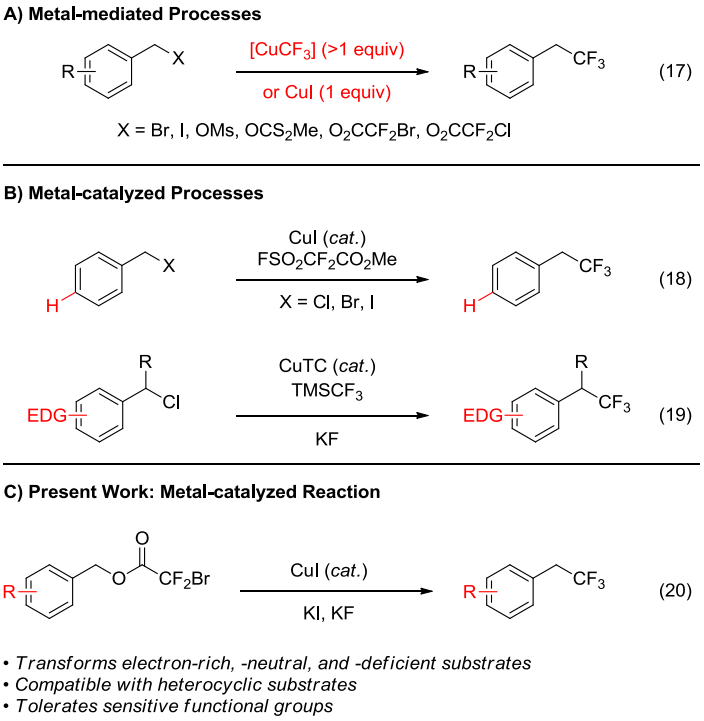


3.2. Nucleophilic trifluoromethylation of benzylic electrophiles.

A direct strategy for generating trifluoroethylarenes involved trifluoromethylation of benzylic electrophiles; however, no general catalytic system could transform a broad spectrum of (hetero)benzylic electrophiles. Most systems for benzylic trifluoromethylation required either stoichiometric Cu (Scheme 3.4, eq 17),[18] or exclusively transformed electron-neutral (eq 18)[19] or electron-rich substrates (eq 19).[20]

Thus, there was a need for a catalytic system that could transform electron-deficient benzylic electrophiles and heterocyclic derivatives into trifluoroethyl(hetero)arenes. Herein, we report such a general catalytic system that enabled access to a broad array of trifluoroethyl(hetero)arenes (eq 20). Further, we propose a revised mechanism that accounts for the expanded functional group tolerance. After the publication of our work, a similar strategy for Cu-catalyzed benzylic trifluoromethylation was reported.[21]

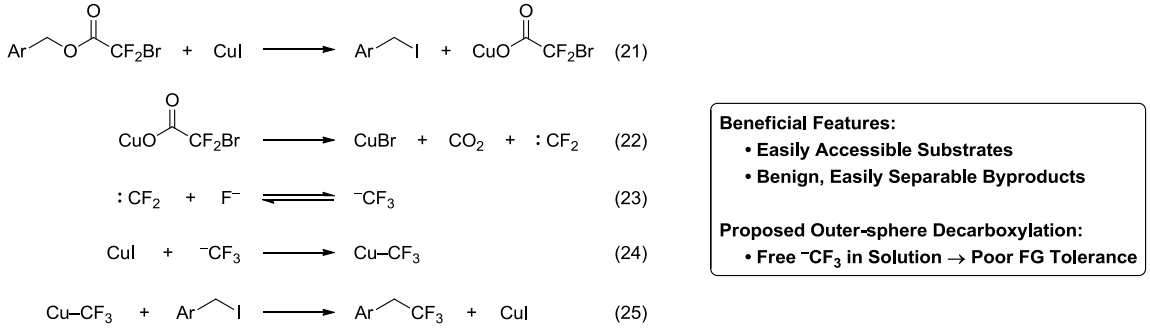
Scheme 3.4. Trifluoromethylation of Benzylic Electrophiles Typically Requires Stoichiometric Copper.



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.[18f] Beneficial features of this early system included: 1) facile access to substrates derived

from simple benzylic alcohols, which are synthetically accessible and already found in a wide variety of synthetic intermediates and building blocks; 2) the formation of just CO_2 and KBr as benign, easily separable by-products. However, this previous transformation was not shown to convert a broad spectrum of substrates,[18f] potentially because the proposed mechanism invoked an outer-sphere decarboxylation that generated free $^{-}CF_3$ (Scheme 3.5).[18d–f] If generated, this reactive intermediate would react with carbonyl-based functional groups *via* 1,2-addition and acidic functional groups *via* deprotonation, which would severely limit the functional group compatibility of the transformation. However, we hypothesized that a catalytic inner-sphere decarboxylation might generate the critical Cu–CF_3 intermediate, which would enable the conversion of substrates bearing sensitive carbonyl and acidic functional groups.

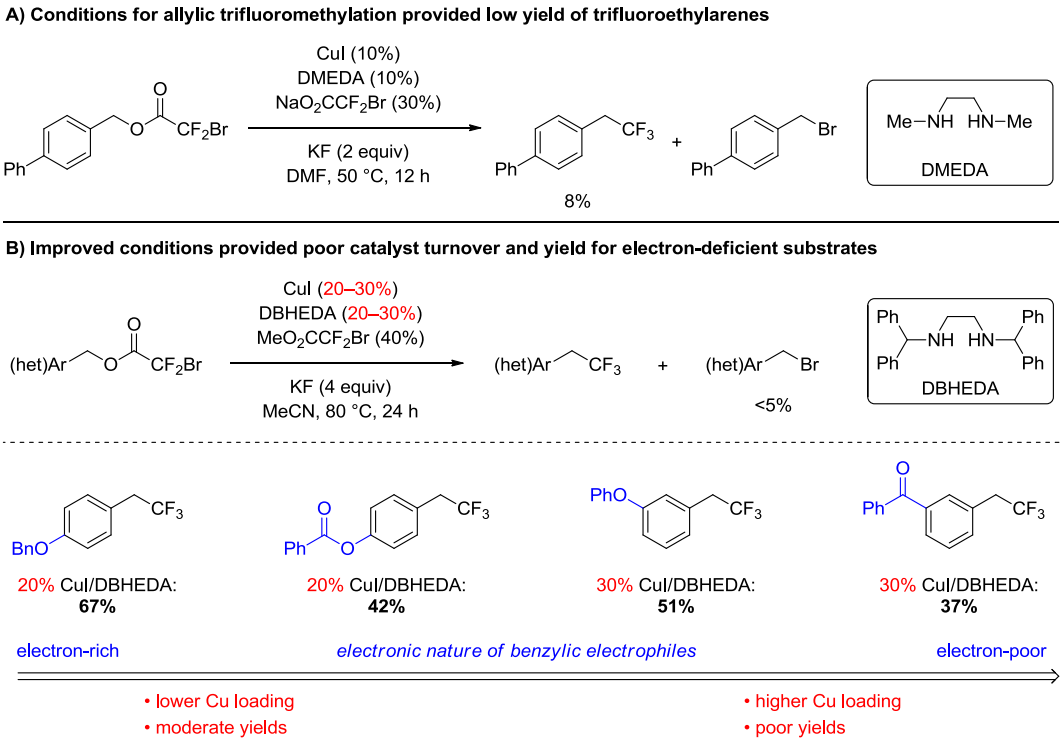
Scheme 3.5. Previously proposed mechanism involves generation of free $^{-}CF_3$.



We hypothesized that the use of ligands could enable Cu-catalyzed benzylic trifluoromethylation. Specifically, since benzylic electrophiles are less reactive than allylic electrophiles, and unstabilized "Cu–CF_3" species decompose rapidly, we aimed to identify ligands that stabilized "Cu–CF_3" towards degradation. Initially, we tested DMEDA, a ligand that promoted Cu-catalyzed allylic trifluoromethylation (Chapter 2). As an initial hit, we obtained product formation without catalyst turnover (8% product, 10% Cu-cat., Scheme 3.6A), and observed benzylic bromide side-product during GC-MS

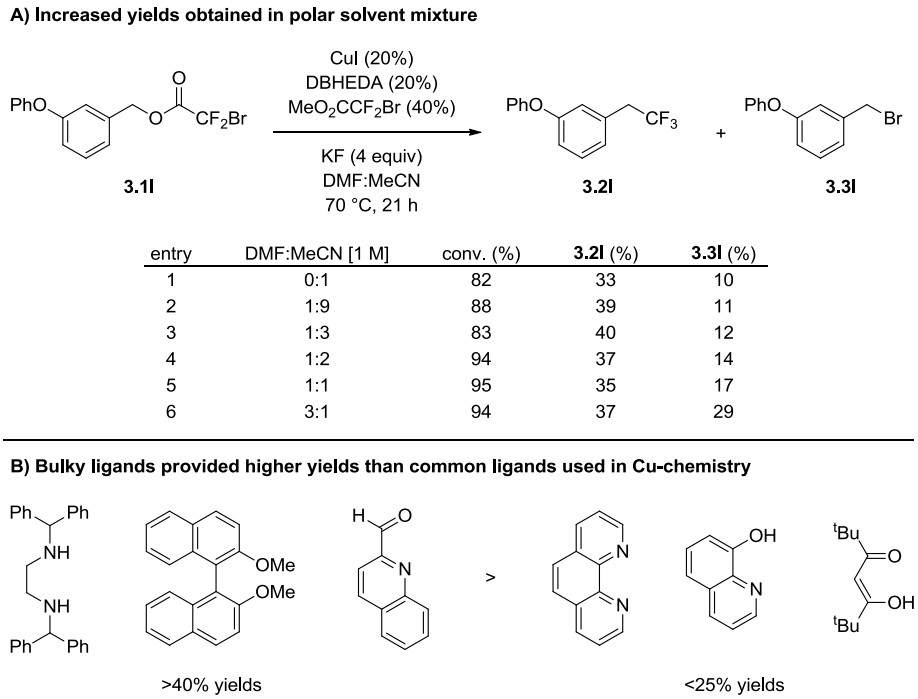
analysis. We reasoned that bromide, formed from decarboxylation of bromodifluoroacetate, reacted with benzylic bromodifluoroacetates to generate benzylic bromide side-products or intermediates. We also speculated that decomposition of [(DMEDA)Cu–CF_3] was more rapid than trifluoromethylation of the benzylic electrophile, and that alternate ligands could better stabilize this reactive intermediate. A coworker, Dr. Lingui Zhu, extensively screened ligands and conditions, and determined that a bulkier ligand, dibenzhydrylethylenediamine (DBHEDA), provided moderate yields of trifluoroethylarenes, while suppressing benzylic bromide side-products (Scheme 3.6B). Unfortunately, this system still struggled to convert electron-deficient benzylic bromodifluoroacetates to trifluoromethanes, and required near-stoichiometric Cu-loading for difficult substrates.

Scheme 3.6. Bulky diamines improved Cu-catalyzed benzylic trifluoromethylation in MeCN



In order to develop a catalyst system that more efficiently converted electron-deficient benzylic bromodifluoroacetates to trifluoroethylarenes, we reoptimized the reaction using 3-phenoxy-benzyl bromodifluoroacetate **3.1l** as a substrate (Scheme 3.7). Previously, MeCN was employed for promoting the reaction that suppressed the formation of benzylic bromide side products. We hypothesized that, for this less reactive system, a more polar solvent mixture might better stabilize the reaction's transition state. Therefore, we evaluated various solvents and solvent mixtures, and determined that a mixture of DMF and MeCN increased both product and benzylic bromide side-product (Scheme 3.7A). With the change of solvent, we screened various N-, O-, and P-based ligands. Notably, bulky ligands, such as DBHEDA, bis(methoxy)naphthylene, and 2-quinolinecarboxaldehyde provided higher yields than ligands with high affinity for Cu, such as 1,10-phenanthroline, 8-hydroxyquinoline, and 2,2,6,6-tetramethyl-3,5-heptanedione (Scheme 3.7B). While under previously explored reaction conditions, ligands appeared to improve benzylic trifluoromethylation, we realized that the revised DMF/MeCN solvent combination, bulky ligands might not associate with Cu over the course of the reaction. Indeed, control reactions revealed that these bulky ligands performed similarly to a ligand-free system. Therefore, we reexamined the mechanism to find other ways to improve the reaction.

Scheme 3.7. Polar solvent mixture more important than ligands in trifluoromethylation of electron deficient benzylic bromodifluoroacetates.

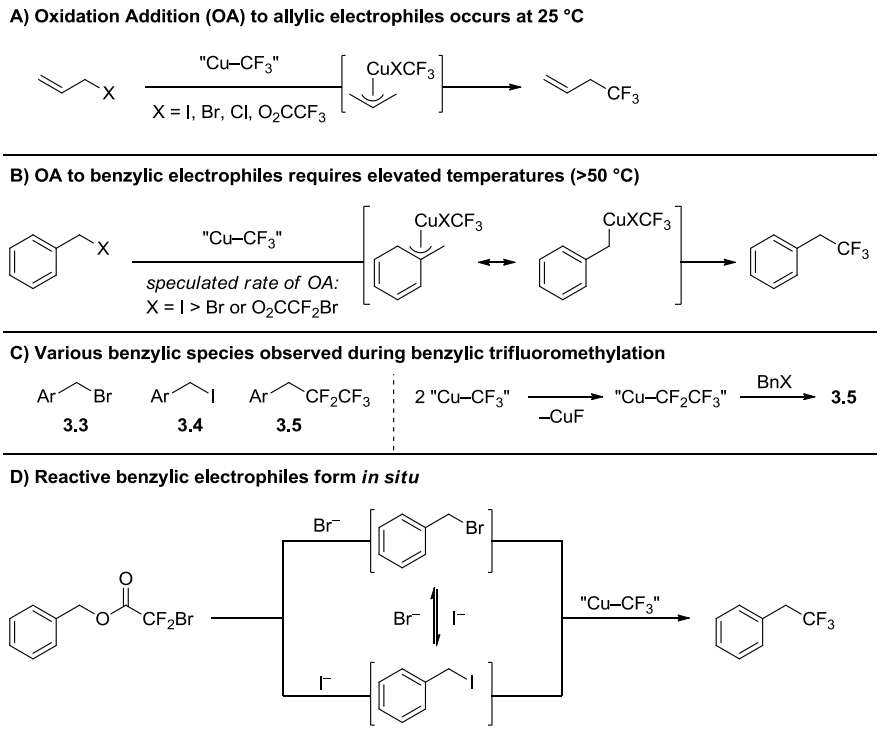


entry	DMF:MeCN [1 M]	conv. (%)	**3.2l** (%)	**3.3l** (%)
1	0:1	82	33	10
2	1:9	88	39	11
3	1:3	83	40	12
4	1:2	94	37	14
5	1:1	95	35	17
6	3:1	94	37	29

We hypothesized that benzylic trifluoromethylation occurs *via* an analogous mechanism to allylic trifluoromethylation, in which oxidative addition (OA) of "Cu–CF_3" to an allylic electrophile generates a Cu^{III}–π-allyl intermediate, and reductively eliminates (RE) to form allylic trifluoromethanes (Scheme 3.8A). While trifluoromethylation of allylic electrophiles occurred at 25 °C,[22] trifluoromethylation of benzylic electrophiles required elevated temperatures (50 to >100 °C).[18] Presumably, OA to benzylic electrophiles is difficult, since the resulting intermediate is a less stable Cu^{III}–η^1-benzyl or partially dearomatized Cu^{III}–η^3-benzyl intermediate (Scheme 3.8B). Considering potential benzylic electrophiles, we observed several benzylic intermediates/side-products observed in our reactions. Specifically, benzylic bromide (**3.3**) and pentafluoropropylaryl (**3.5**) species were generated in many of our reactions, and these products formed in

greater yields for benzylic substrates bearing electron-poor aromatic systems (Scheme 3.8C). Since during OA, positive charge accumulates at the benzylic position, electron-deficient benzylic electrophiles react more slowly than electron-rich benzylic electrophiles. Therefore, for electron-deficient substrates, side-reactions, such as decomposition of "Cu–CF_3", became competitive with trifluoromethylation. The formation of pentafluoropropylaryl species (**3.5**) supported this hypothesis, since "Cu–CF_3" could degrade to generate CuF and "Cu–CF_2CF_3", and then react with benzylic electrophiles to form **3.5**. In addition, benzylic bromides (**3.3**) could be reaction intermediates that persist after "Cu–CF_3" fully decomposed.

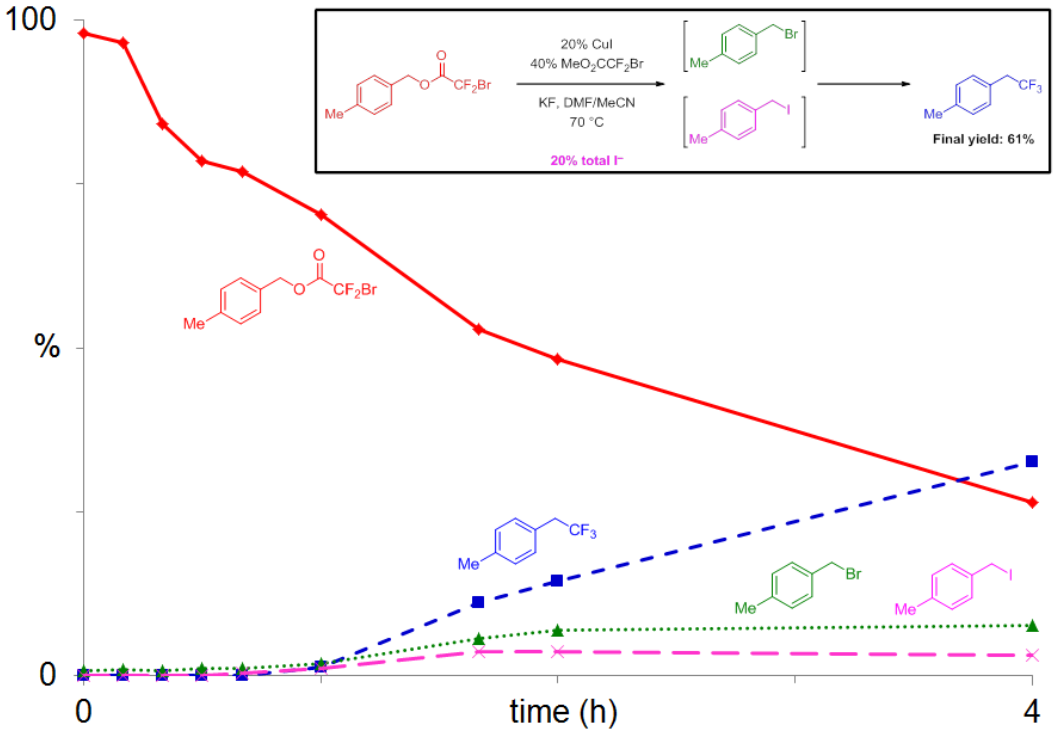
Scheme 3.8. Formation of reactive electrophiles is essential for benzylic trifluoromethylation.



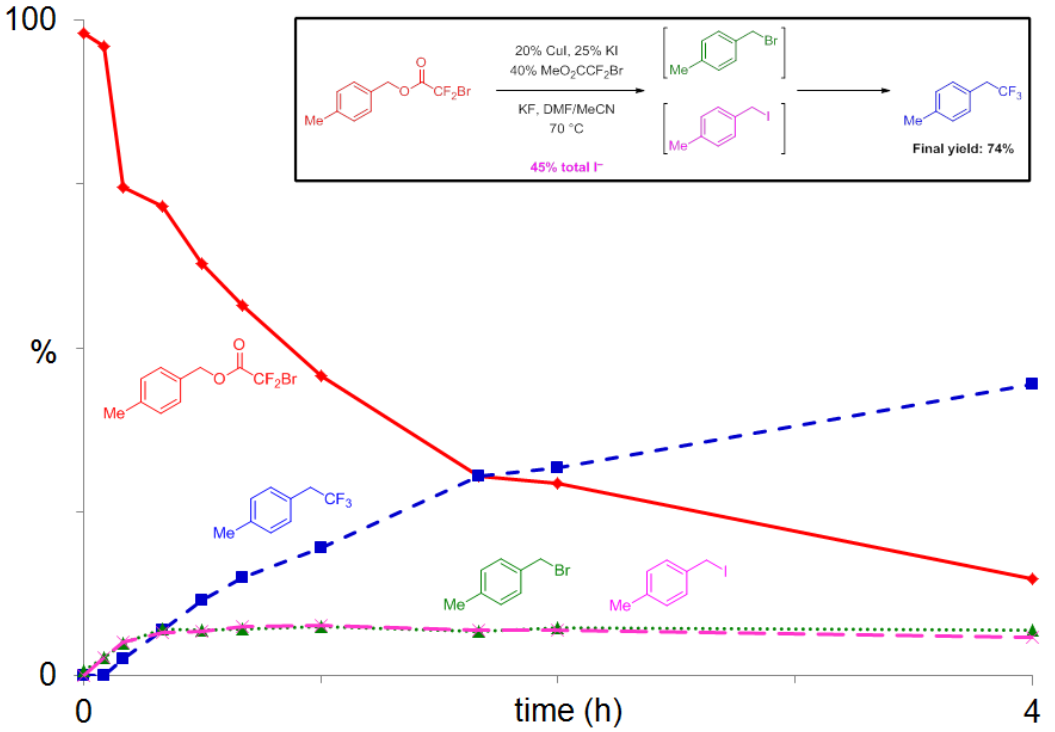
We proposed that generating more reactive benzylic electrophiles *in situ* could favor OA and productive trifluoromethylation over decomposition of "Cu–CF_3" and

generation of undesired side-products. While kinetic data for rates of "Cu–CF_3" OA to benzylic electrophiles was not known, we assumed the following trend based on temperatures required for various benzylic trifluoromethylation reactions: rate of OA for Bn–I > Bn–Br > Bn–O_2CCF_2Br.[18,23] We observed the formation of these more reactive benzylic electrophiles (Bn–Br **3.3** and Bn–I **3.4**) during reaction optimization and speculated that they formed from reactions with Br^- (generated upon decarboxylation of $^-O_2CCF_2Br$) and I^- (from CuI; Scheme 3.8D). In order to better understand the role of these electrophilic species in the reaction, we conducted a time-course study (Scheme 3.9) and monitored Bn–O_2CCF_2Br (red), Bn–Br (green) and Bn–I (pink) intermediates, and Bn–CF_3 product (blue). We observed three key points from this study: 1) the reaction had a 1 h induction period, where substrate decomposed without productive formation of intermediates or products;[24] 2) formation of product did not occur prior to generation of BnBr or BnI intermediates; and 3) steady-state concentrations of BnBr (ca. 7%) and BnI (ca. 3%) were established after several hours. Based on this information, we identified two aims to improve the reaction: 1) overcome the induction period by generating active nucleophile or electrophile; and 2) increase the steady-state concentration of Bn–I, which would react with "Cu–CF_3" faster than Bn–Br or Bn–O_2CCF_2Br, and relatively disfavor decomposition of "Cu–CF_3".

Scheme 3.9. Substrate decomposed and reactive intermediates slowly formed with 20% I⁻-loading.



Scheme 3.10. Reactive intermediates and product rapidly formed with 45% I⁻-loading.

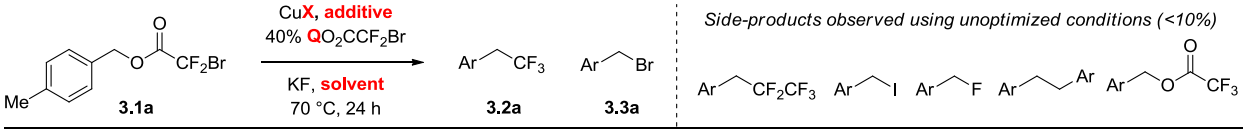


We reasoned that the induction period in benzylic trifluoromethylation was caused by slow conversion of unreactive Bn–O_2CCF_2Br to reactive Bn–Br or Bn–I (Scheme 3.8D). Under the standard reaction conditions (20% CuI, 40% MeO_2CCF_2Br, 4 equiv KF), reactive nucleophiles (I^- or Br^-) did not exist freely in solution. Therefore, a reaction to generate free nucleophiles (I^- or Br^-) was required to initiate trifluoromethylation (e.g. CuI + KF → CuF + KI; decomposition of Me– or Bn–O_2CCF_2Br to generate Br^-). To overcome this problem, we hypothesized that the addition of exogenous I^- would facilitate the conversion of Bn–O_2CCF_2Br to Bn–I. After investigating several I^- sources and loadings, we determined that the addition of 25% KI reduced the induction period from 1 h to <5 min, and improved reaction yields (61% yield w/o KI, 74% w/KI, Schemes 3.9–10). The addition of KI also increased the steady-state of Bn–I (ca. 7%), which promoted productive trifluoromethylation relative to decomposition of "Cu–CF_3". We also tested several procedures that assist with the generation of "Cu–CF_3" at the start of the reaction; however, these methods had no benefit on the reaction. Taken together, this data implicates that the generation of reactive Bn–I (or less reactive Bn–Br) is the essential step for initiating benzylic trifluoromethylation.

We conducted a series of reaction to identify the key features of the current reaction, and highlight improvements to previous systems (Scheme 3.11). Chen's original reaction of **3.1a** with stoichiometric CuI provided trifluoroethylarene **3.2a** in 71% yield;[18f] however, according to the previous protocol, **3.1a** was slowly added to the reaction mixture over 2 h, which can be labor intensive and operationally challenging for small scale reactions.[18f] To explore a more user-friendly protocol, we charged the vessel

with the full quantity of **3.1a** at the outset of the reaction. Using stoichiometric CuI, this procedure lowered the yield of **3.2a** and formed benzylic bromide **3.3a** as a side product (entry 1). Adapting conditions that effectively catalyzed the decarboxylative trifluoromethylation of allylic bromodifluoroacetates (cat. CuI, DMEDA, NaO_2CCF_2Br, DMF) also provided poor yields of **3.2a** (entry 2), along with several side products in 2–10% yield (Bn–CF_2CF_3, Bn–I, Bn–F, Bn–Bn, and Bn–O_2CCF_3). Using a DMF-ligated system, and MeO_2CCF_2Br as an additive,[18d] a modest yield of **3.2a** was observed, and benzylic bromide **3.3a** was identified as the major side-product (entry 3). The formation of **3.3a** could be suppressed by replacement of DMF with MeCN, but this change also afforded a less active system (entry 4). Based on these observations, we hypothesized that the use of a DMF/MeCN solvent mixture would provide an active system that would minimize the formation of **3.3a**. Indeed, employment of a 1:1 mixture of DMF/MeCN improved the yield of desired product **3.2a**, and minimized formation of the benzylic bromide side-product **3.3a** (entry 5).

Scheme 3.11. Solvent and I^- Critical for Developing a Cu-catalyzed Reaction.[a]



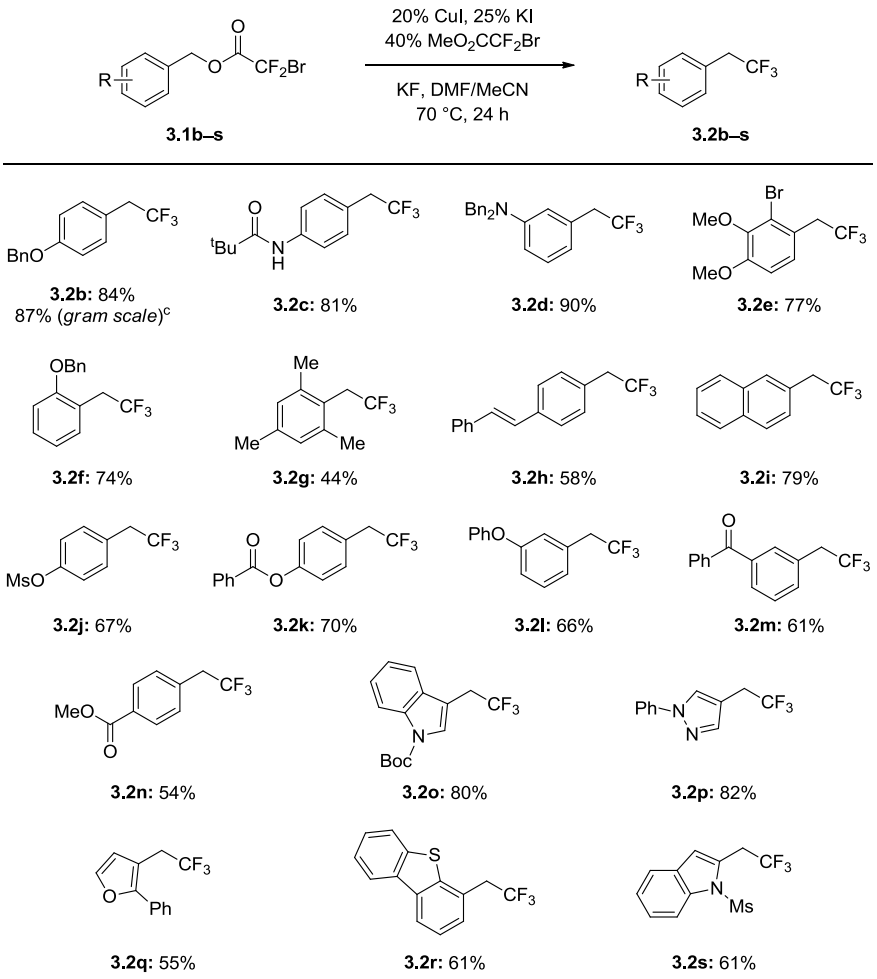
entry	solvent	CuX (mol %)	additive (mol %)	total % I^-	Q	conversion (%)	**3.2a** (%)	**3.3a** (%)
1[b]	DMF	**CuI (100)**	–	100	–	>99	22	8
2	DMF	CuI (20)	**DMEDA (20)**	20	**Na**	>99	23	10
3	**DMF**	CuI (20)	–	20	Me	>99	30	19
4	**MeCN**	CuI (20)	–	20	Me	35	13	3
5	**DMF/MeCN**	CuI (20)	–	20	Me	>99	61	5
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 **3.1a**, 0.080 mmol of QO_2CCF_2Br, 0.80 mmol of KF, 0.20 mL of solvent. Conversion and yield data were determined by GC/FID

analysis, and represent the average of a minimum of two independent experiments; [b]80 °C; [c]No side-products > 2% were detected by GC/FID analysis.

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.[18f] In contrast, a recent Cu-catalyzed trifluoromethylation of allylic bromodifluoroacetates could occur in the complete absence of I^-.[25a] 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 **3.2a**, and minimized formation of benzylic bromide **3.3a** 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 **3.3a** (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 **3.2a** (entry 9). In addition, removal of the MeO_2CCF_2Br additive from the system resulted in decreased yield of **3.2a**, and increased benzyl bromide **3.3a** (entry 10). Ultimately, we selected a general system that employed 20% CuI, 25% KI, 40% MeO_2CCF_2Br and super-stoichiometric KF in MeCN/DMF (1:1), which minimized the formation of side-products (<2%) and provided good yield of trifluoroethylarene **3.2a**.

Scheme 3.12. Copper-catalyzed decarboxylative trifluoromethylation tolerates important functional groups and heterocycles.[a,b]



[a]0.25 mmol **3.1b–s,** 0.050 mmol CuI, 0.063 mmol KI, 0.10 mmol MeO_2CCF_2Br, 1.0 mmol KF, 0.13 mL DMF, 0.13 mL MeCN; [b]The yields represent the average of two independent experiments; [c]6.0 mmol scale, single experiment.

The present Cu-catalyzed reaction tolerated a broad array of useful functional groups (Scheme 3.12), including: ethers (**3.2b**, **3.2e**–**f**, **3.2l**), a secondary amide (**3.2c**), a substituted aniline (**3.2d**), an aryl bromide (**3.2e**), an alkene (**3.2h**), a mesylate (**3.2j**), esters (**3.2k**, **3.2n**), and a ketone (**3.2m**). Substrates bearing (pseudo)ortho substituents

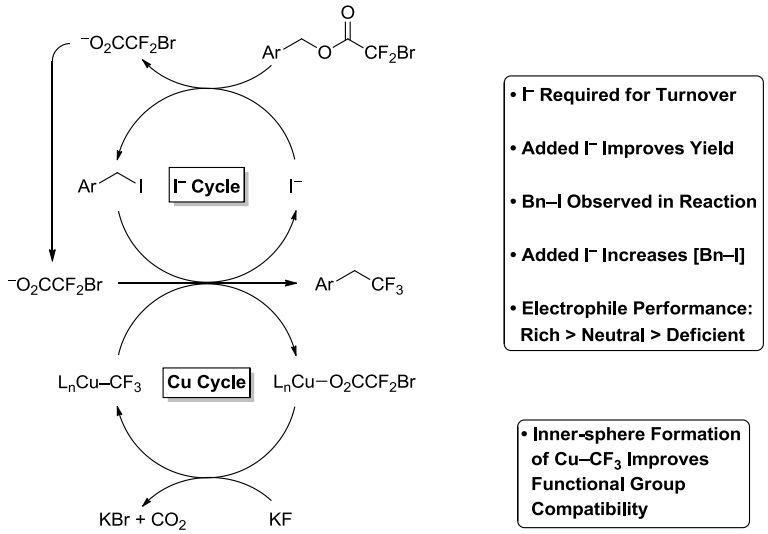
provided lower yields of products (**3.2e**–**f**, **3.2q**–**s**), and a sterically hindered 2,6-disubstitued benzylic electrophile afforded product in modest yield (**3.2g**). The present reaction also tolerated heterobenzylic substrates that incorporated N, O, and S atoms (**3.2o**–**s**). When the reaction was conducted on gram-scale, the yield of the reaction was maintained (**3.2b**), which indicates that this process would be useful for the preparation of larger quantities of target trifluoroethyl(hetero)arene compounds.

3.3. Mechanistic considerations for Cu-catalyzed decarboxylative trifluoromethylation of benzylic electrophiles.

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)[26] would react with sensitive functional groups. However, the tolerance of carbonyls (**3.2k**, **3.2m**–**o**) and an acidic amide (**3.2c**, pk_a ca. 13.8 in H_2O),[27] suggest that free $^{-}CF_3$ must not exist in solution. Additionally, in the reaction of **3.1m–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 **3.1a** 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.[28] 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.[25]

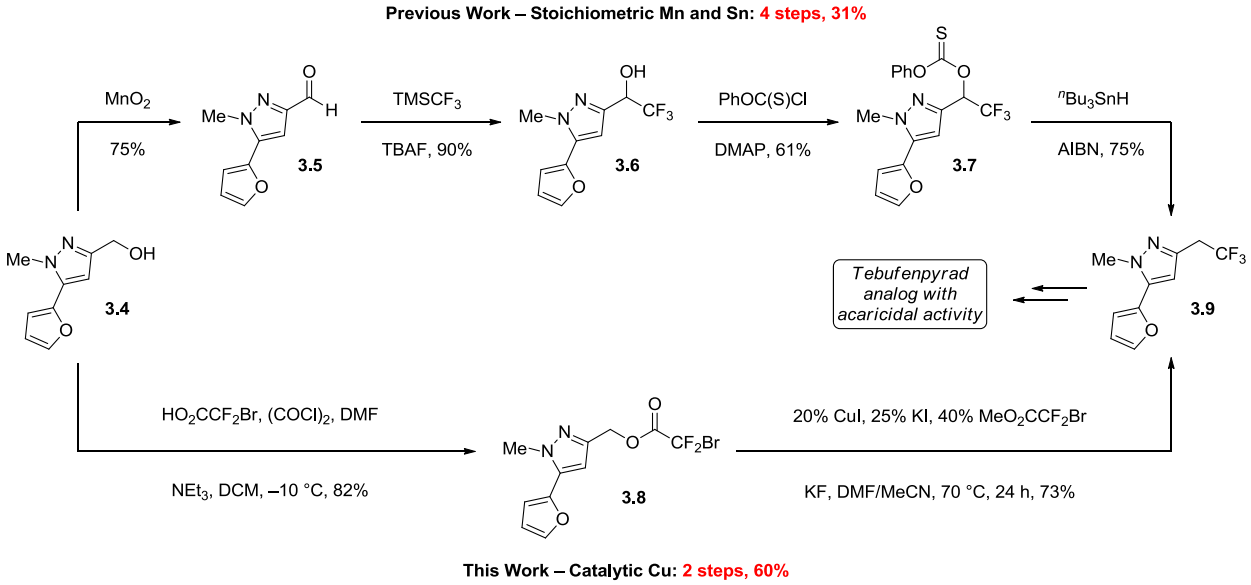
Circumstantial evidence implicates that, as previously suggested,[18f] the present reaction may involve *in situ* conversion of Bn–O_2CCF_2Br to a Bn–I intermediate prior to trifluoromethylation. First, the catalytic system required I^- for turnover, and added I^- facilitated the transformation (*vide 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.[28] Third, the electronic nature of the arene ring noticeably perturbed the reactivity of the substrates, with electron-rich substrates (**3.2b**–**f**) providing higher yields than electron-neutral (**3.2i**–**l**) and electron-deficient substrates (**3.2j–k**)**.** The latter trend may suggest that the benzylic position develops cationic character at a transition state of the reaction, which may implicate a S_N1- or S_N2-like step in the mechanism. Based on these pathways, the more slowly reacting electron-deficient electrophiles may allow decomposition of Cu–CF_3[29] 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 (Scheme 3.13). 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^-.

Scheme 3.13. Iodide plays an essential role in benzylic trifluoromethylation.



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 3.14). In a previous report, alcohol **3.4** was transformed into fluorinated intermediate **3.9** through a 4-step procedure that employed stoichiometric Mn and Sn and afforded product in 31% overall yield.[30] In contrast, the present 2-step procedure converted **3.4** to **3.9** in 60% total yield utilizing catalytic Cu. Thus, the present protocol demonstrated several desirable traits including: 1) improvement of overall yield of trifluoroethylheteroarene; 2) avoidance of oxidation and reduction reactions; 3) decrease in time and resource costs; 4) reduction of metal-containing waste products (stoichiometeric Mn and Sn vs. catalytic Cu). These attractive features should be useful for both agricultural and medicinal chemists.

Scheme 3.14. Copper-catalyzed reaction improves access to target compounds.[a–f]



[a]MnO_2, MeCN, reflux, 75%; [b]Me_3SiCF_3, TBAF (cat.) THF, rt, 90%; [c]PhOC(S)Cl, DMAP, 4 Å M.S., PhMe, 50–60 °C, 61%; [d]*n*-Bu_3SnH, AIBN (cat.), PhMe, 80 °C, 75%; [e]**3.4**, HO_2CCF_2Br, $(COCl)_2$, DMF, NEt_3, DCM, –10 °C, 82%; [f]0.25 mmol (Het)$ArCH_2O_2CCF_2Br$ (**3.8**), 0.050 mmol CuI, 0.063 mmol KI, 0.10 mmol MeO_2CCF_2Br, 1.0 mmol KF, 0.13 mL DMF, 0.13 mL MeCN, 70 °C, 24 h, 73%.

3.4. Conclusions.

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 supports a metal-centered decarboxylation event, that 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.

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Chapter 3 Appendix

Experimental procedures and spectra for compounds in Chapter 3

Table of Contents

General Considerations:

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^{TM} Silica Gel HLF 250 micron glass plates precoated with 230–400 mesh silica impregnated with a fluorescent indicator (250 nm), visualizing by quenching of fluorescence, $KMnO_4$ solution, or *p*-anisaldehyde solution. Silica gel for chromatographic purifications was purchased from Sorbent Technologies (cat. #30930M-25, 60 Å, 40–63 μm).

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

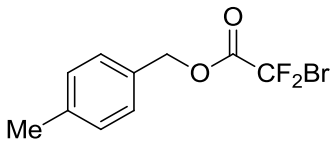
Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 or 500 MHz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 101 or 126 MHz. Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded at 376 MHz. Chemical shifts (δ) for protons are reported 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 millions, and are referenced to $PhCF_3$ (δ = –63.72 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constant in Hertz (Hz), and integration.

Exact mass determinations were obtained by the following methods; electron impact ionization (EI) on a ZG analytical ZAB mass spectrometer, electrospray ionization (ESI) on a Waters LCT Premier^{TM} mass spectrometer, or atmospheric-pressure chemical ionization (APCI–hexane/PhMe) on a Waters Q-Tof Premier^{TM}, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were used as ionization solvent. Melting points were uncorrected and measured on a Thomas Hoover Capillary Melting Point Apparatus.

Synthesis of Benzylic Bromodifluoroacetates:

General Procedure A

HO_2CCF_2Br (1.45 equiv) was added to a round-bottom flask, which was sealed with a rubber septum and attached to an oil bubbler. DCM and DMF were injected, and the solution was cooled to 0 °C. Oxalyl chloride (1.4 equiv) was injected (caution: evolution of noxious gas), and after 5 min, the mixture was allowed to warm to rt. After 2 h, the mixture was cooled to 0 °C, and a solution of benzylic alcohol (1.0 equiv) and NEt_3 (2–3 equiv) in DCM was added. The reaction was monitored by TLC analysis, and after consumption of the benzylic alcohol (usually within 1–2 h), the reaction was quenched with water, and the aqueous layer was extracted with DCM or EtOAc (4x). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After the removal of solvent, the residue was purified by flash column chromatography to afford bromodifluoroacetates **3.1a**–**s**.



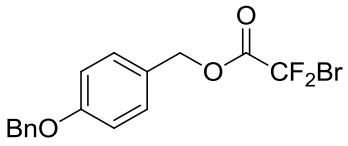
3.1a

4-Methylbenzyl 2-bromo-2,2-difluoroacetate[1]

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).



3.1b

4-(Benzyloxy)benzyl 2-bromo-2,2-difluoroacetate

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%).

m.p.: 64–65 °C.

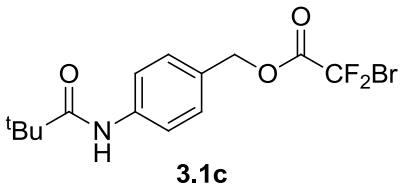
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.31 (m, 7 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 5.31 (s, 2 H), 5.10 (s, 2 H).

^{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).

IR (film): 2945, 2866, 1769, 1609, 1585, 1518, 1454, 1302, 1246, 1161, 1126, 1018, 955, 870, 814, 742, 706, 613 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}BrF_2O_3$: 370.0016; found: 370.0012 (1.1 ppm).



3.1c

4-Pivalamidobenzyl 2-bromo-2,2-difluoroacetate

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%).

m.p.: 86–87 °C.

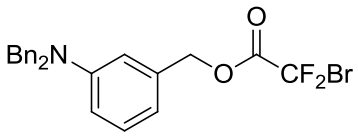
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.56 (m, 2 H), 7.42 (s, 1 H), 7.39–7.34 (m, 2 H), 5.31 (s, 2 H), 1.32 (s, 9 H).

^{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).

IR (film): 3292, 2975, 1771, 1655, 1599, 1520, 1460, 1294, 1157, 955, 820, 700, 604 cm^{-1}.

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).



3.1d

3-(Dibenzylamino)benzyl 2-bromo-2,2-difluoroacetate

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%).

m.p.: 67–68 °C.

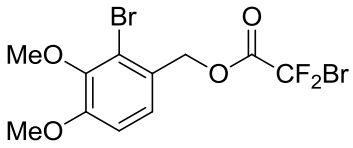
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.34 (m, 4 H), 7.33–7.25 (m, 6 H), 7.25–7.18 (m, 1 H), 6.80–6.72 (m, 3 H), 5.27 (s, 2 H), 4.71 (s, 4 H).

^{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).

IR (film): 3028, 2866, 1774, 1605, 1582, 1495, 1452, 1294, 1167, 1122, 953, 775, 733, 694 cm^{-1}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{23}H_{20}BrF_2NO_2$: 459.0645; found: 459.0644 (0.2 ppm).



3.1e

2-Bromo-3,4-dimethoxybenzyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using (2-bromo-3,4-dimethoxyphenyl) methanol[2] (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)].

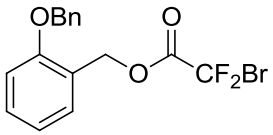
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.5 Hz, 1 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 5.41 (s, 2 H), 3.90 (s, 3 H), 3.88 (s, 3 H).

^{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).

IR (film): 2943, 2839, 1772, 1595, 1493, 1410, 1296, 1122, 1036, 941, 806, 750, 702 cm^{-1}.

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).



3.1f

2-(Benzyloxy)benzyl 2-bromo-2,2-difluoroacetate

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%).

m.p.: 45–46 °C.

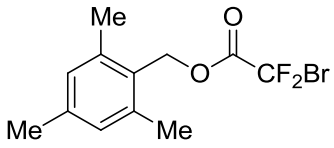
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.32 (m, 7 H), 7.05–6.97 (m, 2 H), 5.49 (s, 2 H), 5.16 (s, 2 H).

^{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).

IR (film): 3034, 1774, 1605, 1498, 1452, 1379, 1296, 1250, 1165, 1126, 1024, 949, 806, 754, 696 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}BrF_2O_3$: 370.0016; found: 370.0023 (1.9 ppm).



3.1g

2,4,6-Trimethylbenzyl 2-bromo-2,2-difluoroacetate

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%).

m.p.: 45–46 °C.

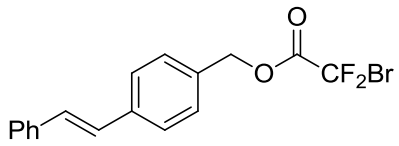
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 2 H), 5.45 (s, 2 H), 2.39 (s, 6 H), 2.31 (s, 3 H).

^{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).

IR (film): 3011, 2974, 2957, 2922, 2866, 1772, 1614, 1583, 1448, 1375, 1302, 1288, 1167, 1126, 1032, 951, 912, 851, 771, 700 cm^{-1}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{12}H_{13}BrF_2O_2$: 306.0067; found: 306.0080 (4.2 ppm).



3.1h

(*E*)-4-Styrylbenzyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using (*E*)-(4-styrylphenyl) methanol[3] (0.72 g, 3.4 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless solid (1.1 g, 86%).

m.p.: 75–76 °C.

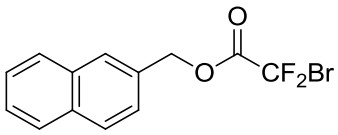
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, *J* = 7.5 Hz, 4 H), 7.45–7.36 (m, 4 H), 7.34–7.28 (m, 1 H), 7.21–7.09 (m, 2 H), 5.38 (s, 2 H).

^{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).

IR (film): 3026, 1772, 1514, 1448, 1383, 1296, 1165, 1126, 966, 949, 866, 818, 704, 690 cm^{-1}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{17}H_{13}BrF_2O_2$: 366.0067; found: 366.0055 (3.3 ppm).



3.1i

Naphthalen-2-ylmethyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using (naphthalen-2-yl)methanol (0.63 g, 4.0 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless solid (1.1 g, 88%).

m.p.: 32–33 °C.

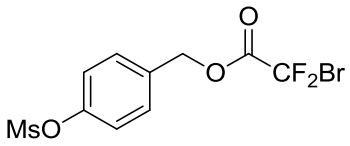
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.83 (m, 4 H), 7.58–7.53 (m, 2 H), 7.51 (d, *J* = 8.7 Hz, 1 H), 5.54 (s, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.6 (t, *J* = 31.5 Hz), 133.6, 133.2, 130.9, 129.0, 128.4, 128.3, 127.9, 127.0, 126.8, 125.8, 108.9 (t, *J* = 315.0 Hz), 70.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.68 (s, 2 F).

IR (film): 3056, 2964, 1774, 1508, 1375, 1296, 1171, 1124, 947, 854, 816, 750, 698 cm^{-1}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{13}H_9BrF_2O_2$: 313.9754; found: 313.9763 (2.9 ppm).



3.1j

4-((Methylsulfonyl)oxy)benzyl 2-bromo-2,2-difluoroacetate

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%).

m.p.: 48–49 °C.

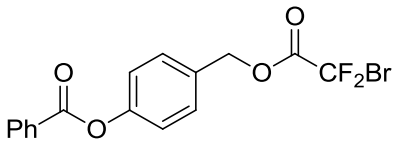
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.47 (m, 2 H), 7.38–7.33 (m, 2 H), 5.38 (s, 2 H), 3.19 (s, 3 H).

^{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).

IR (film): 3033, 2941, 1774, 1606, 1506, 1456, 1420, 1371, 1298, 1178, 1153, 1122, 970, 872, 835, 710, 679 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_9BrF_2O_5S$: 357.9322; found: 357.9329 (2.0 ppm).



3.1k

4-((2-Bromo-2,2-difluoroacetoxy)methyl)phenyl benzoate

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%).

m.p.: 65–66 °C.

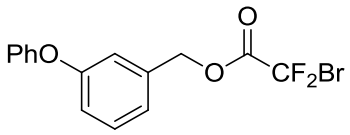
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27–8.18 (m, 2 H), 7.71–7.63 (m, 1 H), 7.58–7.46 (m, 4 H), 7.32–7.27 (m, 2 H), 5.39 (s, 2 H).

^{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).

IR (film): 3065, 1776, 1740, 1601, 1510, 1452, 1379, 1298, 1265, 1204, 1123, 1061, 1024, 951, 876, 804, 706, 604 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{11}BrF_2O_4$: 383.9809; found: 383.9810 (0.3 ppm).



3.1l

3-Phenoxybenzyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using (3-phenoxyphenyl)methanol (0.69 g, 3.4 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→19:1) afforded the title compound as a colorless oil (0.99 g, 80%).

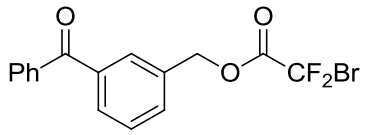
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.34 (m, 3 H), 7.18–7.10 (m, 2 H), 7.07–7.00 (m, 4 H), 5.33 (s, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.5 (t, *J* = 31.6 Hz), 158.0, 156.7, 135.4, 130.4, 130.0, 123.9, 122.9, 119.5, 119.3, 118.3, 108.7 (t, *J* = 314.4 Hz), 69.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.83 (s, 2 F).

IR (film): 3065, 3040, 2964, 1778, 1585, 1489, 1448, 1377, 1301, 1259, 1213, 1173, 1122, 945, 874, 847, 777, 692, 604 cm^{-1}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{15}H_{11}BrF_2O_3$: 355.9860; found: 355.9845 (4.2 ppm).



3.1m

3-Benzoylbenzyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using (3-(hydroxylmethyl)phenyl)(phenyl)-methanone. Workup and chromatographic purification (hexanes/EtOAc, 1:0→21:4) afforded the title compound as a pale yellow oil (1.6 g, 88%).

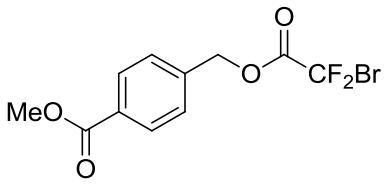
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.77 (m, 4 H), 7.67–7.59 (m, 2 H), 7.58–7.47 (m, 3 H), 5.43 (s, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 196.1, 159.4 (t, *J* = 31.5 Hz), 138.3, 137.3, 133.9, 132.9, 132.3, 130.9, 130.2, 130.0, 129.1, 128.5, 108.7 (t, *J* = 314.3 Hz), 69.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.81 (s, 2 F).

IR (film): 3065, 3040, 2964, 1778, 1585, 1489, 1448, 1377, 1301, 1259, 1213, 1173, 1122, 945, 874, 847, 777, 692, 604 cm^{-1}.

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).



3.1n

Methyl 4-((2-bromo-2,2-difluoroacetoxy)methyl)benzoate

General Procedure A was followed using methyl 4-(hydroxymethyl) benzoate (0.55 g, 3.3 mmol). Workup and chromatographic purification (hexanes/EtOAc, 1:0→19:1) afforded the title compound as a colorless oil (0.91 g, 85%).

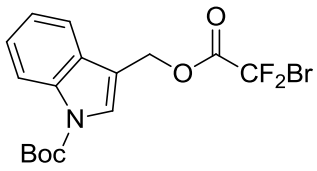
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.9 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 5.41 (s, 2 H), 3.94 (s, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.6, 159.4 (t, *J* = 31.7 Hz), 138.3, 130.9, 130.2, 128.1, 108.6 (t, *J* = 314.2 Hz), 68.9, 52.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.86 (s, 2 F).

IR (film): 2955, 1778, 1724, 1616, 1437, 1379, 1283, 1171, 1111, 1020, 955, 847, 756, 708, 602 cm^{-1}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{11}H_9BrF_2O_4$: 321.9652; found: 321.9639 (4.0 ppm).



3.1o

Tert-butyl 3-((2-bromo-2,2-difluoroacetoxy)methyl)-1H-indole-1-carboxylate

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%).

m.p.: 47–49 °C.

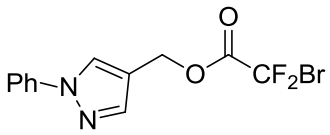
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.3 Hz, 1 H), 7.77 (s, 1 H), 7.64 (dt, *J* = 7.8, 1.0 Hz, 1 H), 7.39 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1 H), 7.31 (td, *J* = 7.6, 1.1 Hz, 1 H), 5.54 (d, *J* = 0.7 Hz, 2 H), 1.69 (s, 9 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.7 (t, *J* = 31.5 Hz), 149.5, 135.7, 128.9, 127.1, 125.2, 123.3, 119.2, 115.6, 113.3, 108.8 (t, *J* = 314.5 Hz), 84.5, 62.0, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.7 (s, 2 F).

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}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{16}H_{16}BrF_2NO_4$: 403.0231; found: 403.0222 (2.2 ppm).



3.1p

(1-Phenyl-1*H*-pyrazol-4-yl)methyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using (1-phenyl-1*H*-pyrazol-4-yl)methanol[4] (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%).

m.p.: 60–61 °C.

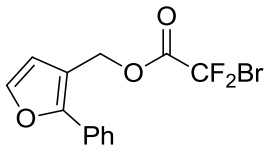
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1 H), 7.81 (s, 1 H), 7.71–7.66 (m, 2 H), 7.51–7.44 (m, 2 H), 7.36–7.30 (m, 1 H), 5.36 (s, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.7 (t, *J* = 31.7 Hz), 141.7, 139.8, 129.7, 128.2, 127.2, 119.5, 116.0, 108.9 (t, *J* = 314.5 Hz), 61.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.90 (s, 2 F).

IR (film): 3057, 2970, 1774, 1514, 1489, 1375, 1292, 11689, 1122, 1067, 943, 887, 842, 771, 736, 692, 660 cm^{-1}.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{10}BrF_2N_2O_2$: 330.9781; found: 330.9788 (2.1 ppm).



3.1q

(2-Phenylfuran-3-yl)methyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using (2-phenylfuran-3-yl)methanol[5] (0.52 g, 3.0 mmol). Workup provided the title compound as a yellow oil (0.93 g, 93%).

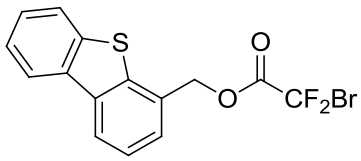
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.59 (m, 2 H), 7.51–7.45 (m, 3 H), 7.43–7.37 (m, 1 H), 6.61 (d, *J* = 1.9 Hz, 1 H), 5.40 (s, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.7 (t, *J* = 31.6 Hz), 153.4, 142.1, 129.9, 129.1, 128.7, 126.6, 113.56, 113.54, 108.8 (t, *J* = 314.6 Hz), 62.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.75 (s, 2 F).

IR (film): 3057, 2970, 1774, 1514, 1489, 1375, 1292, 11689, 1122, 1067, 943, 887, 842, 771, 736, 692, 660 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_9BrF_2O_3$: 329.9703; found: 329.9701 (0.6 ppm).



3.1r

Dibenzo[*b,d*]thiophen-4-ylmethyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using dibenzo[*b*,*d*]thiophen-4-ylmethanol (1.2 g, 5.6 mmol). Workup and chromatographic purification (hexanes) provided the title compound as a colorless solid (1.9 g, 89%).

m.p.: 90–91 °C.

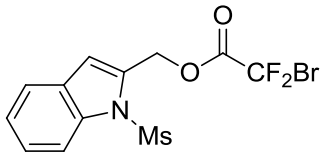
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22–8.15 (m, 2 H), 7.94–7.86 (m, 1 H), 7.57–7.47 (m, 4 H), 5.63 (s, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.6 (t, *J* = 31.7 Hz), 139.24, 139.15, 136.6, 135.4, 127.7, 127.37, 127.33, 124.90, 124.86, 123.0, 122.6, 122.0, 108.7 (t, *J* = 314.5 Hz), 68.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.52 (s, 2 F).

IR (film): 3064, 2931, 1778, 1585, 1443, 1408, 1298, 1180, 1136, 1047, 982, 941, 883, 827, 789, 746, 710, 669 cm^{-1}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{15}H_9BrF_2O_2S$: 369.9475; found: 369.9471 (1.1 ppm).



3.1s

(1-(Methylsulfonyl)-1*H*-indol-2-yl)methyl 2-bromo-2,2-difluoroacetate

General Procedure A was followed using [1-(methylsulfonyl)-1*H*-indol-2-yl]methanol[6] (1.1 g, 5.0 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→9:1) provided the title compound as a grey solid (1.1 g, 70%).

m.p.: 87–88 °C.

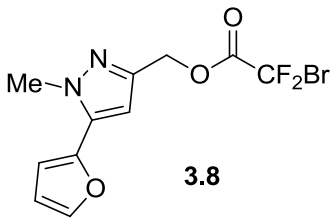
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dt, *J* = 8.3, 1.0 Hz, 1 H), 7.66–7.61 (m, 1 H), 7.47–7.40 (m, 1 H), 7.38–7.31 (m, 1 H), 6.91 (s, 1 H), 5.69 (s, 2 H), 3.19 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.8 (t, *J* = 31.7 Hz), 137.2, 131.7, 128.3, 126.5, 124.3, 122.0, 114.8, 114.1, 108.7 (t, *J* = 314.3 Hz), 62.7, 41.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.63 (s, 2 F).

IR (film): 3028, 1778, 1452, 1369, 1292, 1175, 1121, 964, 916, 823, 771, 748, 719, 685 cm^{-1}.

HRMS (APCI–hexane/PhMe): *m/z* $[M]^+$ calcd for $C_{12}H_{10}BrF_2NO_4S$: 380.9482; found: 380.9479 (0.8 ppm).



3.8

(5-(Furan-2-yl)-1-methyl-1H-pyrazol-3-yl)methyl 2-bromo-2,2-difluoroacetate

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[7] (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 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. Chromatographic purification (hexanes/EtOAc 1:0→3:2) provided the title compound as a yellow solid (0.29 g, 82%).

m.p.: 39–40 °C.

^{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{^{1}H} 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).

IR (film): 3128, 1776, 1531, 1475, 1448, 1362, 1302, 1163, 1124, 1011, 947, 903, 885, 800, 741, 702 cm^{-1}.

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).

Synthesis of Trifluoroethyl(hetero)arenes:

General Procedure B (solid substrates)

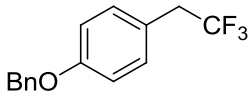
An oven-dried 15 mL screw-top vial was sealed with a PTFE septum and cooled under an atmosphere of dry N_2. CuI (9.5 mg, 0.050 mmol) and (hetero)benzyl bromodifluoroacetate (0.25 mmol) were added to the vial, which was transferred into a N_2-filled glovebox. Anhydrous KF (58.1 mg, 1.00 mmol) and anhydrous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

vacuo. The residue was purified via silica gel chromatography to provide the corresponding trifluoroethyl(hetero)arene.

General Procedure C (liquid substrates)

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

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).



3.2b

1-(Benzyloxy)-4-(2,2,2-trifluoroethyl)benzene[2]

General Procedure B was followed using **3.1b** (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%).

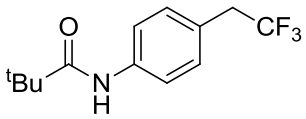
m.p.: 78–79 °C (lit.[8] 82–84 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.39 (m, 4 H), 7.39–7.33 (m, 1 H), 7.27–7.21 (m, 2 H), 7.01–6.96 (m, 2 H), 5.09 (s, 2 H), 3.33 (q, *J* = 10.8 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –66.4 (3 F, t, *J* = 10.9 Hz).

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), **3.1b** (2.2 g, 6.0 mmol), and DMF (3.0 mL) were injected into the flask, which was placed in a pre-heated oil bath (70 °C) and stirred for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (75 mL). The mixture

was washed with H_2O (75 mL) and brine (75 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified via silica gel chromatography (hexanes/Et_2O 39:1) to provide **3.2b** as a colorless solid (1.4 g, 87%). The ^1H and ^{19}F NMR spectrum were consistent with the data described above.



3.2c

N-(4-(2,2,2-Trifluoroethyl)phenyl)pivalamide

General Procedure B was followed using **3.1c** (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%).

m.p.: 132–133 °C.

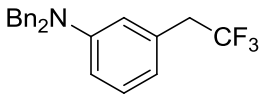
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.4 Hz, 2 H), 7.37 (s, 1 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 3.33 (q, *J* = 10.8 Hz, 2 H), 1.32 (s, 9 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 176.8, 138.1, 130.8, 125.9 (q, *J* = 3.0 Hz), 125.8 (q, *J* = 276.7 Hz), 120.2, 39.76, 39.74 (q, *J* = 29.8 Hz), 27.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.65 (t, *J* = 10.8 Hz, 3 F).

IR (film): 3317, 2978, 2873, 1654, 1599, 1522, 1412, 1315, 1265, 1244, 1138, 1072, 905, 806, 698, 656 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{16}F_3NO$: 259.1184; found: 259.1189 (1.9 ppm).



3.2d

N,N-Dibenzyl-3-(2,2,2-trifluoroethyl)aniline

General Procedure B was followed using **3.1d** (115 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→17:3) afforded the title compound as a colorless oil (80.6 mg, 91%).

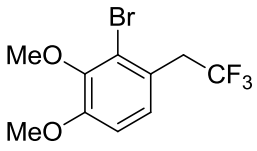
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.33 (m, 4 H), 7.32–7.25 (m, 6 H), 7.17 (t, *J* = 7.9 Hz, 1 H), 6.73 (dd, *J* = 8.4, 2.7 Hz, 1 H), 6.70–6.64 (m, 2 H), 4.68 (s, 4 H), 3.26 (q, *J* = 11.0 Hz, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.6, 138.4, 131.2 (q, *J* = 2.8 Hz), 129.6, 128.8, 127.1, 126.8, 126.0 (q, *J* = 277.0 Hz), 118.6, 114.3, 112.3, 54.3, 40.7 (q, *J* = 29.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.68 (t, *J* = 10.9 Hz, 3 F).

IR (film): 3061, 3030, 2922, 2860, 1605, 1582, 1499, 1452, 1358, 1259, 1132, 1078, 1028, 991, 964, 922, 777, 729, 696 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{22}H_{20}F_3N$: 355.1548; found: 355.1561 (3.7 ppm).



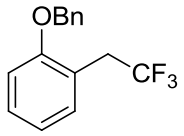
3.2e

2-Bromo-3,4-dimethoxy-1-(2,2,2-trifluoroethyl)benzene[9]

General Procedure C was followed using **3.1e** (101 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→17:3) afforded the title compound as a colorless oil (57.9 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.5 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.60 (q, *J* = 10.6 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.48 (t, *J* = 10.5 Hz, 3 F).



3.2f

1-(Benzyloxy)-2-(2,2,2-trifluoroethyl)benzene

General Procedure B was followed using **3.1f** (92.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/DCM 1:0→19:1) afforded the title compound as a colorless oil (50.7 mg, 76%).

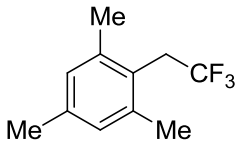
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.30 (m, 7 H), 7.07–6.93 (m, 2 H), 5.15 (s, 2 H), 3.57 (q, *J* = 11.0 Hz, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.2, 137.0, 132.0, 129.6, 128.7, 128.1, 127.3, 126.3 (q, *J* = 277.3 Hz), 120.9, 119.3 (q, *J* = 2.8 Hz), 112.2, 70.3, 33.7 (q, *J* = 30.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.34 (t, *J* = 10.9 Hz, 3 F).

IR (film): 3005, 2943, 1595, 1494, 1406, 1360, 1285, 1246, 1138, 1092, 1036, 947, 901, 806, 766, 681, 646 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{13}F_3O$: 266.0918; found: 266.0920 (0.8 ppm).



3.2g

1,3,5-Trimethyl-2-(2,2,2-trifluoroethyl)benzene

General Procedure C was followed using **3.1g** (76.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless oil (22.4 mg, 46%).

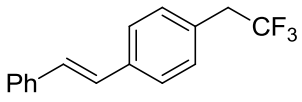
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (s, 2 H), 3.48 (q, *J* = 10.8 Hz, 2 H), 2.35 (s, 6 H), 2.29 (s, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 138.3, 137.7, 129.4, 126.9 (q, *J* = 278.3 Hz), 125.6 (q, *J* = 2.47 Hz), 33.6 (q, *J* = 29.6 Hz), 21.0, 20.4 (q, *J* = 2.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.8 (t, *J* = 10.8 Hz, 3 F).

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}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{13}F_3$: 202.0969; found: 202.0978 (4.5 ppm).



3.2h

(*E*)-1-Styryl-4-(2,2,2-trifluoroethyl)benzene

General Procedure B was followed using **3.1h** (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%).

m.p.: 135–136 °C.

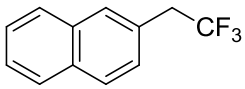
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.51 (m, 4 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.36–7.29 (m, 3 H), 7.17–7.14 (m, 2 H), 3.40 (q, *J* = 10.8 Hz, 2 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 137.4, 137.2, 130.6, 129.45 (q, *J* = 2.9 Hz), 129.41, 128.8, 128.0, 127.9, 126.8, 126.7, 125.9 (q, *J* = 276.9 Hz), 40.1 (q, *J* = 29.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.81 (t, *J* = 10.8 Hz, 3 F).

IR (film): 3022, 1448, 1429, 1420, 1356, 1258, 1147, 1119, 1078, 964, 908, 820, 792, 754, 739, 692, 658 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}F_3$: 262.0969; found: 262.0968 (0.4 ppm).



3.2i

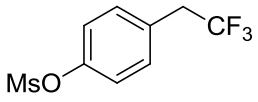
2-(2,2,2-Trifluoroethyl)naphthalene[10]

General Procedure B was followed using **3.1i** (78.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes) afforded the title compound as a colorless solid (42.3 mg, 81%).

m.p.: 51–53 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.81 (m, 3 H), 7.79 (s, 1 H), 7.55–7.48 (m, 2 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 3.55 (q, *J* = 10.8 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.65 (t, *J* = 10.8 Hz, 3 F).



3.2j

4-(2,2,2-Trifluoroethyl)phenyl methanesulfonate

General Procedure B was followed using **3.1j** (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%).

m.p.: 75–76 °C.

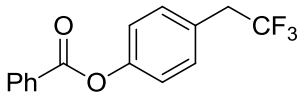
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.5 Hz, 2 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 3.39 (q, *J* = 10.7 Hz, 2 H), 3.15 (s, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 149.1, 132.0, 129.6 (q, *J* = 3.0 Hz), 125.6 (q, *J* = 276.8 Hz), 122.4, 39.6 (q, *J* = 30.1 Hz), 37.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.36 (t, *J* = 10.7 Hz, 3 F).

IR (film): 3031, 2945, 1608, 1502, 1456, 1421, 1361, 1302, 1177, 1153, 1132, 974, 876, 832, 707, 681 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_9H_9F_3O_3S$: 254.0225; found: 254.0229 (1.6 ppm).



3.2k

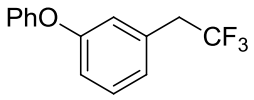
4-(2,2,2-Trifluoroethyl)phenyl benzoate[11]

General Procedure B was followed using **3.1k** (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%).

m.p.: 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).



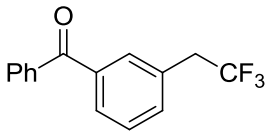
3.2l

1-Phenoxy-3-(2,2,2-trifluoroethyl)benzene[12]

General Procedure C was followed using **3.1l** (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).



3.2m

Phenyl(3-(2,2,2-trifluoroethyl)phenyl)methanone

General Procedure C was followed using **3.1m** (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%).

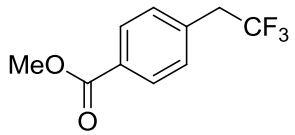
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.71 (m, 4 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.57–7.45 (m, 4 H), 3.45 (q, *J* = 10.7 Hz, 2 H).

^{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).

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}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{11}F_3O$: 264.0762; found: 264.0763 (0.4 ppm).



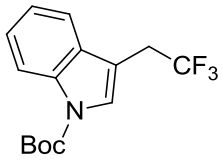
3.2n

Methyl 4-(2,2,2-trifluoroethyl)benzoate[10]

General Procedure C was followed using **3.1n** (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).



3.2o

Tert-butyl 3-(2,2,2-trifluoroethyl)-1*H*-indole-1-carboxylate

General Procedure B was followed using **3.1o** (101 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc, 39:1) afforded the title compound as a colorless solid (58.1 mg, 78%).

m.p.: 79–80 °C.

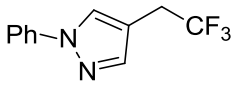
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 6.7 Hz, 1 H), 7.61 (s, 1 H), 7.56 (d, *J* = 7.8 Hz, 1 H), 7.37 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1 H), 7.30 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1 H), 3.51 (qd, *J* = 10.6, 0.9 Hz, 2 H), 1.69 (s, 9 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 149.6, 135.4, 130.0, 125.93 (q, *J* = 276.9 Hz), 125.92, 124.9, 123.0, 119.0, 115.5, 109.5 (q, *J* = 3.3 Hz), 84.2, 30.5 (q, *J* = 31.7 Hz), 28.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.57 (t, *J* = 10.7 Hz, 3 F).

IR (film): 3057, 2982, 2934, 1736, 1452, 1375, 1350, 1277, 1259, 1229, 1153, 1138, 1101, 1016, 914, 856, 770, 744 cm^{-1}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{16}F_3NO_2$: 299.1133; found: 299.1122 (3.7 ppm).



3.2p

1-Phenyl-4-(2,2,2-trifluoroethyl)-1*H*-pyrazole

General Procedure B was followed using **3.1p** (82.8 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 1:0→9:1) afforded the title compound as a colorless solid (47.2 mg, 83%).

m.p.: 45–46 °C.

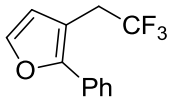
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (s, 1 H), 7.70–7.65 (m, 3 H), 7.49–7.42 (m, 2 H), 7.33–7.28 (m, 1 H), 3.36 (q, *J* = 10.7 Hz, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 141.6, 140.0, 129.6, 127.0, 126.9, 125.7 (q, *J* = 276.2 Hz), 119.3, 111.8 (q, *J* = 3.3 Hz), 30.1 (q, *J* = 31.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –66.02 (t, *J* = 10.7 Hz, 3 F).

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}.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{10}F_3N_2$: 227.0796; found: 227.0794 (0.9 ppm).



3.2q

2-Phenyl-3-(2,2,2-trifluoroethyl)furan

General Procedure C was followed using **3.1q** (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%).

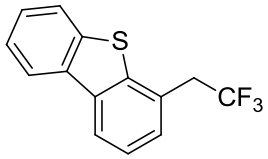
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61–7.57 (m, 2 H), 7.51–7.44 (m, 3 H), 7.41–7.36 (m, 1 H), 6.53 (s, 1 H), 3.45 (q, *J* = 10.5 Hz, 2 H).

^{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).

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}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{12}H_9F_3O$: 226.0605; found: 226.0597 (3.5 ppm).



3.2r

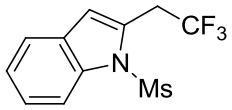
4-(2,2,2-Trifluoroethyl)dibenzo[*b,d*]thiophenes[2]

General Procedure B was followed using **3.1r** (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%).

m.p.: 102–103 °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).



3.2s

1-(Methylsulfonyl)-2-(2,2,2-trifluoroethyl)-1*H*-indole

General Procedure B was followed using **3.1s** (95.5 mg, 0.250 mmol). Workup and chromatographic purification (hexanes/EtOAc 9:1→2:1) afforded the title compound as a colorless solid (42.6 mg, 61%).

m.p.: 95–96 °C.

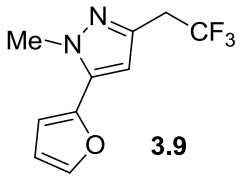
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03–7.99 (m, 1 H), 7.64–7.59 (m, 1 H), 7.41 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1 H), 7.34 (td, *J* = 7.5, 1.1 Hz, 1 H), 6.80 (s, 1 H), 4.04 (q, *J* = 10.2 Hz, 2 H), 3.13 (s, 3 H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 136.8, 129.4 (q, *J* = 3.5 Hz), 129.0, 125.5, 125.2 (q, *J* = 277.1 Hz), 124.2, 121.3, 114.3, 113.1, 40.9, 32.8 (q, *J* = 31.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –64.76 (t, *J* = 10.2 Hz, 3 F).

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}.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{10}F_3NO_2S$: 277.0384; found: 277.0382 (0.7 ppm).



3.9

5-(Furan-2-yl)-1-methyl-3-(2,2,2-trifluoroethyl)-1H-pyrazole[7]

General Procedure B was followed using **3.8** (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).

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Chapter 4: Regioselective Cu-Catalyzed Decarboxylative Trifluoromethylation of Propargylic Bromodifluoroacetates to Generate Propargylic Trifluoromethanes and Trifluoromethylallenes

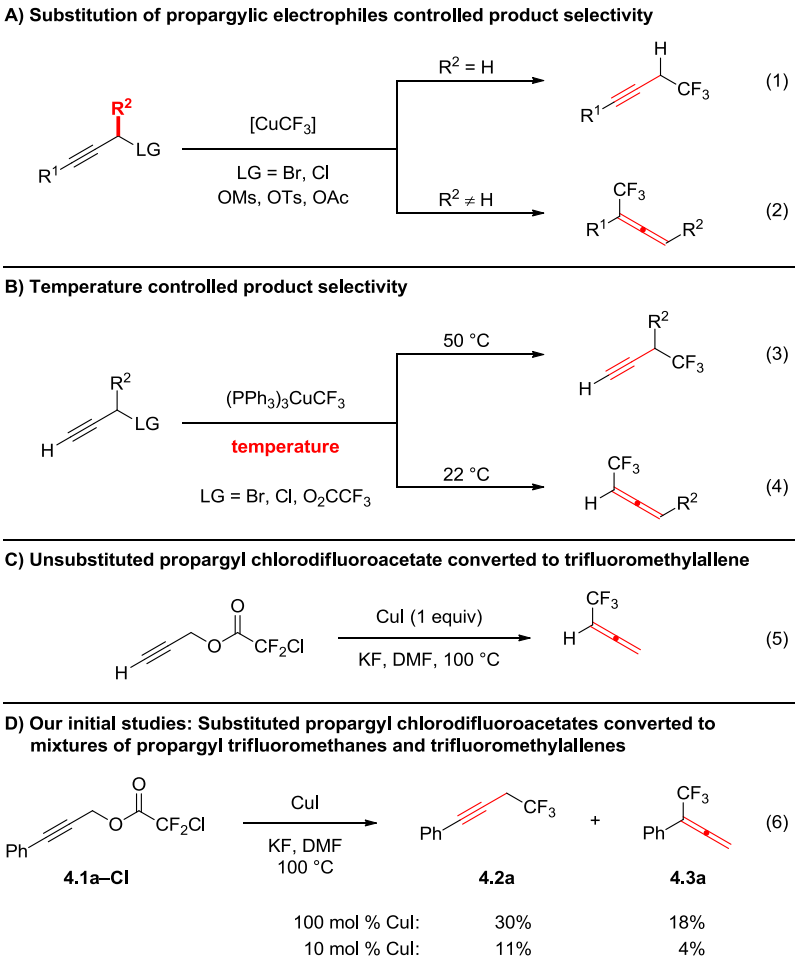
4.1. Cu-promoted trifluoromethylation of propargylic electrophiles provides propargylic trifluoromethanes and trifluoromethylallenes.

Copper-mediated and -catalyzed nucleophilic trifluoromethylation is a popular strategy for accessing CF_3-based products.[1] While the fundamental reactivity of Cu–CF_3 with sp^2- and activated sp^3-electrophiles has long been established,[2] recent advances greatly improved the practical utility and economic viability of these methods.[3–5] One important advancement involved the use of ligands to stabilize the reactive Cu–CF_3 species, and to accelerate reactions with electrophiles.[3,5,6] These two features allowed reactions to proceed under milder conditions that tolerated a broad array of functional groups and heterocycles.[3,5,6] While many of these new Cu-mediated and -catalyzed trifluoromethylation reactions displayed excellent chemoselectivity, ligands have not previously influenced regiochemical outcomes of reactions. Herein, we studied the effect of ligands on the trifluoromethylation of propargyl halodifluoroacetates, and report the first example of a regioselective trifluoromethylation reaction in which a ligand overrode the intrinsic reactivity of unligated "Cu–CF_3" with electrophiles. Further, we showed that the products can serve as useful synthetic building blocks by providing access to 2° trifluoromethanes that otherwise, would be difficult to synthesize.

Propargyl electrophiles, including –Br,[7–9] –Cl,[8–11] –OMs,[12] –OTs,[10] –OAc,[13] and –O_2CCF_2X (X = F, Cl, Br),[8,14,15c] reacted using either catalytic[11,15c] or stoichiometric[7–10,12–14] "Cu–CF_3" to generate propargyl and/or allenyl products with minimal control of

regiochemistry (Scheme 4.1). Unsubstituted propargyl electrophiles provided trifluoromethylallene;[9,10,14] however, reactions of substituted substrates displayed distinct selectivities. In most cases, the product distribution was dictated by the substitution pattern of the substrate, where 1° electrophiles provided propargyl products, and 2° and 3° electrophiles provided allenyl products (eq 1–2).[7,10–14] In contrast, a Cu/PPh_3-based system depended on reaction temperature to dictate the regioisomeric ratio of branched and linear products (eq 3–4).[8] However, for many cases, the intrinsic reactivity of the substrate overrode the control by temperature, and thus, many allenyl products were not accessible.[8]

Scheme 4.1. Substrate and temperature-controlled regioselective trifluoromethylation.



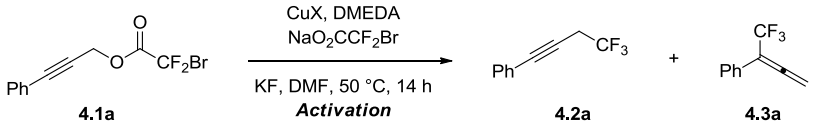
4.2. Cu-catalyzed trifluoromethylation of propargylic halodifluoroacetates to generate propargylic trifluoromethanes.

Given our interest in developing Cu-catalyzed decarboxylative trifluoromethylation reactions, we were intrigued by a single report in which unsubstituted propargyl chlorodifluoroacetate converted to trifluoromethylallene in the presence of stoichiometric Cu (Scheme 4.1C).[14] In order to establish whether this strategy could be applied to substituted propargylic substrates, we investigated the reactivity of 3-phenylpropynyl chlorodifluoroacetate (**4.1a–Cl**). Initially, we treated this substrate with stoichiometric CuI using the previously reported conditions,[14] and obtained a 1.7 : 1 mixture of propargyl (**4.2a**) : allenyl (**4.3a**) products (Scheme 4.1D). Next, we established that Cu could serve as a catalyst for this process, and using 10% CuI, observed a turnover number of 1.5 (Scheme 4.1D).

We aimed to develop a Cu-catalyzed decarboxylative trifluoromethylation reaction that would selectively provide propargylic trifluoromethanes (**4.2**) over trifluoromethylallenes (**4.3**). Initially, we investigated reactions of different halodifluoroacetates, and determined that propargylic bromodifluoroacetates (**4.1a**) were more reactive than chlorodifluoroacetates (**4.1a–Cl**). Using stoichiometric CuI, propargylic bromodifluoroacetates reacted at lower temperatures than chlorodifluoroacetates (Br: 50 °C; Cl: 100 °C); however, similar yields of trifluoromethylated products were obtained [Br: 57% (Scheme 4.2, entry 1); Cl: 48% (Scheme 4.1D)]. Using catalytic CuI (10%), a more pronounced difference between substrates was noted [Br: 65% (Scheme 4.2, entry 2); Cl: 15% (Scheme 4.1D)]. Based on previous our previous work with allylic trifluoromethylation (Chapter 2), we

hypothesized that the addition of *N*,*N'*-dimethylethylenediamine (DMEDA), and the use of an activation procedure might improve the reaction. While the use of DMEDA alone was harmful to the reaction (entry 3), possibly because of side-reactivity between the diamine and substrate, using DMEDA with an activation procedure provided 75% of trifluoromethane-containing product and a 2.7 : 1 ratio of **4.2a** : **4.3a** (Table 1, entry 4). We hypothesized that the activation procedure, which involved heating CuI, DMEDA, KF, and NaO_2CCF_2Br in DMF at 50 °C for 10 min prior to the addition of substrate, facilitated the formation of an active (DMEDA)Cu–CF_3 species (Chapter 2) and circumvented an induction period where the substrate was destroyed *via* non-productive pathways.

Scheme 4.2. Catalytic decarboxylative trifluoromethylation improved by DMEDA and an activation procedure.[a]



4.1a **4.2a** **4.3a**

entry	CuX (mol %)	DMEDA (mol %)	solvent [M]	activation[b]	% yield[c] (**4.2** : **4.3**)[d]
1	I (100)	0	DMF [0.33]	–	57 (2.6 : 1)
2	I (10)	0	DMF [1.0]	–	65 (3.3 : 1)
3	I (10)	10	DMF [1.0]	–	51 (3.6 : 1)
4	I (10)	10	DMF [1.0]	√	75 (2.7 : 1)
5	TC (10)	10	DMF [1.0]	√	52 (2.7 : 1)
6[e]	TC (5)	0	THF [0.17]	–	0 (–) [25% conv]
7[e,f]	TC (5)	0	THF [0.17]	–	<5 (N.D.)

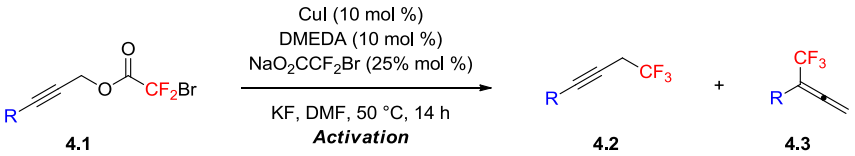
[a] Reactions were performed with 0.20 mmol **4.1a**, and 0.40 mmol KF in 0.20 mL of DMF. [b] Activation involved heating CuI, DMEDA, NaO_2CCF_2Br, and KF in DMF for 10 min prior to injection of **4.1a**. [c] Combined yield of **4.2a** and **4.3a** as determined by ^{19}F NMR analysis, using α,α,α-trifluorotoluene as an internal standard. [d] Determined by ^{19}F NMR analysis. [e] 0.30 mmol KF, 1.2 mL of THF, 60 °C, 20 h. [f] 0.30 mmol of $TMSCF_3$ was added to the reaction.

Attempted optimization of several other parameters did not improve the yield and selectivity for formation of **4.2a**. A broad screen of N-, O-, and P-based ligands revealed that most ligands provided similar regioselectivity, and that DMEDA provided the highest yield of products. In addition, the regioselectivity was not dramatically influenced by temperature, and isomerization between alkynes and allenes was not observed upon prolonged heating. Incomplete conversion of starting material was observed at 8–10 h time points; therefore, an extended reaction time of 14 h was selected for the general reaction conditions.

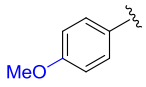
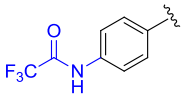
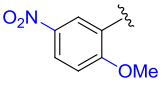
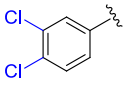
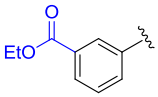
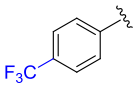
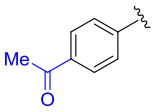
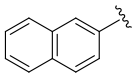
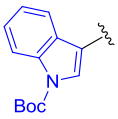
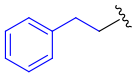
Several important features of the Cu-catalyzed trifluoromethylation of propargylic bromodifluoroacetates are highlighted by comparing this system to the recently reported Cu-catalyzed trifluoromethylation of propargylic chlorides. Specifically, 1° propargylic chlorides were converted to propargyl trifluoromethanes using Cu(I) thiophene-2-carboxylate (CuTC; 5 mol%), $TMSCF_3$ (1.5 equiv), and KF (1.5 equiv) in THF at 60 °C. For the trifluoromethylation of propargylic bromodifluoroacetates, we screened several Cu-sources, and determined that CuI provided slightly higher yields than other Cu^I salts, such as CuTC (Scheme 4.2, entry 4 vs entry 5). Changing from DMF to less polar solvents, such as THF, completely ablated reactivity (entry 6). Highly polar solvents are required to facilitate decarboxylation of bromodifluoroacetate at moderate temperatures (<70 °C), and we concluded that "Cu–CF_3" was not generated in THF. In addition, propargylic bromodifluoroacetates displayed different reactivity than propargylic chlorides, and conditions that converted propargylic chlorides to trifluoromethanes (73% yield; 5% CuTC, 1.5 equiv $TMSCF_3$, and 1.5 equiv KF in THF at 60 °C for 20 h)[11] failed to similarly convert propargylic bromodifluoroacetates (<5% yield; entry 7).

The CuI/DMEDA-catalyzed trifluoromethylation of propargyl bromodifluoroacetates (**4.1**) tolerated many useful and important functional groups. Electron-donating aryl ethers provided trifluoromethane-containing products in moderate yield (Scheme 4.3, entries 1–2). A variety of carbonyl containing functional groups were compatible with the reaction conditions, including: esters, ketones, carbamates, and trifluoroacetamides (entries 3–6). In addition, the successful reaction of the trifluoroacetamide provided the desired product, albeit in low yield, which provides additional evidence that Cu–CF_3 species tolerate protic functional groups (entry 6).[16] When conducted on an increased scale (7 mmol), the present reaction provided a typical yield by ^{19}F NMR (entry 9). In addition to aromatic substrates, an aliphatic substrate also afforded trifluoromethylated product in moderate yield, and displayed distinct regioselectivity compared to the aromatic substrates (entry 10). Based on the similarity of propargyl bromodifluoroacetates and cinnamyl bromodifluoroacetates, and the identical catalyst systems employed for decarboxylative trifluoromethylation, it is anticipated that other functional groups, including aryl bromides and triflates, thiophenes, anilines, and phthalimides would also be tolerated under the reaction conditions.[15a] While attempts were made to separate regioisomeric products, we were unable to achieve sufficient separation via standard silica gel chromatography to enable practical isolation of pure products.

Scheme 4.3. CuI/DMEDA-catalyzed reaction tolerates important functional groups.[a]



4.1 **4.2** **4.3**

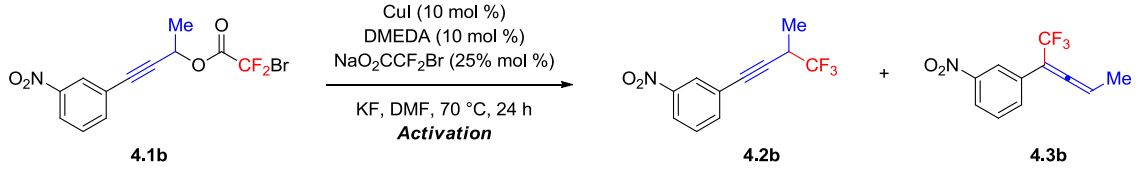
entry	R	yield (%)[b]	**4.2** : **4.3**[c]	entry	R	yield (%)[b]	**4.2** : **4.3**[c]
1		72 (77)	4.0 : 1 (3.5 : 1)	6		40 (44)	6.3 : 1 (3.4 : 1)
2		70 (78)	2.1 : 1 (2.3 : 1)	7		79 (84)	2.2 : 1 (2.5 : 1)
3		78 (83)	2.3 : 1 (2.6 : 1)	8		70 (73)	1.7 : 1 (1.8 : 1)
4		66 (70)	2.6 : 1 (2.9 : 1)	9[d]	 *gram scale*	57 (77)	3.8 : 1 (2.2 : 1)
5		59 (62)	3.0 : 1 (2.9 : 1)	10		70 (69)	1 : 2.1 (1 : 1.6)

[a] Reactions were performed with 0.20 mmol **4.1**, 0.020 mmol CuI, 0.020 mmol DMEDA, 0.050 mmol NaO_2CCF_2Br, and 0.40 mmol KF in 0.20 mL DMF at 50 °C for 14 h following 10 min activation. [b] Isolated yield of a purified mixture of regioisomers **4.2** and **4.3**; number in parentheses represents the combined yield of **4.2** and **4.3** as determined by ^{19}F NMR analysis, using α,α,α-trifluorotoluene as an internal standard. [c] Ratio of regioisomers in isolated material as determined by ^{1}H NMR analysis; ratio in parentheses represents ratio of isomers in the crude reaction mixture as determined by ^{19}F NMR analysis. [d] Reaction conducted on a 7 mmol scale.

Using the standard reaction conditions, a 2° propargyl substrate (**4.1b**) was less reactive than 1° substrates, and provided 16% of trifluoromethylated product after 12 h at 50 °C. However, under more forcing conditions (70 °C and 24 h), both propargyl

trifluoromethane (**4.2b**) and trifluoromethyl allene (**4.2c**) were formed (Scheme 4.4). For the reaction of propargyl bromodifluoroacetates, both 1° and 2° substrates provided similar regiochemical outcomes, and propargylic trifluoromethanes were observed as major products (Schemes 4.3–4). In contrast, previous Cu–catalyzed trifluoromethylation reactions of propargyl electrophiles displayed substrate dependent regioselectivity, with 1° electrophiles providing propargyl trifluoromethanes, and 2° electrophiles yielding trifluoromethyl allenes (Scheme 4.1A).[11]

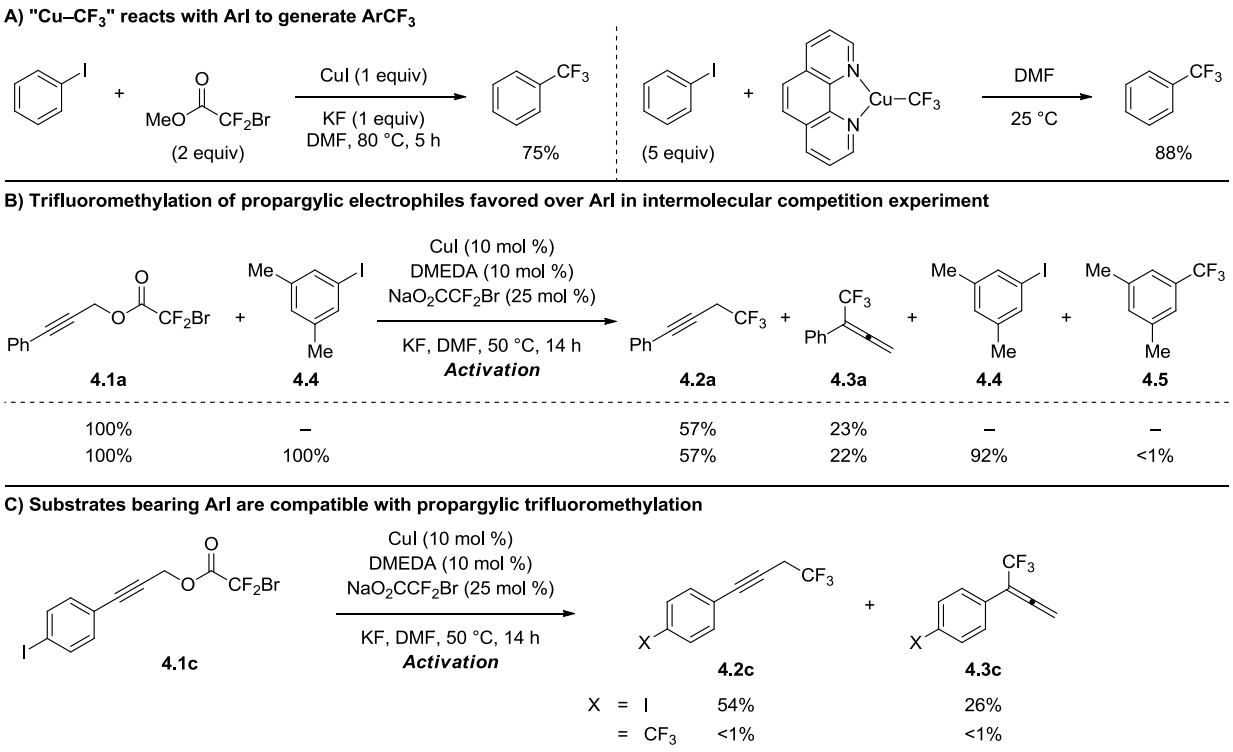
Scheme 4.4. Cu-catalyzed decarboxylative trifluoromethylation of secondary propargyl bromodifluoroacetates displays atypical reactivity.



The present Cu–DMEDA-based catalyst system demonstrated unique chemoselectivity compared to other Cu-based catalyst systems. Several Cu–CF_3 complexes commonly react with aryl iodides under mild reaction conditions to furnish trifluoromethylarenes (Scheme 4.5A).[3a,17] In order to determine whether propargylic trifluoromethylation could be selectively achieved in the presence of aryl iodides, an exogenous aryl iodide was added to a standard decarboxylative trifluoromethylation reaction. The addition of 1 equivalent of aryl iodide **4.4** had no effect on the yield or selectivity of the reaction (Scheme 4.5B). GC analysis of the reaction revealed that 92% of the aryl iodide remained unconsumed. In addition, <1% of trifluoromethylarene **4.5** was observed, which demonstrated the unique reactivity of this system. In order to confirm that substrates containing aryl iodides were compatible with the reaction

conditions, 4-iodophenylpropynyl bromodifluoroacetate (**4.1c**) was subjected to decarboxylative trifluoromethylation. As expected, a good yield (80%) of trifluoromethylated products **4.2c** and **4.3c** was obtained with typical regioselectivity (2.1 : 1, Scheme 4.5C). Again, only trace amounts (<1%) of aromatic trifluoromethyl products were observed.

Scheme 4.5. Propargylic trifluoromethylation is selectively accomplished in the presence of aryl iodides.

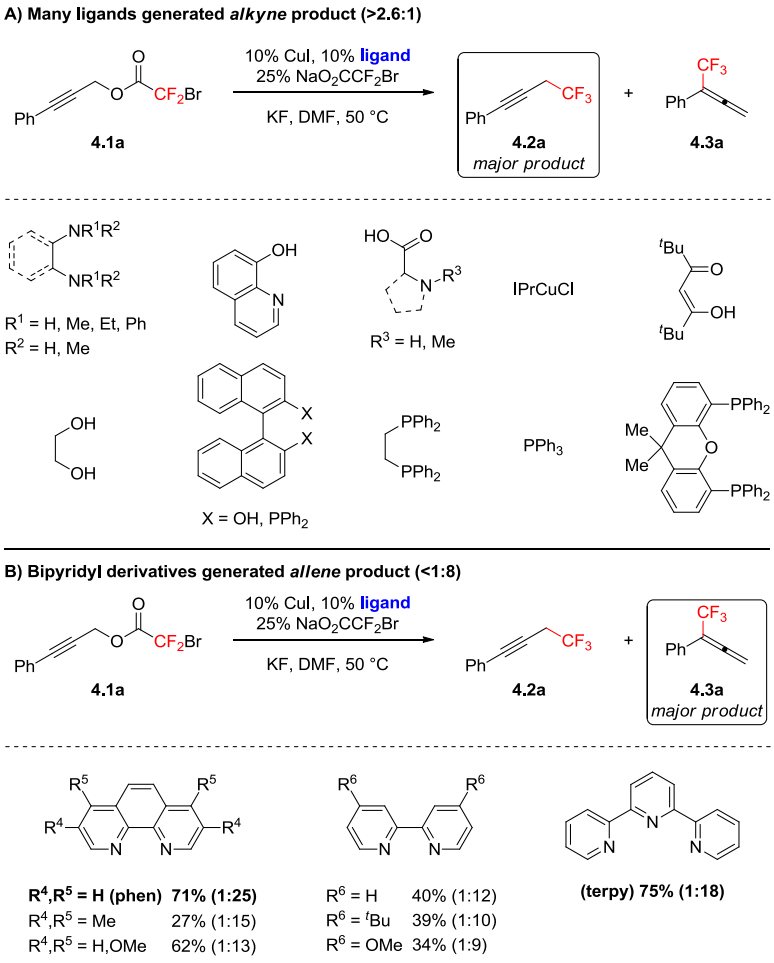


4.3. Regioselective ligand-controlled Cu-catalyzed trifluoromethylation of bromodifluoroacetates to generate trifluoromethylallenes.

We hypothesized that ligands could control the regioselectivity of trifluoromethylation of propargylic bromodifluoroacetates as described in the previous section. Many N-, O- and P-based ligands provided propargyl products with the same modest regioselectivity as unligated "Cu–CF_3" (ca. 3:1 alkyne : allene; Scheme 4.6A).

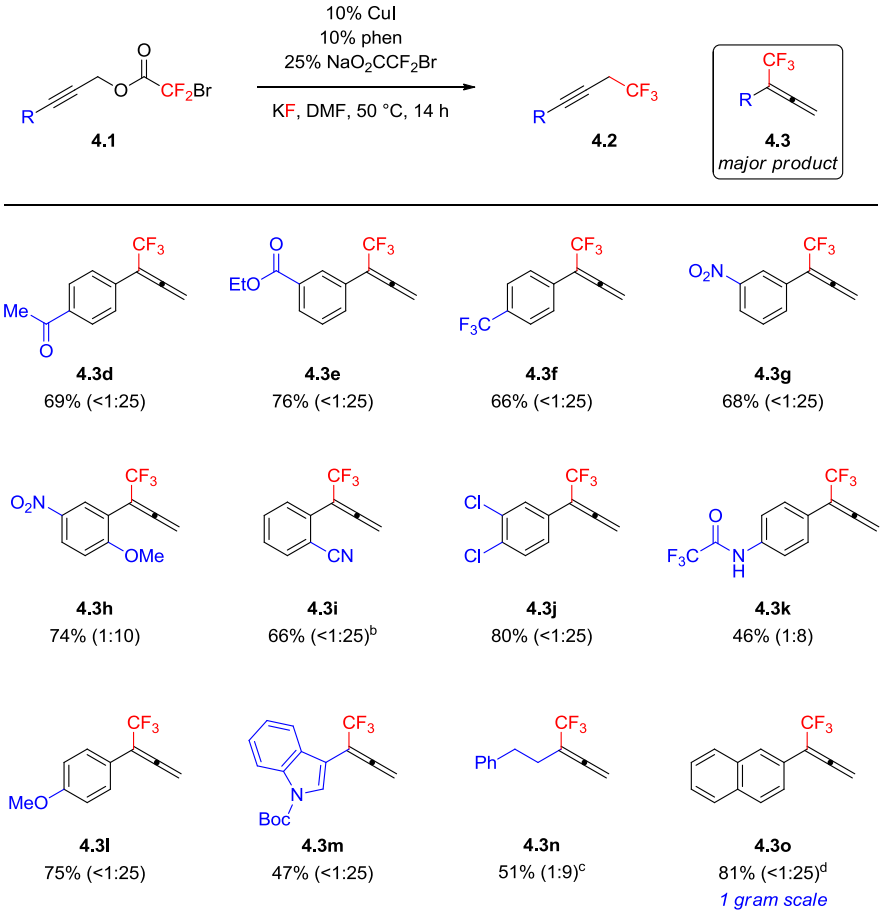
However, the use of 1,10-phenanthroline-based and 2,2'-bipyridine-based ligands reversed the regioselectivity of the transformation, and afforded trifluoromethylallene **4.3a** with high regioselectivity (<1:8; Scheme 4.6B). For these bipyridines and phenanthrolines, the use of ligands bearing electron-donating aliphatic and methoxy groups did not significantly modulate the selectivity of reactions. Thus, the geometric influence of the bipyridyl substructure presumably controlled the regioselectivity of the transformation. Since electron-donating groups decreased the activity of the catalysts, 1,10-phenanthroline (phen) and terpyridine (terpy) were identified as the optimal ligands for the current transformation.

Scheme 4.6. Ligand-controlled regioselective trifluoromethylation.



Employing phen as a ligand, various 1° propargyl bromodifluoroacetates were converted to 1,1-disubstituted trifluoromethylallenes with good to excellent selectivity (Scheme 4.7). Initial efforts focused on the synthesis of 1-aryl-1-trifluoromethylallenes, which could not be selectively accessed *via* other Cu-mediated or -catalyzed processes,[7–14] and otherwise required multi-step sequences that afforded low yields of product.[18] Propargyl electrophiles conjugated with electron-rich, -neutral, and -deficient aromatic moieties all formed allene products in excellent selectivity (**4.3d–g**, **j–m**).[19] When the reaction was conducted on a gram-scale, good yield and excellent selectivity were maintained (**4.3o**). In contrast to substrates bearing *m*- and *p*-substituted aryl moieties, substrates bearing *o*-substituted aryl systems afforded products in lower selectivity (ca. 10:1; **4.3h–i**). Using phen as a ligand, a 1° aliphatic-substituted substrate was not effectively converted to product; however, the use of terpy as a ligand provided trifluoromethylallene **4.3n** in synthetically useful yield and selectivity. The reaction tolerated many important functional groups, including carbonyl groups (**4.3d–e, k, m**), nitro groups (**4.3g–h**), nitriles (**4.3i**), and ethers (**4.3l**). The carbonyl-containing groups are particularly interesting, because they are prone to react with free CF_3^- to provide β,β,β-trifluoroethyl alcohols.[1d,4,20] Since products of 1,2-addition were not observed in these reactions, free $^-CF_3$ must not have existed in solution. Therefore, generation of the reactive (phen)Cu-CF_3 species likely involved an inner-sphere process that did not generate free $^-CF_3$.

Scheme 4.7. Reactions of primary propargyl bromodifluoroacetates generated 1,1-disubstituted trifluoromethylallenes.[a]

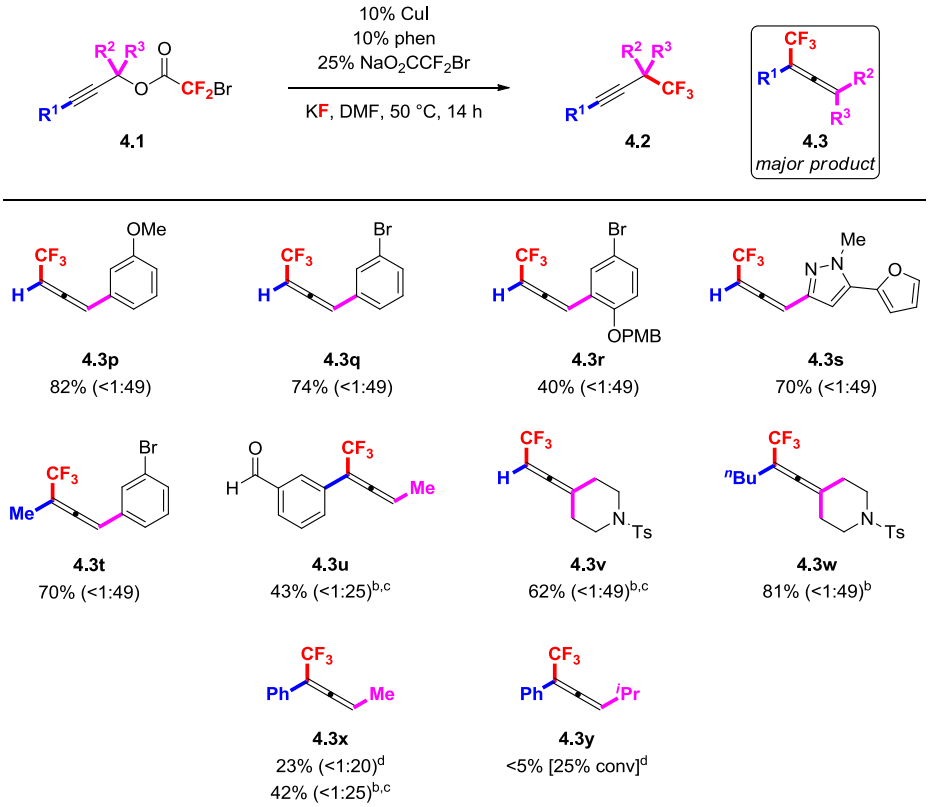


[a] Conditions: **4.1d–o** (1 equiv), CuI (10 mol %), phen (10 mol %), NaO_2CCF_2Br (25 mol %), KF (2 equiv), DMF (1.0 M), 50 °C, 14 h. The numbers in parentheses represent the ratios of **4.2 : 4.3** in purified product as determined by ^{1}H NMR spectroscopy. [b] 1:12 Mixture of **4.2 : 4.3** prior to chromatographic purification as determined by ^{19}F NMR spectroscopy. [c] Terpy (10 mol %) employed as a ligand. [d] Reaction conducted on a 7 mmol scale.

Utilizing similar reaction conditions to those used for 1° bromodifluoroacetates, 2° and 3° propargyl electrophiles were also regioselectively converted to di-, tri-, and tetra-substituted trifluoromethylallenes in high regioisomeric ratios (Scheme 4.8). Generally,

2° 1-aryl propargyl substrates provided 1,3-disubstituted trifluoromethylallenes in synthetically useful yields and excellent selectivities (**4.3p–s**). In addition, the standard conditions converted a 2° substrate to a trisubstituted allene product (**4.3t**); however, the standard conditions did not effectively transform several challenging substrates. For example, substrates bearing aliphatic groups at the α position reacted sluggishly, and provided low yields of allene products (**4.3u–y**). For these less reactive 2° and 3° alkyl-substituted bromodifluoroacetates, the use of terpyridine as a ligand and/or more forcing conditions (60 °C, 24 h) facilitated the formation of trisubstituted (**4.3u–v, x**) and tetrasubstituted (**4.3w**) allenes. Notably, the decarboxylative trifluoromethylation reaction tolerated aryl bromides (**4.3p–r, t**), which can undergo Cu-catalyzed nucleophilic trifluoromethylation under similar conditions.[3a] Although substrates bearing free amines decomposed under the reaction conditions, protection of these groups as amides, carbamates, and sulfonamides permitted catalyst turnover (**4.3k, m, v–w**). Finally, the catalyst system tolerated several important heterocycles, including indole (**4.3m**), pyrazole (**4.3s**), and furan (**4.3s**), which may be useful for the design of biological probes and agrochemicals.

Scheme 4.8. Reactions of substituted propargyl bromodifluoroacetates provided di-, tri- and tetra-substituted trifluoromethylallenes.



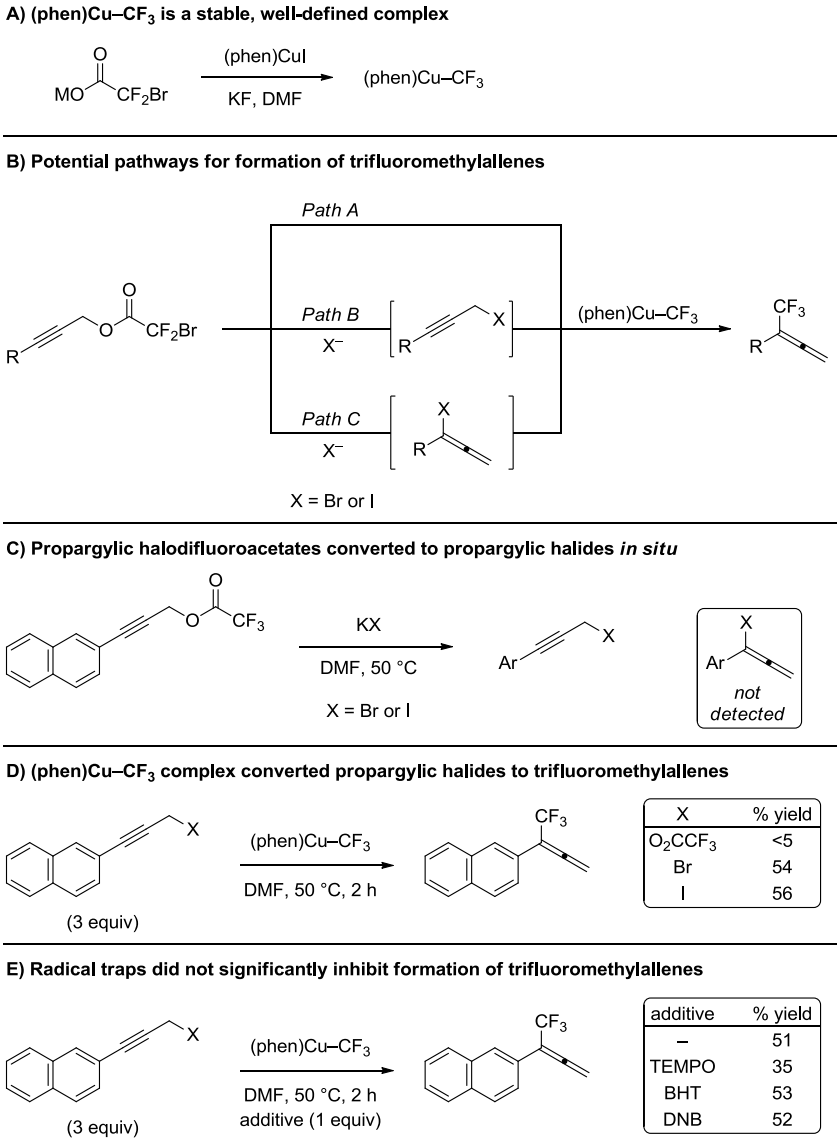
[a] Conditions: **4.1p–y** (1 equiv), CuI (10 mol %), phen (10 mol %), NaO_2CCF_2Br (25 mol %), KF (2 equiv) DMF (1.0 M), 50 °C, 14 h. The numbers in parentheses represent the ratios of **4.2 : 4.3** in purified product as determined by ^{1}H NMR spectroscopy. [b] 60 °C, 24 h. [c] Terpy (10 mol %) employed as a ligand. [d] Estimated by ^{19}F NMR spectroscopy.

4.4. Trifluoromethylallenes form via propargylic halide intermediates.

We conducted a series of experiments to better understand the mechanism through which propargylic bromodifluoroacetates convert to trifluoromethylallenes. First, we hypothesized that (phen)Cu–CF_3, a stable, well-defined complex, was the active trifluoromethylating species, and was generated *via* decarboxylation/fluorination of bromodifluoroacetate (Scheme 4.9A). Additionally, we envisioned that several

electrophilic species could react with this (phen)Cu–CF_3 intermediate, including: propargylic bromodifluoroacetates (Scheme 4.9B, Path A); propargylic halides (Path B); or allenyl halides (Path C). To determine whether these species formed under the reaction conditions, we treated propargyl trifluoroacetate (selected instead of bromodifluoroacetate to avoid decarboxylation and release of Br^-) with KBr or KI in DMF at 50 °C, and observed the formation of propargylic halides (Scheme 4.9C). Notably, we did not detect allenyl halides by GC/MS or NMR analysis under various reaction conditions. Next, treating propargylic electrophiles with stoichiometric (phen)Cu–CF_3 provided modest yields of trifluoromethylallenes for propargylic bromides and iodides, but not for trifluoroacetates (Scheme 4.9D). We do not believe that this process proceeds *via* a radical mechanism, since radical traps [TEMPO, 3,5-di-*tert*-butyl-4-methylphenol (BHT), or 1,4-dinitrobenzene (DNB)] did not significantly inhibit the reaction (Scheme 4.9D). In addition, these radical trapping reagents did not dramatically impact the yield or selectivity of either phen- or DMEDA-ligated Cu-catalyzed trifluoromethylation reactions. These experiments implicate the mechanism in Path B, in which propargylic bromodifluoroacetates convert to propargylic halides, and then react with (phen)Cu–CF_3 to form trifluoromethylallenes.

Scheme 4.9. (phen)Cu–CF_3 converted propargylic halides to trifluoromethylallenes.

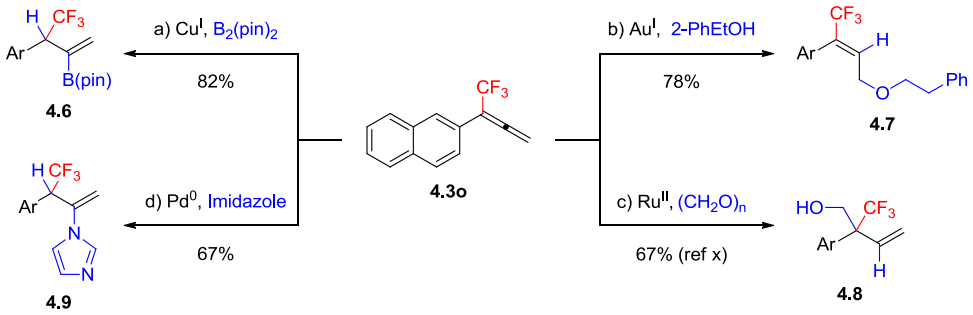


4.5. Trifluoromethylallenes are useful fluorinated building blocks.

Allenes serve as a useful building block for accessing complex substructures,[21] and in recent years, considerable attention focused on both the synthesis of allenes,[22] and transformations of allene-based building blocks.[23] Given the synthetic potential of allenes, trifluoromethylallenes should be useful synthetic precursors for various fluorinated motifs. However, few modern transformations of trifluoromethylallenes have

been disclosed,[18c, 24] which restricted the use of these fluorinated substructures as intermediates in synthetic sequences. To showcase the potential synthetic utility of trifluoromethylallenes, **4.3o** was subjected to metal-catalyzed hydrofunctionalization reactions to generate C–B,[25] C–O,[26] C–N,[27] and C–C[18c] bonds (Scheme 4.10). In all cases, the reactions of **4.3o** provided products (**4.6–9**) in good yields and excellent regioselectivity,[28] with minimal optimization of previously reported systems.[29] In most cases, the regioselectivities of the transformations matched those of previous reports;[25–26] however, the product of the hydroamination reaction did not match the predicted regiochemical outcome,[27] indicating that some reactions of trifluoromethylallenes may generate unique products (Scheme 4.9, d). Nonetheless, all functionalization reactions provide trifluoromethyl-containing products that would otherwise be challenging to prepare.

Scheme 4.10. Direct conversion of trifluoromethylallenes to functionalized trifluoromethylated motifs.



[a] $B_2(pin)_2$ (1.1 equiv), CuCl (5 mol %), IPr•HCl (5 mol %), NaO^{t}Bu (40 mol %), MeOH (6 equiv), THF, 23 °C. [b] 2-phenylethanol (1.1 equiv), AuIPrCl (10 mol %), AgOTf (10 mol %), PhMe, 23 °C. [c] $(CH_2O)_n$ (2 equiv), $RuHCl(CO)(PPh_3)_3$ (5 mol %), dppm (5 mol %), ^{i}PrOH (4 equiv), PhMe, 105 °C. [d] Imidazole (1.2 equiv), $[PdCl(C_3H_5)]_2$ (2.5 mol %), dppf (5 mol %), THF, 80 °C.

4.6. Conclusion.

In conclusion, the use of bipyridyl-derived ligands overrode the intrinsic regioselectivity of Cu-catalyzed trifluoromethylation reactions of propargyl electrophiles, and provided di-, tri-, and tetra-substituted trifluoromethylallenes bearing synthetically important functional groups. More broadly, this transformation was the first example of a Cu-catalyzed trifluoromethylation reaction in which a ligand controlled the regiochemical outcome.

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28) The major isomers were formed in >19:1 selectivity as determined by ^{1}H NMR spectroscopy.

29) Only the reaction to form **4.7** required a higher catalyst loading and extended reaction time.

Chapter 4 Appendix

Experimental procedures and spectra for compounds in Chapter 4

Table of Contents

General Considerations:

Unless otherwise noted, all reactions were performed using oven-dried glassware under an atmosphere of dry N_2. Trifluoromethylation reactions were performed in resealable 15 mL screw-top vial sealed with PTFE septa. All other reactions were performed in round-bottom flasks, which were sealed with rubber septa. Stainless steel syringes were used to transfer air- or moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE™ Silica Gel HLF 250 micron glass plates precoated with 230–400 mesh silica impregnated with a fluorescent indicator (250 nm), visualizing by quenching of fluorescence, $KMnO_4$ solution, or *p*-anisaldehyde solution. A CombiFlash® RF–4x purification system was used for chromatographic purifications. Silica gel was purchased from Sorbent Technologies (cat. #30930M-25, 60 Å, 40–63 μm).

Unless otherwise noted, reagents were purchased from commercial sources, and used as received. Anhydrous potassium fluoride (KF) was dried in a vacuum-oven at 200 °C for at least 24 h prior to use. Anhydrous *N*,*N*′-dimethylformamide (DMF), acetonitrile (CH_3CN), 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.

Proton nuclear magnetic resonance (^1H NMR) spectra, and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 500 AVANCE spectrometer (500 and 126 MHz, respectively) or a Bruker 400 AVANCE spectrometer (400 and 101 MHz, respectively). Fluorine nuclear magnetic resonance (^{19}F NMR)

spectra were recorded on a Bruker 400 AVANCE spectrometer (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 ppm 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 ppm, and are referenced to $PhCF_3$ (δ = –63.72 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constant in Hertz (Hz), and integration.

Exact mass determinations were obtained by the following methods; electron impact ionization (EI) on a ZG analytical ZAB mass spectrometer, electrospray ionization (ESI) on a Waters LCT Premier™ mass spectrometer, or atmospheric-pressure chemical ionization (APCI–hexane/PhMe) on a Waters Q-Tof Premier™, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were used as ionization solvent. Low-resolution mass data (CI) were recorded on a Shimadzu GCMS-QP2010 SE mass spectrometer. Infrared spectra were measured using a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Uncorrected melting points were measured on a Thomas Hoover Capillary Melting Point Apparatus.

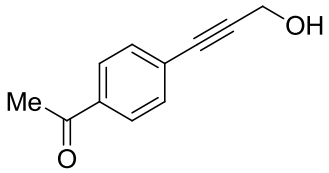
Synthesis of Propargyl Alcohols:

General Procedure A:

An oven-dried Schlenk flask was charged with iodoarene (1.0 equiv), CuI (0.040 equiv), $Pd(PPh_3)_2Cl_2$ (0.020 equiv), and a magnetic stir bar. The flask was evacuated and backfilled with N_2 three times. MeCN (1 M) was injected, and the suspension was cooled to –10 °C. NEt_3 (4.5 equiv) was injected dropwise, and the mixture was stirred at –10 °C for 10 min. Propargyl alcohol (1.1 equiv) was injected dropwise, and the mixture was allowed to warm to rt. The reaction was monitored by TLC, and upon consumption of starting iodoarene (typically < 4 h), the solvent was removed *in vacuo*. The crude mixture was dissolved in EtOAc, and filtered through a pad of silica (eluted with additional EtOAc). The solvent was removed *in vacuo*, and the crude material was purified by flash chromatography to afford the 3-arylpropargyl alcohol.

General Procedure B:

An oven-dried Schlenk flask was charged with benzaldehyde (1.0 equiv), and a magnetic stir bar. The flask was evacuated and backfilled with N_2 three times. THF was injected, and the solution was cooled to 0 °C. Ethynylmagnesium bromide (0.5 M in THF, 1.2–1.5 equiv) was injected dropwise, and the reaction was stirred at 0 °C for 1 h. The mixture was allowed to warm to rt, and monitored by TLC. After consumption of the aldehyde, the reaction was quenched with $NH_4Cl_{(aq.)}$, and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over Na_2SO_4, and filtered. The solvent was removed *in vacuo*, and chromatographic purification of the resulting residue afforded the 1-arylpropargyl alcohol



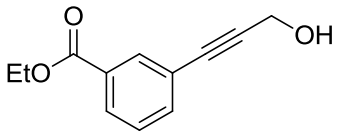
4.1d.1

1-(4-(3-Hydroxyprop-1-yn-1-yl)phenyl)ethanone[1]

General procedure A was followed using 4-iodoacetophenone (2.46 g, 10.0 mmol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), NEt_3 (6.3 mL, 45 mmol), propargyl alcohol (0.64 mL, 11 mmol) and MeCN (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 4:1) afforded the title product as a yellow solid (1.23 g, 71%).

m.p.: 74–76 °C (lit.[1] 76–77).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–7.88 (m, 2 H), 7.56–7.49 (m, 2 H), 4.54 (s, 2 H), 2.61 (s, 3 H), 1.60 (s, 1 H).



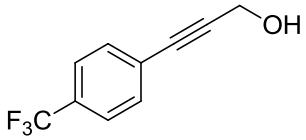
4.1e.1

Ethyl 3-(3-hydroxyprop-1-yn-1-yl)benzoate[2]

General procedure A was followed using ethyl 3-iodobenzoate (2.76 g, 10.0 mmol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), NEt_3 (6.3 mL, 45 mmol), propargyl alcohol (0.64 mL, 11 mmol) and MeCN (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 4:1) afforded the title product as a yellow solid (1.99 g, 98%).

m.p.: 47–49 °C (lit.[2] 48–50 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (t, *J* = 1.7 Hz, 1 H), 8.01 (dt, *J* = 7.9, 1.4 Hz, 1 H), 7.61 (dt, *J* = 7.6, 1.4 Hz, 1 H), 7.41 (t, *J* = 7.8 Hz, 1 H), 4.52 (d, *J* = 6.1 Hz, 2 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 1.72 (ddd, *J* = 7.4, 6.0, 1.7 Hz, 1 H), 1.41 (t, *J* = 7.1 Hz, 3 H).



4.1f.1

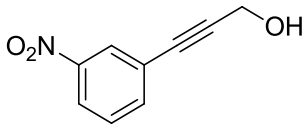
3-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-ol[1]

General procedure A was followed using 4-iodobenzotrifluoride (2.72 g, 10.0 mmol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), NEt_3 (6.3 mL, 45 mmol), propargyl alcohol (0.64 mL, 11 mmol) and MeCN (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 5:1) afforded the title product as yellow crystals (1.84 g, 92%).

m.p.: 35–37 °C (lit.[1] 35–36 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.54 (m, 4 H), 4.53 (s, 2 H), 1.68 (s, 1 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.95 (s, 3 F).



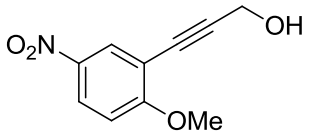
4.1g.1

3-(3-Nitrophenyl)prop-2-yn-1-ol[3]

General procedure A was followed using 1-iodo-3-nitrobenzene (2.49 g, 10.0 mmol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), NEt_3 (6.3 mL, 45 mmol),

propargyl alcohol (0.64 mL, 11 mmol) and MeCN (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 4:1) afforded the title product as a viscous amber oil (1.55 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (t, *J* = 1.9 Hz, 1 H), 8.19 (ddd, *J* = 8.4, 2.3, 1.1 Hz, 1 H), 7.75 (dt, *J* = 7.7, 1.3 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 4.54 (d, *J* = 6.2 Hz, 2 H), 1.73 (t, *J* = 6.2 Hz, 1 H).



4.1h.1

3-(2-methoxy-5-nitrophenyl)prop-2-yn-1-ol

General procedure A was followed using 2-iodo-4-nitroanisole (2.8 g, 0.010 mol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), NEt_3 (6.3 mL, 45 mmol), propargyl alcohol (0.64 mL, 11 mmol) and MeCN (15 mL) as solvent. Chromatographic purification (hexanes / EtOAc 9:1 → 3:1) afforded the title product as a pale yellow solid (1.1 g, 53%).

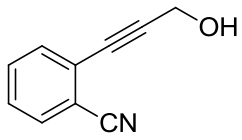
m.p.: 117–118 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, *J* = 2.8 Hz, 1 H), 8.22 (dd, *J* = 9.2, 2.8 Hz, 1 H), 6.96 (d, *J* = 9.2 Hz, 1 H), 4.57 (d, *J* = 6.3 Hz, 2 H), 4.00 (s, 3 H), 1.77 (t, *J* = 6.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.7, 141.2, 129.5, 126.0, 113.0, 110.4, 93.5, 79.8, 56.8, 51.8.

IR (film): 3381, 3090, 2978, 2945, 1605, 1576, 1510, 1493, 1439, 1352, 1279, 1238, 1188, 1144, 1095, 1015, 974, 899, 879, 820, 746, 723, 638 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{10}H_{10}NO_4$) requires *m/z* 208.0610, found *m/z* 208.0610 (0.0 ppm).



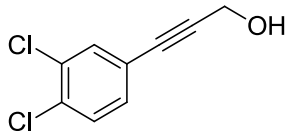
4.1i.1

2-(3-Hydroxyprop-1-yn-1-yl)benzonitrile[4]

General procedure A was followed using 2-iodobenzonitrile (2.3 g, 0.010 mol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 mg, 0.20 mmol), NEt_3 (6.3 mL, 45 mmol), propargyl alcohol (0.64 mL, 11 mmol) and MeCN (15 mL) as solvent. Chromatographic purification (hexanes / EtOAc 4:1 → 3:2) afforded the title product as a tan solid (1.41 g, 90%).

m.p.: 60–61 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.60 (m, 1 H), 7.59–7.50 (m, 2 H), 7.47–7.37 (m, 1 H), 4.58 (s, 2 H), 2.39–1.97 (m, 1 H).



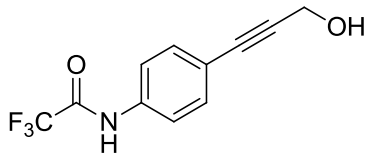
4.1j.1

3-(3,4-Dichlorophenyl)prop-2-yn-1-ol[5]

General procedure A was followed using 1,2-dichloro-4-iodobenzene (2.72 g, 10.0 mmol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), NEt_3 (6.3 mL, 45 mmol), propargyl alcohol (0.64 mL, 11 mmol) and MeCN (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 5:1) afforded the title product as a pale brown solid (1.70 g, 85%).

m.p.: 64–65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 1.9 Hz, 1 H), 7.40 (d, *J* = 8.3 Hz, 1 H), 7.28–7.25 (m, 1 H), 4.50 (d, *J* = 6.2 Hz, 2 H), 1.65 (td, *J* = 6.3, 2.0 Hz, 1 H).



4.1k.1

2,2,2-Trifluoro-*N*-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)acetamide

4-Bromoaniline (2.6 g, 15 mmol) was added to an oven-dried 250 mL Schlenk flask. THF (0.050 L) and pyridine (1.8 mL, 23 mmol) were injected, and the solution was cooled to 0 °C. A solution of trifluoroacetic anhydride (2.5 mL, 18 mmol) in THF (0.010 L) was slowly injected over a 5 min period, and the reaction was stirred at 0 °C for 1.5 h. The solution was allowed to warm to rt, stirred for an additional 1.5 h, and then quenched with brine (50 mL). The mixture was extracted with EtOAc (100 mL, 2 x 50

mL), and the combined organic solution was washed with 1 N HCl (2 x 75 mL), $NaHCO_{3\,(aq.)}$ (50 mL), and brine (50 mL). The solution was dried over $MgSO_4$, and filtered through a pad of silica gel (eluted with 100 mL EtOAc). The solvent was removed *in vacuo* to provide *N*-(4-bromophenyl)-2,2,2-trifluoroacetamide as a brown solid (3.7 g, 92 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1 H), 7.56–7.51 (m, 2 H), 7.51–7.46 (m, 2 H).

N-(4-bromophenyl)-2,2,2-trifluoroacetamide (1.7 g, 6.4 mmol), CuI (0.12 g, 0.32 mmol), and NaI (1.9 g, 13 mmol) were added to a 50 mL Schlenk flask. The flask was evacuated and backfilled with dry N_2 (3x), and trans-*N,N'*-dimethyl-1,2-cyclohexanediamine (0.050 mL, 0.64 mmol) and 1,4-dioxane (6.4 mL) were injected. The flask was sealed with a screw-top PTFE stopper, and immersed in a 110 °C oil bath. After 16 h, the mixture was allowed to cool to rt, and poured onto 1 N HCl (25 mL). The mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL). The organic solution was dried over $MgSO_4$, filtered through a pad of silica gel, and the solvent was removed *in vacuo*. Analysis of the material by GC revealed a 3:1 mixture of ArI / ArBr, and the material was used without further purification. General procedure A was followed using the haloarene mixture, CuI (34 mg, 0.18 mmol), $Pd(PPh_3)_2Cl_2$ (62 mg, 0.090 mmol), NEt_3 (2.8 mL, 0.020 mol), propargyl alcohol (0.28 mL, 4.9 mmol) and MeCN (0.010 L) as solvent. Chromatographic purification (DCM / acetone 1:0 → 9:1) afforded the title product as a tan solid (0.51 g, 33% over 2 steps).

m.p.: 148–149 °C.

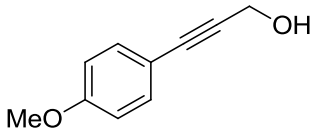
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1 H), 7.58–7.52 (m, 2 H), 7.51–7.45 (m, 2 H), 4.51 (s, 2 H), 1.64 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.8 (q, *J* = 37.7 Hz), 135.2, 132.9, 120.7, 120.3, 115.7 (q, *J* = 288.8 Hz), 88.1, 84.9, 51.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –76.68 (s, 3 F).

IR (film): 3421, 3308, 3200, 3074, 3065, 1720, 1609, 1549, 1510, 1412, 1358, 1281, 1244, 1215, 1182, 1153, 1014, 953, 903, 837, 741, 685 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{11}H_9NO_2F_3$) requires *m/z* 244.0585, found *m/z* 244.0585 (0.0 ppm).



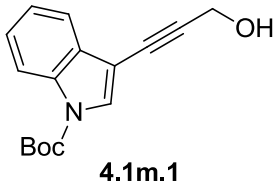
4.1l.1

3-(4-Methoxyphenyl)prop-2-yn-1-ol[6]

General procedure A was followed using 4-iodoanisole (2.34 g, 10.0 mmol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), NEt_3 (6.3 mL, 45 mmol), propargyl alcohol (0.64 mL, 11 mmol) and MeCN (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 4:1) afforded the title product as a pale yellow solid (1.56 g, 96%).

m.p.: 67–68 °C (lit.[6] 62.5–64.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 2 H), 6.89–6.81 (m, 2 H), 4.49 (d, *J* = 6.1 Hz, 2 H), 3.82 (s, 3 H), 1.64 (t, *J* = 6.1 Hz, 1 H).



4.1m.1

Tert-butyl 3-(3-hydroxyprop-1-yn-1-yl)-1H-indole-1-carboxylate

NaOH (1.7 g, 43 mmol) was added to a solution of indole (2.0 g, 17 mmol) in DMF (0.030 L). The mixture was stirred for 15 min, after which I_2 (4.4 g, 17 mmol) was added to the reaction. After 4 h of stirring at 22 °C, the mixture was poured over ice H_2O (400 mL), and the resulting precipitate was collected by filtration, washed with ice H_2O (3 x 20 mL), and dried *via* azeotropic distillation with toluene. The crude material was dissolved in DCM (0.050 L). 4-(dimethylamino)pyridine (210 mg, 1.7 mmol) and NEt_3 (3.6 mL, 26 mmol) were added. The solution was cooled to 0 °C, and di-*tert*-butyl dicarbonate (4.1 g, 19 mmol) was added. The reaction was allowed to warm to rt, and stirred for 12 h. DCM (150 mL) was added, and the mixture was washed with $NH_4Cl_{(aq.)}$ (2 x 100 mL), H_2O (100 mL), and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The material was filtered through a pad of silica (hexanes / EtOAc 19:1), and then the solvent was removed *in vacuo*. The crude material was transferred to a 50 mL Schlenk flask, and then CuI (130 mg, 0.68 mmol) and $Pd(PPh_3)_2Cl_2$ (240 mg, 0.34 mmol) were added to the flask. The system was sealed with a rubber septum, and the flask was evacuated and backfilled with N_2 three times. MeCN (25 mL) and NEt_3 (11 mL, 77 mmol) were injected into the flask, and then the solution was cooled to –10 °C. Next, propargyl alcohol (1.1 mL, 19 mmol) was added to the reaction. After 1 h, the mixture was allowed to warm to 22 °C, and stirred for 12 h. The reaction mixture was poured over $NH_4Cl_{(aq.)}$ (50 mL), and

diluted with EtOAc (200 mL). The phases were separated, and the organic layer was washed with $NH_4Cl_{(aq.)}$ (100 mL), H_2O (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 1:0 → 7:3) afforded the title compound as a brown solid (3.2 g, 69%).

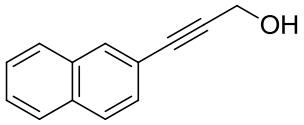
m.p.: 73–75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.2 Hz, 1 H), 7.78 (s, 1 H), 7.67 (dt, *J* = 7.5, 1.0 Hz, 1 H), 7.37 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1 H), 7.30 (td, *J* = 7.5, 1.1 Hz, 1 H), 4.58 (s, 2 H), 1.87 (s, 1 H) 1.68 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 149.2, 134.7, 130.5, 129.4, 125.3, 123.4, 120.1, 115.4, 102.8, 90.8, 84.6, 77.9, 52.0, 28.3.

IR (film): 3396, 3153, 3053, 2978, 2932, 2866, 1734, 1609, 1558, 1474, 1450, 1373, 1308, 1275, 1232, 1155, 1099, 1049, 1034, 1013, 912, 852, 746 cm^{-1}.

HRMS (EI$^+$): exact mass calculated for $[M]^+$ ($C_{16}H_{17}NO_3$) requires *m/z* 271.1208, found *m/z* 271.1217 (3.3 ppm).



4.1o.1

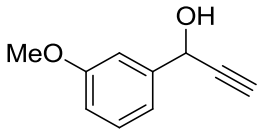
3-(Naphthalen-2-yl)prop-2-yn-1-ol[7]

CBr_4 (33.2 g, 0.100 mol) was added to an oven-dried 500 mL round bottom flask. DCM (75 mL) was injected, and the solution was cooled to 0 °C. A solution of PPh_3 (52.5 g, 0.200 mol) in DCM (75 mL) was added over 15 min, resulting in a brown mixture. The reaction was stirred for 10 additional minutes, after which a solution of 2-

naphthaldehyde (7.81 g, 50.0 mmol) in DCM (50 mL) was slowly added. After stirring for 1 h at 0 °C, the reaction was quenched with H_2O (100 mL), and the organic phase was further washed with $NaHCO_{3\ (aq)}$ (100 mL), $NH_4Cl_{\ (aq)}$, and brine (100 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes) provided 2-(2,2-dibromovinyl)naphthalene as a pale tan solid (12.9 g, 41.3 mmol, 83%). The material was added to an oven-dried 1 L Schlenk flask, which was sealed with a rubber septum and evacuated and backfilled with N_2 three times. THF (0.300 L) was added as solvent, and the solution was cooled to –78 °C. A solution of ^{n}BuLi (2.15 M in hexanes, 40.4 mL, 86.8 mmol) was injected over a 10 min period, and the dark brown solution was stirred at –78 °C for 1 h. The flask was placed under a positive pressure of N_2, the rubber septum was removed, and paraformaldehyde (3.72 g, 124 mmol) was added. The flask was resealed, the mixture was allowed to warm to rt and stir for an additional 12 h. The reaction was cooled to 0 °C and quenched with $NH_4Cl_{\ (aq.)}$ (150 mL). The aqueous phase was extracted with Et_2O (2 x 150 mL), and the organic extracts were washed with H_2O (2 x 300 mL) and brine (300 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 9:1 → 3:1) afforded the title compound as a pale tan solid (6.48 g, 86%).

m.p.: 61–63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.96 (m, 1 H), 7.85–7.75 (m, 3 H), 7.53–7.46 (m, 3 H), 4.57 (s, 2 H), 1.99 (s, 1 H).

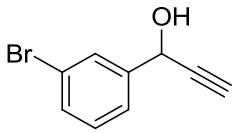


4.1p.1

1-(3-Methoxyphenyl)prop-2-yn-1-ol[8]

General procedure B was followed using *m*-anisaldehyde (0.61 mL, 5.0 mmol), a solution of ethynylmagnesium bromide (12 mL, 0.5 M in THF, 6.0 mmol), and THF (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 9:1) afforded the title product as a yellow oil (0.67 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.9 Hz, 1 H), 7.17–7.10 (m, 2 H), 6.93–6.86 (m, 1 H), 5.46 (d, *J* = 2.4 Hz, 1 H), 3.84 (s, 3 H), 2.68 (d, *J* = 2.2 Hz, 1 H), 2.18 (s, 1 H).

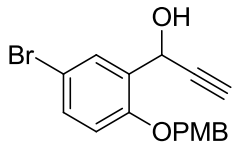


4.1q.1

1-(3-Bromophenyl)prop-2-yn-1-ol[9]

General procedure B was followed using 3-bromobenzaldehyde (0.58 mL, 5.0 mmol), a solution of ethynylmagnesium bromide (12 mL, 0.5 M in THF, 6.0 mmol), and THF (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 9:1) afforded the title product as a yellow oil (0.80 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (t, *J* = 1.9 Hz, 1 H), 7.48 (dd, *J* = 7.9, 1.8 Hz, 2 H), 7.27 (t, *J* = 7.9 Hz, 1 H), 5.45 (d, *J* = 2.2 Hz, 1 H), 2.71 (d, *J* = 2.3 Hz, 1 H), 2.31 (s, 1 H).



4.1r.1

1-(5-Bromo-2-((4-methoxybenzyl)oxy)phenyl)prop-2-yn-1-ol

General procedure B was followed using 5-bromo-2-((4-methoxybenzyl)oxy)benzaldehyde[10] (1.61 g, 5.0 mmol), a solution of ethynylmagnesium bromide (12 mL, 0.5 M in THF, 6.0 mmol), and THF (0.010 L) as solvent. Chromatographic purification (hexanes / EtOAc 19:1 → 4:1) afforded the title product as a colorless solid (0.67 g, 83%).

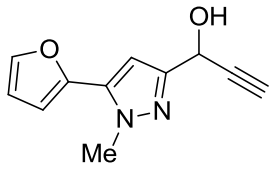
m.p.: 89–91 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 2.5 Hz, 1 H), 7.40 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.38 – 7.33 (m, 2 H), 6.96–6.90 (m, 2 H), 6.87 (d, *J* = 8.7 Hz, 1 H), 5.67 (dd, *J* = 6.3, 2.3 Hz, 1 H), 5.07 (d, *J* = 2.1 Hz, 2 H), 3.83 (s, 3 H), 2.92 (d, *J* = 6.3 Hz, 1 H), 2.65 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.8, 155.1, 132.5, 130.9, 130.8, 129.3, 128.1, 114.3, 114.2, 113.5, 82.6, 74.8, 70.7, 60.7, 55.5.

IR (film): 3427, 3290, 3070, 3001, 2934, 2835, 2118, 1612, 1589, 1514, 1485, 1464, 1441, 1406, 1381, 1304, 1277, 1244, 1175, 1122, 1032, 951, 849, 822, 810, 654 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M–OH]^+$ ($C_{17}H_{14}O_2Br$) requires *m/z* 329.0177, found *m/z* 329.0176 (0.3 ppm).



4.1s.1

1-(5-(Furan-2-yl)-1-methyl-1H-pyrazol-3-yl)prop-2-yn-1-ol

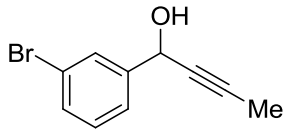
General procedure B was followed using 5-(furan-2-yl)-1-methyl-1H-pyrazole-3-carbaldehyde[11] (0.35 mL, 2.0 mmol), a solution of ethynylmagnesium bromide (5.0 mL, 0.5 M in THF, 2.5 mmol), and THF (7.0 mL) as solvent. Chromatographic purification (hexanes / EtOAc 19:1 → 14:1) afforded the title product as a yellow oil (0.37 g, 91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 1.9, 0.8 Hz, 1 H), 6.61 (s, 1 H), 6.57 (dd, *J* = 3.4, 0.8 Hz, 1 H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1 H), 5.56 (d, *J* = 2.2 Hz, 1 H), 4.03 (s, 3 H), 3.23 (s, 1 H), 2.63 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 150.9, 144.5, 143.0, 135.4, 111.6, 109.0, 103.0, 83.0, 73.8, 58.9, 38.8.

IR (film): 3290, 3130, 2951, 2881, 2118, 1529, 1483, 1433, 1381, 1366, 1288, 1232, 1221, 1161, 1067, 1009, 935, 901, 885, 783, 743, 665, 592 cm^{-1}.

HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{11}H_{10}N_2O_2Na$) requires *m/z* 225.0640, found *m/z* 225.0636 (1.8 ppm).



4.1t.1

1-(3-Bromophenyl)but-2-yn-1-ol

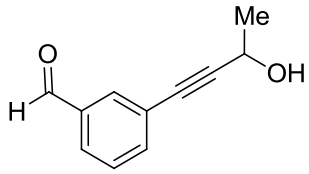
General procedure B was followed using 3-bromobenzaldehyde (0.82 mL, 7.0 mmol), a solution of propynylmagnesium bromide (21 mL, 0.5 M in THF, 11 mmol), and THF (0.020 L) as solvent. Chromatographic purification (hexanes / EtOAc 1:0 → 4:1) afforded the title product as a yellow oil (1.5 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 1.9 Hz, 1 H), 7.48–7.43 (m, 2 H), 7.28–7.21 (m, 1 H), 5.43–5.37 (m, 1 H), 2.22 (d, *J* = 4.8 Hz, 1 H), 1.92 (d, *J* = 2.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.4, 131.2, 130.1, 129.7, 125.2, 122.6, 83.8, 78.6, 64.1, 3.7.

IR (film): 3346, 3061, 2959, 2918, 2853, 2226, 1593, 1572, 1472, 1427, 1377, 1313, 1298, 1275, 1258, 1188, 1138, 1092, 1070, 997, 889, 862, 766, 700, 671, 635 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{10}H_9BrO$) requires *m/z* 224.0, found *m/z* 224.0.



4.1u.1

3-(3-Hydroxybut-1-yn-1-yl)benzaldehyde

An oven-dried Schlenk flask was charged with CuI (9.5 mg, 0.050 mmol), $Pd(PPh_3)_2Cl_2$ (0.070 g, 0.10 mmol), and a magnetic stir bar. The flask was evacuated and backfilled with N_2 three times. MeCN (0.010 mL), 3-bromobenzaldehyde (0.58 mL, 5.0 mmol),

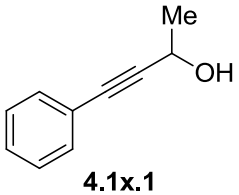
NEt_3 (0.010 mL), and but-3-yn-2-ol (0.47 mL, 6.0 mmol) were sequentially injected. The flask was placed in a 60 °C oil bath for 14 h. The reaction was allowed to cool, and the solvent was removed *in vacuo*. The residue was dissolved in Et_2O (50 mL), and washed with 1 N HCl (50 mL), H_2O (50 mL), and brine (50 mL). The organic solution was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 1:0 → 3:1) afforded the title product as a yellow oil (0.72 g, 82%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.99 (s, 1 H), 7.94–7.90 (m, 1 H), 7.83 (dt, *J* = 7.7, 1.5 Hz, 1 H), 7.67 (dt, *J* = 7.7, 1.5 Hz, 1 H), 7.49 (t, *J* = 7.7 Hz, 1 H), 4.78 (q, *J* = 6.6 Hz, 1 H), 2.13 (s, 1 H), 1.58 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 191.7, 137.3, 136.5, 133.2, 129.3, 129.2, 124.0, 92.7, 82.7, 58.9, 24.4.

IR (film): 3385, 2982, 2932, 2868, 2833, 2729, 1699, 1597, 1576, 1477, 1435, 1389, 1329, 1279, 1161, 1103, 1078, 1038, 957, 903, 822, 797, 725, 685, 648 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{11}H_{11}O_2$) requires *m/z* 175.0759, found *m/z* 175.0730 (2.9 mmu).



4.1x.1

4-Phenylbut-3-yn-2-ol

General procedure A was followed using iodobenzene (1.1 g, 0.010 mol), CuI (19 mg, 0.10 mmol), $Pd(PPh_3)_2Cl_2$ (0.14 g, 0.20 mmol), 3-butyn-2-ol (0.86 mL, 11 mmol) NEt_3

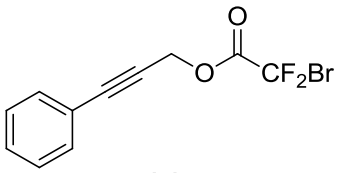
(0.010 L) and MeCN (0.010 L). Chromatographic purification (hexanes / EtOAc 1:0 → 4:1) afforded the title product as a brown oil (1.3 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.41 (m, 2 H), 7.32 (dd, *J* = 5.0, 1.9 Hz, 3 H), 4.77 (q, *J* = 6.6 Hz, 1 H), 2.01 (s, 1 H), 1.57 (d, *J* = 6.6 Hz, 3 H).

Synthesis of Propargyl Bromodifluoroacetates:

General Procedure C:

Bromodifluoroacetic acid (BDFA, 1.4 equiv) was added to an oven-dried round bottom flask sealed with a rubber septum. DCM was injected as solvent, and an oil bubbler was attached to the flask. DMF (0.30 equiv) and oxalyl chloride (1.3 equiv) were sequentially injected (caution: rapid evolution of noxious gases), and the solution was allowed to react for 2 h. In a separate oven-dried round bottom flask sealed with a rubber septum, substituted propargyl alcohol (1.0 equiv) was added to a solution of DCM (0.1–0.4 M), NEt_3 (2.0 equiv), and DMAP (for 2° alcohol substrates, 0.2 equiv). The solution was cooled to 0 °C, and an oil bubbler was attached to the flask. The solution of acid chloride was transferred to the solution of alcohol *via* syringe. The mixture was allowed to warm to rt, and stirred for 2–14 h. The reaction was quenched with 1 N HCl, diluted with DCM, and the organic phase was washed with H_2O and brine. The organic solution was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. Chromatographic purification using a minimum amount of silica gel afforded the desired propargyl bromodifluoroacetate. [Note: some propargyl bromodifluoroacetates are prone to hydrolysis on silica gel].



4.1a

3-Phenylprop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using 3-phenylprop-2-yn-1-ol (1.2 mL, 0.010 mol), BDFA (2.5 g, 14 mmol), oxalyl chloride (1.1 mL, 13 mmol), DMF (0.23 mL, 3.0 mmol), NEt_3 (2.8 mL, 0.020 mol), with DCM (25 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 49:1) afforded the title compound as a yellow oil (2.1 g, 76%).

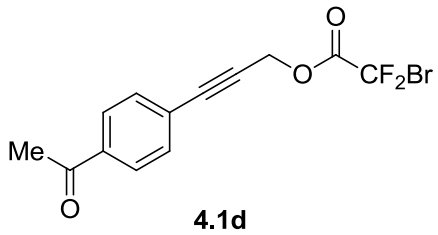
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.47 (m, 2 H), 7.43–7.33 (m, 3 H), 5.19 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0 (t, *J* = 32.0 Hz), 132.0, 129.3, 128.4, 121.4, 108.4 (t, *J* = 314.3 Hz), 88.7, 80.2, 56.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.74 (s, 2 F).

IR (film): 3054, 2996, 2941, 1778, 1596, 1482, 1438, 1401, 1357, 1292, 1148, 1130, 1081, 1073, 942, 906, 850, 756, 714, 601 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_7BrF_2O_2$) requires *m/z* 288.0, found 288.0.



4.1d

3-(4-Acetylphenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1d.1** (0.52 g, 3.00 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a yellow oil (0.74 g, 74%).

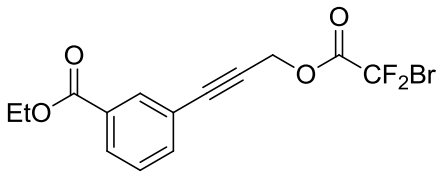
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.89 (m, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 5.19 (s, 2 H), 2.62 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 197.3, 159.1 (t, *J* = 32.1 Hz), 137.2, 132.2, 128.3, 126.2, 108.4 (t, *J* = 314.3 Hz), 87.8, 83.3, 56.2, 26.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.16 (s, 2 F).

IR (film): 3060, 2956, 1782, 1685, 1602, 1359, 1290, 1261, 1166, 1120, 1016, 948, 833, 707, 634 cm^{-1}.

HRMS (EI^+): mass calculated for $[M]^+$ ($C_{13}H_9BrF_2O_3$) requires *m/z* 329.9703, found *m/z* 329.9712 (2.7 ppm).



4.1e

Ethyl 3-(3-(2-bromo-2,2-difluoroacetoxy)prop-1-yn-1-yl)benzoate

General Procedure C was followed using **4.1e.1** (612 mg, 3.00 mmol), BDFA (735 mg, 4.20 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 19:1) afforded the title compound as a pale green oil (650 mg, 60%).

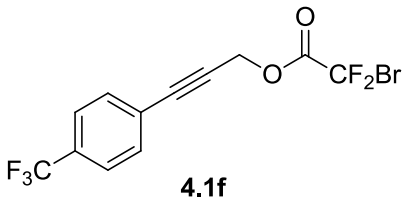
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (t, *J* = 1.7 Hz, 1 H), 8.05 (dt, *J* = 7.9, 1.4 Hz, 1 H), 7.65 (dt, *J* = 7.8, 1.4 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 5.18 (s, 2 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.7, 159.1, 136.1, 133.2, 131.0, 130.3, 128.6, 121.9, 108.4, 87.7, 81.1, 61.4, 56.3, 14.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.35 (s, 2 F).

IR (film): 3070, 2983, 1782, 1720, 1433, 1369, 1294, 1232, 1168, 1120, 1027, 952, 754, 682 cm^{-1}.

HRMS (EI^+): mass calculated for $[M]^+$ ($C_{14}H_{11}BrF_2O_4$) requires *m/z* 359.9809, found *m/z* 359.9792 (4.7 ppm).



4.1f

3-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1f.1** (0.60 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes) afforded the title compound as a colorless oil (0.58 g, 54%).

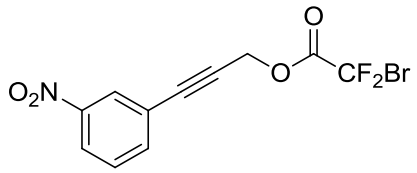
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64–7.57 (m, 4 H), 5.18 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.1 (t, *J* = 32.1 Hz), 132.4, 131.2 (q, *J* = 32.8 Hz), 125.5 (q, *J* = 3.8 Hz), 125.3 (q, *J* = 1.4 Hz), 123.9 (q, *J* = 272.3 Hz), 108.5 (t, *J* = 314.3 Hz), 87.3, 82.7, 56.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.19 (s, 2 F), –63.46 (s, 3 F).

IR (film): 3062, 2952, 1782, 1616, 1569, 1438, 1406, 1375, 1325, 1124, 1068, 1018, 950, 842, 717, 702, 597 cm^{-1}.

HRMS (EI$^+$): mass calculated for $[M]^+$ ($C_{12}H_6BrF_5O_2$) requires *m/z* 355.9471, found *m/z* 355.9465 (1.7 ppm).



4.1g

3-(3-Nitrophenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1g.1** (0.53 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a colorless oil (0.53 g, 53%).

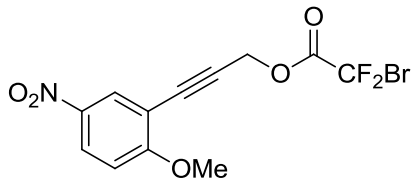
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (t, *J* = 1.9 Hz, 1 H), 8.24 (ddd, *J* = 8.4, 2.3, 1.1 Hz, 1 H), 7.79 (dt, *J* = 7.7, 1.3 Hz, 1 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 5.19 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0 (t, *J* = 32.2 Hz), 148.2, 137.7, 129.7, 126.9, 124.1, 123.3, 108.3 (t, *J* = 314.3 Hz), 86.1, 82.9, 55.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.40 (s, 2 F).

IR (film): 3085, 2925, 1782, 1531, 1352, 1292, 1166, 1124, 1024, 952, 808, 736, 673 cm^{-1}.

HRMS (EI$^+$): mass calculated for $[M]^+$ ($C_{11}H_6NBrF_2O_4$) requires *m/z* 332.9448, found *m/z* 332.9438 (3.0 ppm).



4.1h

3-(2-Methoxy-5-nitrophenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure B was followed using **4.1h.1** (520 mg, 2.5 mmol), BDFA (610 mg, 3.5 mmol), oxalyl chloride (0.28 mL, 3.3 mmol), DMF (58 µL, 0.30 mmol), NEt_3 (0.70 mL, 5.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (DCM) afforded the title compound as a pale yellow solid (0.64 g, 70%).

m.p.: 120–121 °C.

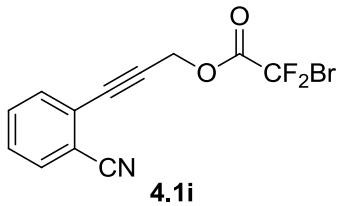
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (d, *J* = 2.8 Hz, 1 H), 8.26 (dd, *J* = 9.2, 2.8 Hz, 1 H), 6.98 (d, *J* = 9.2 Hz, 1 H), 5.21 (s, 2 H), 4.01 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.0, 159.1 (t, *J* = 32.2 Hz), 141.1, 129.7, 126.8, 111.9, 110.6, 108.5 (t, *J* = 314.3 Hz), 86.3, 82.8, 56.8, 56.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.77 (s, 2 F).

IR (film): 3090, 2997, 2957, 1786, 1607, 1580, 1518, 1491, 1462, 1441, 1371, 1348, 1283, 1167, 1148, 1119, 1099, 1018, 1007, 947, 910, 885, 833, 804, 748, 727, 708, 636 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{12}H_9NO_5F_2Br$) requires *m/z* 363.9632, found *m/z* 363.9624 (2.2 ppm).



4.1i

3-(2-Cyanophenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure B was followed using **4.1i.1** (470 mg, 3.0 mmol), BDFA (740 mg, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (10 µL, 0.9 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 4:1) afforded the title compound as an orange oil (0.67 g, 72%).

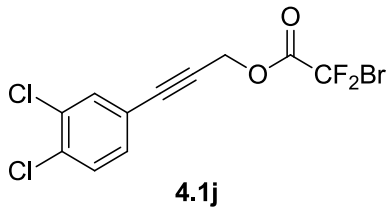
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71–7.66 (m, 1 H), 7.63–7.56 (m, 2 H), 7.49 (ddd, *J* = 7.8, 6.9, 2.1 Hz, 1 H), 5.23 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0 (t, *J* = 32.3 Hz), 133.0, 132.9, 132.6, 129.6, 125.3, 117.2, 115.7, 108.4 (t, *J* = 314.3 Hz), 86.6, 84.6, 55.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.16 (s, 2 F).

IR (film): 3070, 3001, 2955, 2231, 1782, 1593, 1566, 1483, 1447, 1437, 1373, 1290, 1169, 1122, 1040, 1014, 993, 951, 901, 835, 806, 764, 712, 683, 617 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{12}H_7NO_2F_2Br$) requires *m/z* 313.9628, found *m/z* 313.9631 (1.0 ppm).



4.1j

3-(3,4-Dichlorophenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1j.1** (0.60 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes) afforded the title compound as a pale yellow oil (0.91 g, 84%).

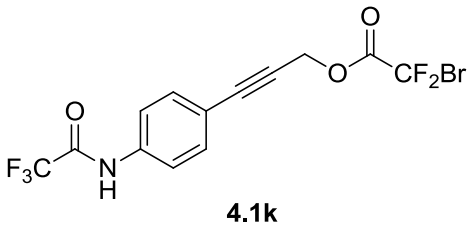
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 1.9 Hz, 1 H), 7.46–7.39 (m, 1 H), 7.30 (dd, *J* = 8.3, 1.8 Hz, 1 H), 5.15 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0 (t, *J* = 32.2 Hz), 134.0, 133.7, 132.9, 131.2, 130.6, 121.4, 108.4 (t, *J* = 314.3 Hz), 86.3, 82.2, 56.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.42 (s, 2 F).

IR (film): 3093, 2948, 1782, 1463, 1375, 1292, 1170, 1120, 950, 819, 802, 682 cm^{-1}.

HRMS (EI$^+$): mass calculated for $[M]^+$ ($C_{11}H_5BrCl_2F_2O_2$) requires *m/z* 355.8818, found *m/z* 355.8817 (0.3 ppm).



4.1k

3-(4-(2,2,2-Trifluoroacetamido)phenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1k.1** (0.35 g, 1.4 mmol), BDFA (0.35 g, 2.0 mmol), oxalyl chloride (0.16 mL, 1.9 mmol), DMF (0.033 mL, 0.43 mmol), NEt_3 (0.40 mL, 2.9 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (DCM : acetone 99:1) afforded the title compound as a tan solid (0.33 g, 58%).

m.p.: 116–117 °C.

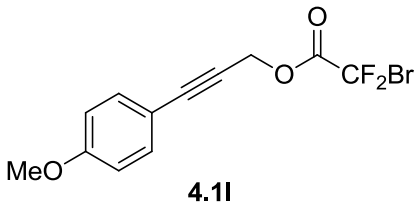
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (s, 1 H), 7.61–7.56 (m, 2 H), 7.55–7.49 (m, 2 H), 5.17 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.2 (t, *J* = 31.9 Hz), 154.8 (q, *J* = 37.7 Hz), 135.9, 133.3, 120.2, 119.3 (d, *J* = 53.8 Hz), 115.7 (d, *J* = 288.7 Hz), 108.5 (t, *J* = 314.4 Hz), 87.8, 81.1, 56.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.86 (s, 2 F), –75.67 (s, 3 F).

IR (film): 3296, 3198, 3134, 2957, 1776, 1703, 1674, 1607, 1543, 1512, 1437, 1410, 1377, 1283, 1265, 1244, 1227, 1202, 1155, 1113, 1018, 945, 906, 837, 806, 741, 719, 689, 619 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{13}H_7NO_3F_5Br$) requires *m/z* 398.9529, found *m/z* 398.9529 (0.0 ppm).



4.1l

3-(4-Methoxyphenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1l.1** (486 mg, 3.00 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 19:1) afforded the title compound as a colorless oil (540 mg, 56%).

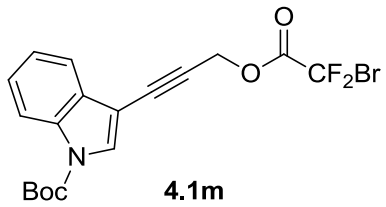
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.38 (m, 2 H), 6.91–6.79 (m, 2 H), 5.16 (s, 2 H), 3.83 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.4, 159.2 (t, *J* = 31.9 Hz), 133.7, 114.1, 113.5, 108.6 (t, *J* = 314.4 Hz), 88.9, 79.1, 56.8, 55.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.30 (s, 2 F).

IR (film): 3010, 2839, 1780, 1606, 1510, 1290, 1249, 1172, 1120, 1031, 946, 833, 709, 603 cm^{-1}.

HRMS (EI^+): exact mass calculated for $[M]^+$ ($C_{12}H_9BrF_2O_3$) requires *m/z* 317.9703, found *m/z* 317.9700 (0.9 ppm).



4.1m

Tert-butyl 3-(3-(2-bromo-2,2-difluoroacetoxy)prop-1-yn-1-yl)-1H-indole-1-carboxylate

General Procedure B was followed using **4.1m.1** (1.1 g, 4.2 mmol), BDFA (1.0 g, 5.8 mmol), oxalyl chloride (0.46 mL, 5.41 mmol), DMF (0.10 mL, 1.3 mmol), NEt_3 (1.2 mL, 8.3 mmol), with DCM (0.040 L) as solvent. Workup (H_2O was used in place of 1 N HCl to quench reaction) and chromatographic purification (hexanes / DCM 7:3) afforded the title compound as a tan solid (1.3 g, 73%).

m.p.: 49–50 °C.

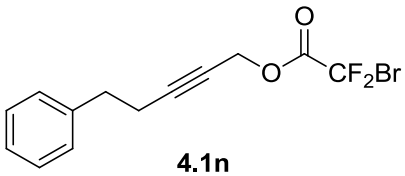
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.3 Hz, 1 H), 7.85 (s, 1 H), 7.67 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1 H), 7.38 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1 H), 7.32 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1 H), 5.24 (s, 2 H), 1.68 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.2 (t, *J* = 32.0 Hz), 149.0, 134.7, 130.5, 130.3, 125.5, 123.6, 120.1, 115.5, 108.6 (t, *J* = 314.6 Hz), 101.8, 84.8, 83.9, 81.4, 56.8, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.86 (s, 2 F).

IR (film): 3153, 3055, 2982, 2935, 1782, 1742, 15558, 1475, 1452, 1371, 1277, 1234, 1155, 1121, 1101, 1051, 1032, 1014, 957, 935, 854, 746 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{18}H_{17}NO_4F_2Br$) requires *m/z* 428.0309, found *m/z* 428.0280 (2.9 mmu).



4.1n

5-Phenylpent-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using 5-phenylpent-2-yn-1-ol[12] (481 mg, 3.00 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 49:1) afforded the title compound as a colorless oil (752 mg, 79%).

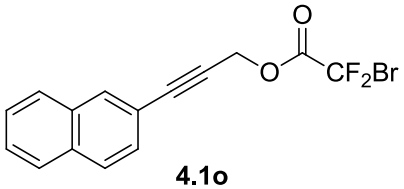
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 2 H), 7.26–7.20 (m, 3 H), 4.91 (t, *J* = 2.2 Hz, 2 H), 2.85 (t, *J* = 7.5 Hz, 2 H), 2.55 (tt, *J* = 7.5, 2.2 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.1 (t, *J* = 31.8 Hz), 140.3, 128.6, 128.6, 126.6, 108.6 (t, *J* = 314.3 Hz), 89.5, 72.6, 56.5, 34.6, 21.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.83 (s, 2 F).

IR (film): 3086, 3063, 3028, 2947, 3932, 2864, 1780, 1603, 1497, 1454, 1375, 1294, 1169, 1121, 1018, 953, 839, 806, 746, 698 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{13}H_{11}O_2F_2Br$) requires *m/z* 315.9910, found *m/z* 315.9897 (4.1 ppm).



4.1o

3-(Naphthalen-2-yl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1o.1** (3.00 g, 16.5 mmol), BDFA (4.03 g, 23.0 mmol), oxalyl chloride (1.82 mL, 21.5 mmol), DMF (0.39 mL, 5.0 mmol), NEt_3 (4.60 mL, 33.0 mmol), with DCM (75 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 49:1) afforded the title compound as a light yellow oil (4.70 g, 84%).

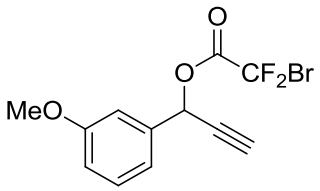
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 1.4 Hz, 1 H), 7.87–7.80 (m, 3 H), 7.57–7.50 (m, 3 H), 5.23 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.2 (t, *J* = 32.0 Hz), 133.4, 132.9, 132.6, 128.3, 128.3, 128.0, 127.9, 127.3, 126.9, 118.8, 108.6 (t, *J* = 314.4 Hz), 89.2, 80.6, 56.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.76 (s, 2 F).

IR (film): 3059, 2949, 2237, 1780, 1597, 1501, 1437, 1375, 1290, 1169, 1121, 1014, 1005, 955, 939, 895, 860, 818, 746, 710 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{15}H_9O_2F_2Br$) requires *m/z* 337.9754, found *m/z* 337.9734 (2.0 mmu).



4.1p

1-(3-Methoxyphenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1p.1** (0.49 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (pentane / Et_2O 19:1) afforded the title compound as a colorless oil (0.90 g, 94%).

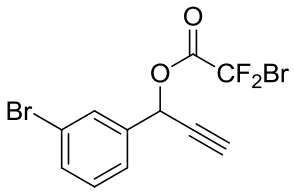
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.33 (m, 1 H), 7.15 (ddt, *J* = 7.6, 1.5, 0.7 Hz, 1 H), 7.11 (dd, *J* = 2.5, 1.7 Hz, 1 H), 6.97 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1 H), 6.50 (d, *J* = 2.3 Hz, 1 H), 3.85 (s, 3 H), 2.83 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.0, 158.5 (t, *J* = 32.0 Hz), 135.7, 130.2, 120.2, 115.7, 113.4, 108.6 (t, *J* = 314.6 Hz), 78.0, 77.8, 69.6, 55.5.

^{19}F NMR (471 MHz, $CDCl_3$): δ –62.06 (s, 2 F).

IR (film): 3296, 3007, 2962, 2943, 2839, 2131, 1778, 1605, 1589, 1491, 1466, 1456, 1437, 1323, 1271, 1167, 1126, 1051, 1018, 957, 908, 868, 835, 785, 752, 694, 656 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{12}H_9O_3F_2Br$) requires *m/z* 317.9703, found *m/z* 317.9685 (1.8 mmu).



4.1q

1-(3-Bromophenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1q.1** (0.63 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 19:1) afforded the title compound as a colorless oil (1.0 g, 91%).

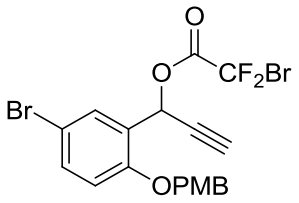
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (t, *J* = 1.9 Hz, 1 H), 7.58 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1 H), 7.52–7.47 (m, 1 H), 7.32 (t, *J* = 7.9 Hz, 1 H), 6.47 (d, *J* = 2.3 Hz, 1 H), 2.86 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.4 (t, *J* = 32.2 Hz), 136.3, 133.3, 131.0, 130.7, 126.6, 123.0, 108.4 (t, *J* = 314.7 Hz), 78.6, 77.2, 68.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.16 (d, *J* = 3.8 Hz, 2 F).

IR (film): 3300, 3065, 2926, 2854, 2131, 1780, 1597, 1574, 1475, 1431, 1333, 1281, 1252, 1173, 1124, 1074, 1001, 957, 920, 899, 874, 812, 785, 712, 692, 673 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_6Br_2F_2O_2$) requires *m/z* 365.9, found 365.9.



4.1r

1-(5-Bromo-2-((4-methoxybenzyl)oxy)phenyl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1r.1** (1.04 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 19:1) afforded the title compound as a tan solid (1.07 g, 71%).

m.p.: 65–68 °C.

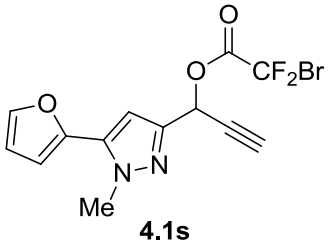
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 2.5 Hz, 1 H), 7.48 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.30–7.27 (m, 2 H), 6.93–6.89 (m, 2 H), 6.88–6.85 (m, 2 H), 5.04 (s, 2 H), 3.82 (s, 3 H), 2.82 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.8, 158.2 (t, *J* = 31.8 Hz), 155.3, 134.2, 132.3, 129.1, 127.8, 124.7, 114.2, 114.1, 113.2, 108.6 (t, *J* = 314.7 Hz), 78.2, 77.1, 70.6, 64.1, 55.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.88 (s, 2 F).

IR (film): 3294, 3011, 2959, 2935, 1776, 1612, 1516, 1487, 1466, 1331, 1288, 1246, 1175, 1124, 1034, 999, 959, 905, 874, 812 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{19}H_{14}Br_2F_2O_4$) requires *m/z* 501.9, found *m/z* 501.9.



4.1s

1-(5-(Furan-2-yl)-1-methyl-1H-pyrazol-3-yl)prop-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1s.1** (1.04 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 19:1) afforded the title compound as a light yellow oil (1.07 g, 71%).

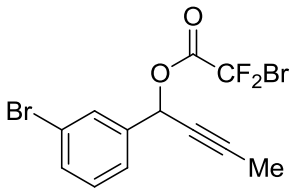
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 1.8, 0.7 Hz, 1 H), 6.71 (s, 1 H), 6.61 (dd, *J* = 3.4, 0.7 Hz, 1 H), 6.58 (d, *J* = 2.3 Hz, 1 H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1 H), 4.07 (s, 3 H), 2.80 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.3 (t, *J* = 32.1 Hz), 145.0, 144.0, 143.1, 135.6, 111.6, 109.2, 108.5 (t, *J* = 314.7 Hz), 104.5, 77.0, 63.9, 39.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ [–61.88]–[–61.96] (m, 2 F).

IR (film): 3298, 3132, 2953, 2131, 1778, 1531, 1474, 1431, 1381, 1366, 1331, 1283, 1234, 1221, 1165, 1124, 1011, 984, 953, 903, 887, 856, 800, 775, 743, 719, 689, 654, 592 cm^{-1}.

HRMS (ESI$^+$): mass calculated for $[M+H]^+$ ($C_{13}H_{10}BrF_2N_2O_3$) requires *m/z* 358.9843, found *m/z* 358.9839 (1.1 ppm).



4.1t

1-(3-Bromophenyl)but-2-yn-1-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1t.1** (0.68 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), with DCM (0.010 L) as solvent. Workup and chromatographic purification (hexanes / EtOAc 19:1) afforded the title compound as a colorless oil (0.57 g, 50%).

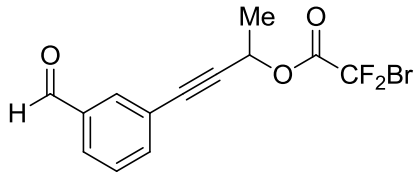
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (t, *J* = 1.9 Hz, 1 H), 7.55 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1 H), 7.47 (dt, *J* = 7.8, 1.3 Hz, 1 H), 7.30 (t, *J* = 7.9 Hz, 1 H), 6.45 (q, *J* = 2.3 Hz, 1 H), 1.96 (d, *J* = 2.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.5 (t, *J* = 31.9 Hz), 137.6, 132.9, 131.0, 130.5, 126.6, 122.9, 108.7 (t, *J* = 314.8 Hz), 87.5, 73.2, 69.8, 4.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.99 (d, *J* = 2.1 Hz, 2 F).

IR (film): 3063, 2961, 2922, 2243, 1776, 1595, 1574, 1474, 1431, 1335, 1317, 1281, 1254, 1171, 1124, 1072, 959, 918, 897, 874, 781, 708, 692 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{12}H_8O_2F_2Br_2$) requires *m/z* 379.8859, found *m/z* 379.8853 (1.6 ppm).



4.1u

4-(3-Formylphenyl)but-3-yn-2-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1u.1** (0.70 g, 4.0 mmol), BDFA (0.98 g, 5.6 mmol), oxalyl chloride (0.44 mL, 5.2 mmol), DMF (0.093 mL, 1.2 mmol), NEt_3 (1.1 mL, 8.0 mmol), DMAP (98 mg, 0.80 mmol) with DCM (15 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 19:1 → 9:1) afforded the title compound as a yellow oil (1.2 g, 88%).

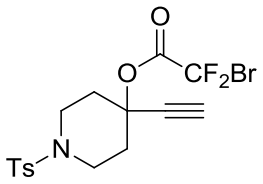
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.97 (td, *J* = 1.7, 0.6 Hz, 1 H), 7.88 (dt, *J* = 7.7, 1.4 Hz, 1 H), 7.71 (dt, *J* = 7.7, 1.4 Hz, 1 H), 7.53 (t, *J* = 7.7 Hz, 1 H), 5.82 (q, *J* = 6.7 Hz, 1 H), 1.75 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 191.4, 158.7 (t, *J* = 31.8 Hz), 137.6, 136.6, 133.4, 130.0, 129.3, 122.9, 108.7 (t, *J* = 314.7 Hz), 86.3, 85.4, 65.5, 21.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ [–61.60]–[–62.04] (m, 1 F), [–62.05]–[–62.48] (m, 1 F).

IR (film): 3069, 2995, 2837, 2241, 1778, 1705, 1601, 1578, 1481, 1447, 1379, 1346, 1323, 1286, 1171, 1136, 1121, 1088, 1024, 955, 847, 797, 756, 714, 683, 604 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{13}H_9F_2BrO_3$) requires *m/z* 329.9703, found *m/z* 329.9702 (0.3 ppm).



4.1v

4-Ethynyl-1-tosylpiperidin-4-yl 2-bromo-2,2-difluoroacetate

4-Ethynyl-1-tosylpiperidin-4-ol was prepared using a previously reported procedure.[13] General Procedure C was followed using 4-ethynyl-1-tosylpiperidin-4-ol (0.58 g, 2.1 mmol), BDFA (0.54 g, 3.1 mmol), oxalyl chloride (0.23 mL, 2.7 mmol), DMF (0.048 mL, 0.63 mmol), NEt_3 (0.58 mL, 4.2 mmol), DMAP (26 mg, 0.21 mmol) with DCM (0.010 L) as solvent. Workup and chromatographic purification (DCM) afforded the title compound as a colorless solid (0.71 g, 78%).

m.p.: 129–131 °C.

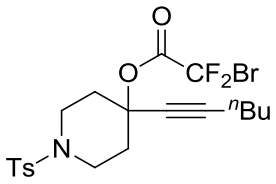
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68–7.64 (m, 2 H), 7.36–7.33 (m, 2 H), 3.27–3.20 (m, 2 H), 3.17–3.08 (m, 2 H), 2.72 (s, 1 H), 2.44 (s, 3 H), 2.38–2.26 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.9 (t, *J* = 31.8 Hz), 144.1, 132.8, 129.9, 127.9, 108.3 (t, *J* = 315.6 Hz), 79.3, 77.7, 76.6, 42.3, 35.4, 21.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.21 (s, 2 F).

IR (film): 3279, 3032, 2978, 2939, 2862, 2120, 1782, 1597, 1495, 1468, 1456, 1356, 1346, 1327, 1304, 1259, 1215, 1167, 1124, 1094, 1051, 1030, 951, 928, 872, 829, 818, 723, 650, 598, 548 cm^{-1}.

HRMS (ESI$^+$): mass calculated for $[M+K]^+$ ($C_{16}H_{16}BrF_2NO_4SK$) requires *m/z* 473.9589, found *m/z* 473.9574 (3.2 ppm).



4.1w

4-(Hex-1-yn-1-yl)-1-tosylpiperidin-4-yl 2-bromo-2,2-difluoroacetate

1-Tosylpiperidin-4-ol was prepared using a previously reported procedure.[14] A 500 mL Schlenk flask was oven-dried was capped with a rubber septum, evacuated and backfilled with dry N_2 (3x), and attached to an oil bubbler. Oxalyl chloride (1.5 mL, 18 mmol) and DCM (0.10 L) were injected, and the solution was cooled to –78 °C. A solution of DMSO (1.9 mL, 26 mmol) in DCM (0.010 L) was injected dropwise over a 5 min period (rapid evolution of noxious gas). After 1 h, a solution of 1-tosylpiperidin-4-ol (2.3 g, 8.8 mmol) in DCM (0.020 mL) was added over a 2 min period. After an additional 1 h, NEt_3 (6.1 mL, 44 mmol) was injected, and the mixture was vigorously stirred. After 15 min, the reaction was allowed to warm to 0 °C and stirred for an additional 1 h. The reaction mixture was washed with H_2O (100 mL) and brine (100 mL). The organic solution was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (DCM / MeOH 1:0 → 99:1) afforded 1-tosylpiperidin-4-one[15] as a colorless solid (1.9 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 3.39 (t, *J* = 6.2 Hz, 4 H), 2.55 (t, *J* = 6.2 Hz, 4 H), 2.45 (s, 3 H).

An oven-dried 100 mL Schlenk flask was sealed with a rubber septum, and evacuated and backfilled with dry N_2 (3x). 1-Hexyne (0.45 mL, 3.9 mmol) and THF (0.010 L) were injected, and the solution was cooled to 0 °C. A solution of ^{n}BuLi (2.5 M in hexane, 1.3 mL, 3.3 mmol) was injected dropwise over a 2 min period. The solution was stirred for

30 min, and a solution of 1-tosylpiperidin-4-one (0.76 g, 3.0 mmol) in THF (0.020 L) was injected over a 5 min period. The solution was allowed to warm to rt, and after 6 h, the reaction was quenched with $NH_4Cl_{(aq)}$ (30 mL). The aqueous phase was extracted with DCM (3 x 20 mL), and the organic extracts were combined. The solution was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (DCM / MeOH 99:1 → 49:1) provided a 4:1 mixture of 4-(hex-1-yn-1-yl)-1-tosylpiperidin-4-ol : 1-tosylpiperidin-4-one, which was used without further purification. General Procedure C was followed using BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), DMAP (73 mg, 0.60 mmol) with DCM (0.010 L) as solvent.. Workup and chromatographic purification (DCM) afforded the title compound as a colorless solid (1.0 g, 68% over two steps).

m.p.: 96–97 °C.

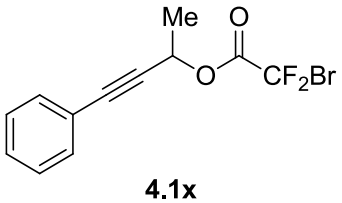
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 3.15 (t, *J* = 5.8 Hz, 4 H), 2.43 (s, 3 H), 2.32–2.20 (m, 4 H), 2.16 (t, *J* = 6.9 Hz, 2 H), 1.44–1.33 (m, 2 H), 1.34–1.24 (m, 2 H), 0.85 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.9 (t, *J* = 31.3 Hz), 143.9, 132.8, 129.8, 127.9, 108.6 (t, *J* = 315.7 Hz), 90.9, 77.9, 76.0, 42.6, 35.9, 30.2, 21.9, 21.6, 18.3, 13.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.12 (s, 2 F).

IR (film): 3030, 2959, 2935, 2862, 2249, 1780, 1597, 1495, 1468, 1454, 1431, 1381, 1358, 1323, 1294, 1259, 1209, 1165, 1130, 1101, 1051, 1018, 949, 912, 866, 818, 802, 731, 717, 650 cm^{-1}.

HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{20}H_{24}BrF_2NO_4SNa$) requires *m/z* 514.0475, found *m/z* 514.0458 (3.3 ppm).



4.1x

4-Phenylbut-3-yn-2-yl 2-bromo-2,2-difluoroacetate

General Procedure C was followed using **4.1x.1** (0.44 g, 3.0 mmol), BDFA (0.74 g, 4.2 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), DMF (0.070 mL, 0.90 mmol), NEt_3 (0.84 mL, 6.0 mmol), DMAP (74 mg, 0.60 mmol) with DCM (12 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 49:1 → 19:1) afforded the title compound as a yellow oil (0.78 g, 86%).

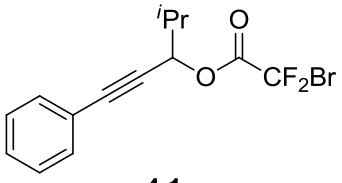
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.45 (m, 2 H), 7.39–7.31 (m, 3 H), 5.82 (q, *J* = 6.7 Hz, 1 H), 1.73 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.8 (t, *J* = 31.6 Hz), 132.1, 129.3, 128.5, 121.7, 108.8 (t, *J* = 314.7 Hz), 87.0, 84.8, 65.9, 21.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ [–61.57]–[–62.01] (m, 1 F) , [–62.02]–[–62.46] (m, 1 F).

IR (film): 3059, 2995, 2939, 1778, 1599, 1491, 1445, 1379, 1346, 1323, 1286, 1169, 1136, 1117, 1086, 1018, 953, 914, 843, 825, 756, 717, 690, 604, 546 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_9BrF_2O_2$) requires *m/z* 302.0, found 302.0.



4.1y

4-Methyl-1-phenylpent-1-yn-3-yl 2-bromo-2,2-difluoroacetate

4-Methyl-1-phenylpent-1-yn-3-ol was prepared using a previously reported procedure.[16] General Procedure C was followed using 4-methyl-1-phenylpent-1-yn-3-ol (0.35 g, 2.0 mmol), BDFA (0.49 g, 2.8 mmol), oxalyl chloride (0.22 mL, 2.6 mmol), DMF (0.046 mL, 0.60 mmol), NEt_3 (0.56 mL, 4.0 mmol), DMAP (49 mg, 0.40 mmol) with DCM (8.0 mL) as solvent. Workup and chromatographic purification (hexanes / EtOAc 49:1 → 19:1) afforded the title compound as a colorless oil (0.45 g, 68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.45 (m, 2 H), 7.39–7.31 (m, 3 H), 5.56 (d, *J* = 5.7 Hz, 1 H), 2.24 (pd, *J* = 6.8, 5.7 Hz, 1 H), 1.16 (d, *J* = 6.7 Hz, 3 H), 1.13 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.9 (t, *J* = 31.5 Hz), 132.1, 129.2, 128.5, 121.8, 108.8 (t, *J* = 314.7 Hz), 88.1, 82.8, 74.2, 32.9, 18.1, 17.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.78 (s, 2 F).

IR (film): 3059, 2970, 2934, 2878, 1778, 1491, 1470, 1445, 1391, 1364, 1340, 1292, 1169, 1124, 1099, 1070, 1030, 991, 957, 937, 895, 864, 854, 756, 690 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{14}H_{13}F_2BrO_2$) requires *m/z* 330.0067, found *m/z* 330.0047 (2.0 mmu).

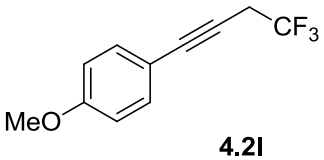
Cu/DMEDA Catalyzed Trifluoromethylation of Propargylic Bromodifluoroacetates:

General procedure D:

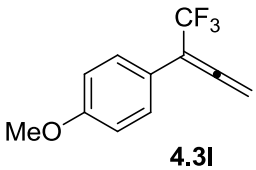
KF (23 mg, 0.40 mmol) was added to a resealable 15 mL test-tube and dried in a vacuum oven for a minimum of 24 h. The vial was removed from the oven, sealed with a PTFE septum, and cooled under N_2. CuI (3.8 mg, 0.020 mmol) and NaO_2CCF_2Br (9.8 mg, 0.050 mmol) were added, and the vial was evacuated and backfilled with N_2 three times. DMEDA (2.2 µL, 0.020 mmol) and DMF (0.20 mL) were injected, and the vial was placed in a 50 °C oil bath. The mixture was heated for 10 min, during which bubbling was observed and the solution changed from teal/blue to yellow. Next, propargyl bromodifluoroacetate (0.20 mmol) was injected, and heating was maintained for 14 h. The reaction mixture was diluted with EtOAc (3 mL), and TFT (24.6 µL, 0.200 mmol) was added as an internal standard. An aliquot was removed, and a ^{19}F NMR spectrum was obtained. The aliquot was recombined, and the reaction mixture was further diluted with EtOAc (15 mL). The organic solution was washed with NH_4Cl(aq) (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. Chromatographic purification afforded a mixture of propargyl trifluoromethane (A) and trifluoromethyl allene (B). The ratio or regioisomers was determined by ^1H NMR (propargylic CH_2 : terminal CH_2 of allene).

Synthesis of Compounds in Schemes 4.3–4.5:

Entry 1:



4.2l



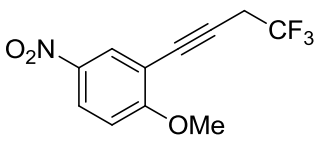
4.3l

General procedure D was followed using **4.1l** (64 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes / EtOAc 1:0 → 49:1) afforded a mixture of regioisomers as a yellow oil (31 mg, 72%). Analysis of the ^{1}H NMR spectrum revealed a 4.0 : 1 ratio of **4.2l** : **4.3l**.[17,18]

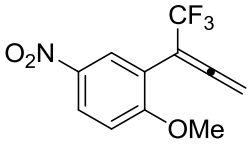
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.34 (m, 2 H, **4.2l**/**4.3l**), 6.94–6.89 (m, 2 H, **4.3l**), 6.88–6.82 (m, 2 H, **4.2l**), 5.51 (q, J = 3.4 Hz, 2 H, **4.3l**), 3.83 (s, 3 H, **4.3l**), 3.82 (s, 3 H, **4.2l**), 3.26 (q, J = 9.6 Hz, 2 H, **4.2l**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.76 (t, J = 3.6 Hz, 3 F, **4.3l**), –67.76 (t, J = 10.0 Hz, 3 F, **4.2l**).

Entry 2:



4.2h



4.3h

General procedure D was followed using **4.1h** (73 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification

(Hexanes / EtOAc 1:0 → 3:1) afforded a mixture of regioisomers as a colorless solid (36 mg, 70%). Analysis of the ^{1}H NMR spectrum revealed a 2.1 : 1 ratio of **4.2h** : **4.3h**.

m.p.: 76–81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 2.8 Hz, 1 H, **4.2h**), 8.28 (dd, J = 9.1, 2.8 Hz, 1 H, **4.3h**), 8.24–8.20 (m, 1 H, **4.2h/4.3h**), 7.01 (d, J = 9.1 Hz, 1 H, **4.3h**), 6.96 (d, J = 9.2 Hz, 1 H, **4.2h**), 5.42 (q, J = 3.4 Hz, 2 H, **4.3h**), 4.00 (s, 3 H, **4.2h**), 3.96 (s, 3 H, **4.3h**), 3.35 (q, J = 9.5 Hz, 2 H, **4.2h**).

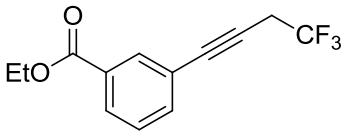
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 209.4 (q, J = 3.7 Hz, **4.3h**), 165.0 (**4.2h**), 162.4 (**4.3h**), 141.2 (**4.3h**), 141.1 (**4.2h**), 129.6 (**4.2h**), 126.7 (**4.3h**), 126.5 (**4.3h**), 126.2 (**4.2h**), 124.1 (q, J = 277.0 Hz, **4.2h**), 122.9 (q, J = 273.9 Hz, **4.3h**), 119.9 (**4.3h**), 112.6 (**4.2h**), 111.0 (**4.3h**), 110.5 (**4.2h**), 95.7 (q, J = 37.2 Hz, **4.3h**), 83.9 (q, J = 5.0 Hz, **4.2h**), 82.2 (**4.3h**), 78.6 (**4.2h**), 56.8 (**4.2h**), 56.6 (**4.3h**), 27.2 (q, J = 34.9 Hz, **4.2h**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.45 (t, J = 3.5 Hz, 3 F, **4.3h**), –67.35 (t, J = 9.9 Hz, 3 F, **4.2h**).

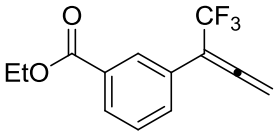
IR (film): 3119, 3094, 2947, 2920, 2847, 1983, 1610, 1580, 1514, 1493, 1492, 1439, 1418, 1344, 1275, 1246, 1190, 1148, 1103, 1018, 968, 906, 891, 868, 833, 797, 750, 735, 694, 665, 638 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_8F_3NO_3$) requires m/z 259.0, found m/z 259.0.

Entry 3:



4.2e



4.3e

General procedure D was followed using **4.1e** (72 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes / EtOAc 1:0 → 49:1) afforded a mixture of regioisomers as a pale green oil (0.040 g, 78%). Analysis of the ^{1}H NMR spectrum revealed a 2.3 : 1 ratio of **4.2e** : **4.3e**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.09 (m, 1 H, **4.2e**/**4.3e**), 8.05–7.97 (m, 1 H, **4.2e**/**4.3e**), 7.66–7.60 (m, 1 H, **4.2e**/**4.3e**), 7.47 (t, J = 7.8 Hz, 1 H, **4.3e**), 7.41 (t, J = 7.8 Hz, 1 H, **4.2e**), 5.61 (q, J = 3.4 Hz, 2 H, **4.3e**), 4.46–4.33 (m, 2 H, **4.2e/4.3e**), 3.30 (q, J = 9.5 Hz, 2H, **4.2e**), 1.41 (t, J = 7.1 Hz, 3 H, **4.2e** : **4.3e**).

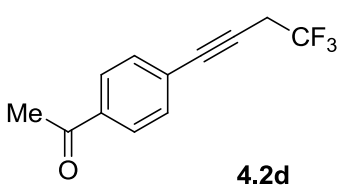
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 208.7 (q, J = 4.0 Hz, **4.3e**), 166.2 (**4.3e**), 165.9 (**4.2e**), 136.0 (**4.2e**), 133.1 (**4.2e**), 131.27 (**4.3e**), 131.26 (q, J = 1.3 Hz, **4.3e**), 130.9 (**4.2e**), 129.9 (**4.2e**), 129.8 (**4.3e**), 129.4 (**4.3e**), 128.9 (**4.3e**), 128.6 (**4.2e**), 128.4 (**4.3e**), 124.2 (q, J = 277.4 Hz, **4.2e**), 123.3 (q, J = 273.9 Hz, **4.3e**), 122.7 (**4.2e**), 101.4 (q, J = 35.7 Hz, **4.3e**), 84.2 (**4.3e**), 83.6 (**4.2e**), 78.6 (q, J = 5.1 Hz, **4.2e**), 61.4 (**4.2e**), 61.4 (**4.3e**), 26.9 (q, J = 34.9 Hz, **4.2e**), 14.5 (**4.2e**/**4.3e**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.59 (t, J = 3.6 Hz, 3 F, **4.3e**), –67.51 (t, J = 10.0 Hz, 3 F, **4.2e**).

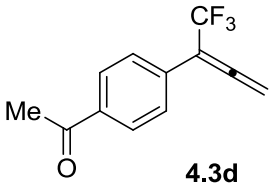
IR (film): 3067, 2984, 2932, 2854, 1971, 1720, 1472, 1367, 1298, 1256, 1231, 1173, 1148, 1111, 1084, 1026, 908, 872, 754 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{13}H_{11}F_3O_2$) requires m/z 256.1, found m/z 256.1.

Entry 4:



4.2d



4.3d

General procedure D was followed using **4.1d** (66 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO2CCF2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes / EtOAc 1:0 → 49:1) afforded a mixture of regioisomers as a yellow oil (0.030 g, 66%). Analysis of the 1H NMR spectrum revealed a 2.6 : 1 ratio of **4.2d** : **4.3d**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 2 H, **4.3d**), 7.94–7.89 (m, 2 H, **4.2d**), 7.57–7.52 (m, 2 H, **4.2d/4.3d**), 5.64 (q, J = 3.3 Hz, 2 H, **4.3d**), 3.32 (q, J = 9.5 Hz, 2 H, **4.2d**), 2.62 (s, 3 H, **4.3d**), 2.61 (s, 3 H, **4.2d**).

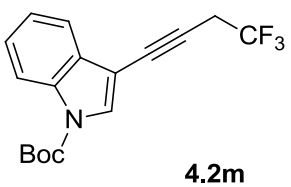
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 209.2 (q, J = 3.9 Hz, **4.3d**), 197.5 (**4.3d**), 197.4 (**4.2d**), 136.8 (**4.2d**), 136.6 (**4.3d**), 134.1 (**4.3d**), 132.2 (**4.2d**), 130.0 (**4.2d**), 128.9 (**4.3d**), 128.4 (**4.2d**), 127.1 (q, J = 1.3 Hz, **4.3d**), 127.1 (**4.2d**), 124.1 (q, J = 277.4 Hz, **4.2d**) 123.2 (q, J = 273.9 Hz, **4.3d**), 101.7 (**4.3d**), 84.5 (**4.3d**), 83.7 (**4.2d**), 81.0 (q, J = 5.1 Hz, **4.2d**), 27.0 (q, J = 35.0 Hz, **4.2d**), 26.81 (A), 26.78 (**4.3d**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = (–63.30)–(–63.53) (m, 3 F, **4.3d**), –67.66 (t, J = 10.0 Hz, 3 F, **4.2d**).

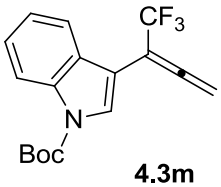
IR (film): 3067, 2964, 2932, 3854, 1969, 1933, 1686, 1603, 1558, 1418, 1404, 1362, 1306, 1263, 1178, 1150, 1109, 1016, 957, 935, 906, 833, 717, 679, 628, 592 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_9F_3O$) requires m/z 226.1, found m/z 226.1.

Entry 5:



4.2m



4.3m

General procedure D was followed using **4.1m** (86 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes / EtOAc 1:0 → 9:1) afforded a mixture of regioisomers as viscous orange oil (38 mg, 59%). Analysis of the ^{1}H NMR spectrum revealed a 3.0 : 1 ratio of **4.2m** : **4.3m**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.5 Hz, 1 H, **4.3m**), 8.15 (d, J = 8.2 Hz, 1 H, **4.2m**), 7.87 (dt, J = 8.0, 1.0 Hz, 1 H, **4.3m**), 7.79 (s, 1 H, **4.2m**), 7.73 (s, 1 H, **4.3m**), 7.68–7.60 (m, 1 H, **4.2m**), 7.37 (td, J = 8.3, 7.7, 1.4 Hz, 1 H, **4.2m/4.3m**), 7.31 (td, J = 7.5, 1.1 Hz, 1 H, **4.2m**), 7.29–7.24 (m, 1 H, **4.3m**), 5.69 (qd, J = 3.0, 0.9 Hz, 2 H, **4.3m**), 3.37 (q, J = 9.6 Hz, 2 H, **4.2m**), 1.70 (s, 9 H, **4.3m**), 1.68 (s, 9 H, **4.2m**).

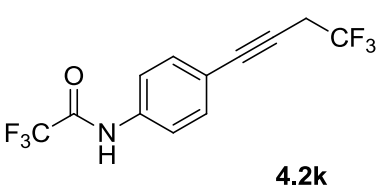
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 208.9 (q, J = 3.7 Hz, **4.3m**), 149.5 (**4.3m**), 149.1 (**4.2m**), 135.5 (**4.3m**), 134.7 (**4.2m**), 130.53 (**4.2m**), 129.6 (**4.2m**), 128.4 (**4.3m**), 125.4 (**4.2m**), 125.2 (**4.3m**), 124.4 (q, J = 277.1 Hz, **4.2m**), 124.2 (q, J = 1.3 Hz, **4.3m**), 123.4 (**4.2m**), 123.3 (q, J = 273.7 Hz, **4.3m**), 123.1 (**4.3m**), 120.1 (**4.2m**), 119.9 (**4.3m**), 115.5 (**4.3m**), 115.4 (**4.2m**), 108.0 (**4.3m**), 102.4 (**4.2m**), 95.7 (q, J = 36.1 Hz, **4.3m**), 84.59 (**4.2m**), 84.58 (**4.2m**), 84.52 (**4.3m**), 81.1 (q, J = 5.1 Hz, **4.2m**), 76.6 (**4.3m**) 28.3 (**4.3m**), 28.3 (**4.2m**), 27.2 (q, J = 34.8 Hz, **4.2m**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.41 (t, J = 3.5 Hz, 3 F, **4.3m**), –67.66 (t, J = 9.9 Hz, 3 F, **4.2m**).

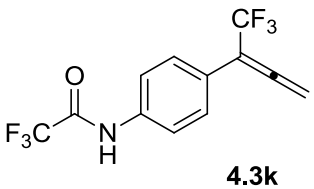
IR (film): 3159, 3055, 2980, 2932, 2851, 1740, 1558, 1475, 1454, 1420, 1375, 1357, 1308, 1279, 1234, 1256, 1234, 1111, 1049, 1032, 854, 831, 746, 729 cm^{-1}.

MS (CI): exact mass calculated for $[2M + Na]^+$ ($C_{34}H_{32}F_6N_2O_4Na$) requires m/z 669.2164, found m/z 669.2179 (2.2 ppm).

Entry 6:



4.2k



4.3k

General procedure D was followed using **4.1k** (0.080 g, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes / DCM 1:0 → 1:1) afforded a mixture of regioisomers as a colorless solid (24 mg, 40%). Analysis of the ^{1}H NMR spectrum revealed a 6.3 : 1 ratio of **4.2k** : **4.3k**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H, **4.2k**), 7.83 (s, 1 H, **4.3k**), 7.62–7.58 (m, 2 H, **4.3k**), 7.58–7.54 (m, 2 H, **4.2k**), 7.52–7.45 (m, 2 H, **4.2k/4.3k**), 5.60 (q, J = 3.4 Hz, 2 H, **4.3k**), 3.29 (q, J = 9.5 Hz, 2 H, **4.2k**).

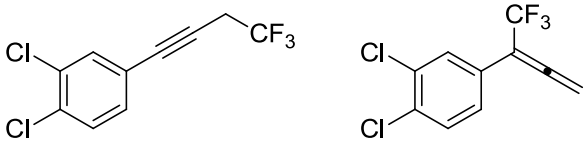
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 208.7 (q, J = 4.4 Hz, **4.3k**), 154.9 (q, J = 37.5 Hz, **4.3k**),154.8 (q, J = 37.5 Hz, **4.2k**), 135.4 (**4.2k**), 135.00 (**4.3k**), 133.1 (**4.2k**), 128.2 (q, J = 1.5 Hz, **4.3k**), 124.3 (q, J = 276.9 Hz, **4.2k**), 123.3 (q, J = 275.6 Hz, **4.3k**), 120.7 (**4.2k**), 120.32 (**4.3k**), 120.25 (**4.2k**), 120.18 (**4.3k**), 115.70 (q, J = 288.8, **4.3k**), 115.69 (q, J = 288.8 Hz, **4.2k**), 101.2 (q, J = 35.4 Hz, **4.3k**), 84.3 (**4.3k**), 83.5 (**4.2k**), 78.5 (q, J = 5.0 Hz, **4.2k**), 26.9 (q, J = 34.8 Hz, **4.2k**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.55 (t, J = 3.0 Hz, 3 F, **4.3k**), –67.35 (t, J = 9.5 Hz, 3 F, **4.2k**), –76.69 (3 F, **4.2k/4.3k**).

IR (film): 3200, 3202, 3136, 2964, 1705, 1607, 1547 1512, 1410, 1366, 1281, 1246, 1202, 1155, 1155, 1107, 959, 906, 839, 727, 704, 654 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_7F_6NO$) requires m/z 295.0, found m/z 295.0.

Entry 7:



4.2j **4.3j**

General procedure D was followed using **4.1j** (72 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes) afforded a mixture of regioisomers as a pale yellow oil (0.040 g, 79%). Analysis of the ^{1}H NMR spectrum revealed a 2.2 : 1 ratio of **4.2j** : **4.3j**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 2.0 Hz, 1 H, **4.2j**), 7.52 (d, J = 2.2 Hz, 1 H, **4.3j**), 7.45 (d, J = 8.5 Hz, 1 H, **4.3j**), 7.40 (d, J = 8.3 Hz, 1 H, **4.2j**), 7.30–7.26 (m, 2 H, **4.2j/4.3j**), 5.63 (q, J = 3.3 Hz, 2 H, **4.3j**), 3.28 (q, J = 9.5 Hz, 2 H, **4.2j**).

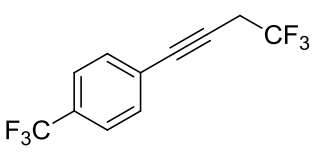
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 208.6 (q, J = 3.9 Hz, **4.3j**), 133.6 (**4.2j**), 133.4 (**4.2j**), 133.2 (**4.3j**), 132.8 (**4.2j**), 132.6 (**4.3j**), 131.1 (**4.2j**), 130.8 (**4.3j**), 130.5 (**4.2j**), 129.4 (**4.3j**), 129.0 (q, J = 1.7 Hz, **4.3j**), 126.3 (q, J = 1.7 Hz, **4.3j**), 124.1 (q, J = 276.9 Hz, **4.2j**), 123.0 (q, J = 273.1 Hz, **4.3j**), 122.2 (**4.2j**), 100.6 (q, J = 35.2 Hz, **4.3j**), 84.7 (**4.3j**), 82.3 (**4.2j**), 79.8 (q, J = 5.1 Hz, **4.2j**), 26.9 (q, J = 34.9 Hz, **4.2j**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.59 (t, J = 3.6 Hz, 3 F, **4.3j**), –67.51 (t, J = 10.0 Hz, 3 F, **4.2j**).

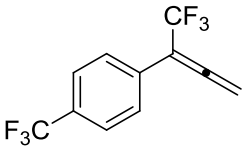
IR (film): 3074, 2928, 1973, 1533, 1475, 1466, 1364, 1352, 1281, 1254, 1178, 1151, 1130, 1111, 1034, 906, 881, 822 cm^{-1}.

HRMS (EI): mass calculated for $[M]^+$ ($C_{10}H_5Cl_2F_3$) requires m/z 251.9720, found m/z 251.9721 (0.3 ppm).

Entry 8:



4.2f



4.3f

General procedure D was followed using **4.1f** (71 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes / EtOAc 1:0 → 49:1) afforded a mixture of regioisomers as a colorless oil (35 mg, 70%). Analysis of the ^{1}H NMR spectrum revealed a 1.7 : 1 ratio of **4.2f** : **4.3f**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.53 (m, 4 H, **4.2f/4.3f**), 5.64 (q, J = 3.4 Hz, 2 H, **4.3f**), 3.31 (q, J = 9.5 Hz, 2 H, **4.2f**).

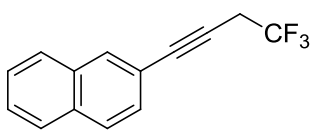
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 209.0 (q, J = 4.1 Hz, **4.3f**), 133.1 (q, J = 1.6 Hz, **4.3f**), 132.3 (**4.2f**), 130.6 (q, J = 32.7 Hz, **4.2f**), 130.4 (q, J = 32.7 Hz, **4.3f**), 127.4 (q, J = 1.6 Hz, **4.3f**), 126.1 (q, J = 1.7 Hz, **4.2f**), 125.8 (q, J = 3.8 Hz, **4.3f**), 125.4 (q, J = 3.9 Hz, **4.2f**), 124.2 (q, J = 278.6 Hz, **4.2f**), 124.0 (q, J = 272.2 Hz, **4.3f**), 123.9 (q, J = 271.8 Hz, **4.2f**), 123.1 (q, J = 274.8 Hz, **4.3f**), 101.3 (q, J = 35.0 Hz, **4.3f**), 84.5 (**4.3f**), 83.2 (**4.2f**), 80.2 (q, J = 5.1 Hz, **4.2f**), 27.0 (q, J = 34.9 Hz, **4.2f**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.50 (t, J = 3.5 Hz, 3 F, **4.3f**), –63.79 (3 F, **4.3f**), –63.93 (3 F, **4.2f**), –67.42 (t, J = 9.9 Hz, 3 F, **4.2f**).

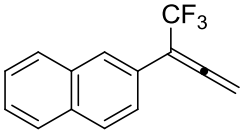
IR (film): 3063, 2934, 1971, 1927, 1618, 1406, 1366, 1329, 1281, 1267, 1151, 1130, 1105, 1068, 1018, 937, 906, 870, 843, 735, 723 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_6F_6$) requires m/z 252.0, found m/z 252.0.

Entry 9:



4.2o



4.3o

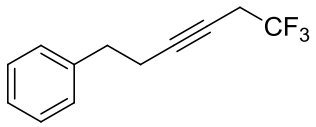
General procedure D was followed using **4.1o** (2.4 g, 7.0 mmol), CuI (130 mg, 0.70 mmol), DMEDA (75 µL, 0.70 mmol), NaO_2CCF_2Br (0.35 g, 1.8 mmol), KF (0.81 g, 14 mmol), with DMF (7.0 mL) as solvent. Workup and chromatographic purification (Hexanes / EtOAc 1:0 → 49:1) afforded a mixture of regioisomers as a pale yellow solid (0.93 g, 57%). Analysis of the ^{1}H NMR spectrum revealed a 3.8 : 1 ratio of **4.2o** : **4.3o**.[17,18]

m.p.: 42–45 °C.

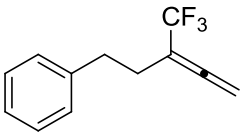
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 1 H, **4.2o**), 7.93 (s, 1 H, **4.3o**), 7.88–7.77 (m, 3 H, **4.2o/4.3o**), 7.57–7.47 (m, 3 H, **4.2o/4.3o**), 5.63 (q, J = 3.3 Hz, 2 H, **4.3o**), 3.34 (q, J = 9.6 Hz, 2 H, **4.2o**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.30 (t, J = 3.6 Hz, 3 F, **4.3o**), –67.56 (t, J = 10.1 Hz, 3 F, **4.2o**).

Entry 10:



4.2n



4.3n

General procedure D was followed using **4.1n** (63 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes) afforded a mixture of regioisomers as a tan oil (0.030 g, 70%). Analysis of the ^{1}H NMR spectrum revealed a 1 : 2.1 ratio of **4.2n** : **4.3n**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 2 H, **4.2n/4.3n**), 7.26–7.19 (m, 3 H, **4.2n/4.3n**), 5.18 (h, J = 3.6 Hz, 2 H, **4.3n**), 3.01 (qt, J = 9.7, 2.4 Hz, 2 H, **4.2n**), 2.90–2.73 (m, 2 H, **4.2n/4.3n**), 2.54–2.41 (m, 2 H, **4.2n/4.3n**).

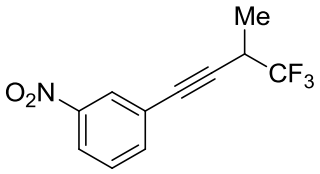
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 206.7 (q, J = 4.1 Hz, **4.3n**), 140.8 (**4.3n**), 140.5 (**4.2n**), 128.59 (**4.2n/4.3n**), 128.56 (**4.3n**), 128.52 (**4.2n**), 126.5 (**4.2n**), 126.35 (**4.3n**), 124.5 (q, J = 277.8 Hz, **4.2n**), 123.9 (q, J = 274.5 Hz, **4.3n**), 98.1 (q, J = 34.0 Hz, **4.3n**), 84.3 (**4.2n**), 82.5 (**4.3n**), 69.2 (q, J = 5.1 Hz, **4.2n**), 34.9 (**4.2n**), 33.6 (**4.3n**), 27.7 (**4.3n**), 26.3 (q, J = 34.6 Hz, **4.2n**), 21.0 (**4.2n**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.60 (t, J = 3.7 Hz, **4.3n**), –67.54 (t, J = 10.0 Hz, **4.2n**).

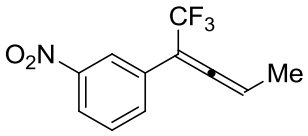
IR (film): 3088, 3065, 3030, 2932, 2862, 1985, 1954, 1605, 1497, 1454, 1366, 1333, 1281, 1261, 1200, 1157, 1115, 1055, 980, 908, 864, 744, 700 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_{11}F_3$) requires m/z 212.1, found m/z 212.1.

Scheme 4.4:



4.2b



4.3b

General procedure D was followed using **4.1b** (0.070 g, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes : EtOAc 1:0 → 9:1) afforded a mixture of regioisomers as a yellow oil (0.020 g, 41%). Analysis of the ^{1}H NMR spectrum revealed a 1.6 : 1 ratio of **4.2b** : **4.3b**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41–8.37 (m, 1 H, **4.2b**), 8.32–8.24 (m, 1 H, **4.2b/4.3b**), 8.14–8.20 (m, 1 H, **4.3b**), 7.85–7.80 (m, 1 H, **4.2b**), 7.79–7.73 (m, 1 H, **4.3b**), 7.63–7.53 (m, 1 H, **4.2b/4.3b**), 6.08 (qt, J = 7.5, 3.1 Hz, 1 H, **4.3b**), 4.43 (qq, J = 7.8, 2.5 Hz, 1 H, **4.2b**), 1.97–1.93 (m, 3 H, **4.2b/4.3b**).

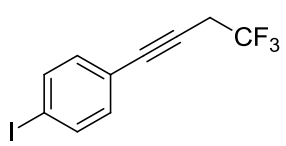
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 205.6 (q, J = 3.9 Hz, **4.3b**), 148.7 (**4.3b**), 148.5 (**4.2b**), 135.5 (**4.2b**), 134.6 (**4.3b**), 132.7 (q, J = 1.8 Hz, **4.3b**), 129.8 (**4.3b**), 129.7 (**4.2b**), 124.62 (**4.2b**) 124.61 (**4.3b**), 124.1 (q, J = 280.4 Hz, **4.2b**), 124.0 (**4.2b**), 123.1 (q, J = 274.8 Hz, **4.3b**), 122.9 (**4.2b**), 122.2 (q, J = 1.8 Hz, **4.3b**), 100.1 (q, J = 35.3 Hz, **4.3b**), 96.6 (**4.3b**), 83.6 (**4.2b**), 70.3 (q, J = 3.4 Hz, **4.2b**), 43.3 (q, J = 31.8 Hz, **4.2b**), 13.4 (**4.3b**), 3.8 (**4.2b**).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.70 (s, 3 F, **4.3b**), –71.74 (d, J = 7.5 Hz, 3 F, **4.2b**).

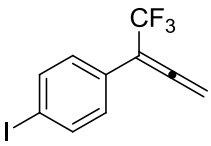
IR (film): 3090, 2961, 2926, 2856, 1963, 1535, 1481, 1441, 1352, 1327, 1248, 1178, 1155, 1119, 980, 964, 926, 901, 806, 739, 710, 687 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{11}H_8F_3NO_2$) requires m/z 243.1, found m/z 243.1.

Scheme 4.5:



4.2c



4.3c

General procedure D was followed using **4.1c** (83 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), DMEDA (2.2 µL, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), with DMF (0.20 mL) as solvent. Workup and chromatographic purification (Hexanes) afforded a mixture of regioisomers as an amorphous tan solid (0.050 g, 81%). Analysis of the ^{1}H NMR spectrum revealed a 2.0 : 1 ratio of **4.2c** : **4.3c**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.69 (m, 2 H, **4.3c**), 7.69–7.64 (m, 2 H, **4.2c**), 7.21–7.15 (m, 2 H, **4.2c/4.3c**), 5.56 (q, J = 3.4 Hz, 2 H, **4.3c**), 3.27 (q, J = 9.5 Hz, 1 H, **4.2c**).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 208.5 (q, J = 4.0 Hz, **4.3c**), 138.0 (**4.3c**), 137.7 (**4.2c**), 133.5 (**4.2c/4.3c**), 128.87 (q, J = 1.5 Hz, **4.3c**), 124.2 (q, J = 276.9 Hz, **4.2c**), 123.2 (q, J = 273.6 Hz, **4.3c**), 121.8 (**4.2c**), 94.9 (**4.2c**), 94.1 (**4.3c**), 84.2 (**4.2c**), 83.6 (**4.3c**), 79.1 (q, J = 5.1 Hz, **4.2c**), 27.0 (q, J = 34.9 Hz, **4.2c**). Note: Terminal substituted carbon of **4.3c** could not be distinguished from the baseline (expected to be a quartet (J ≈ 35 Hz) between δ 102–100).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.60 (t, J = 3.7 Hz, 3 F, **4.3c**), –67.54 (t, J = 10.0 Hz, 3 F, **4.2c**).

IR (film): 3065, 2978, 1961, 1541, 1485, 1391, 1366, 1319, 1279, 1263, 1254, 1173, 1148, 1111, 1061, 1007, 935, 906, 868, 820, 743, 665 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{10}H_6F_3I$) requires m/z 310.0, found m/z 310.0.

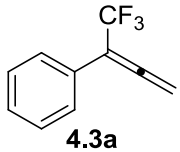
Cu/phen Catalyzed Trifluoromethylation of Propargylic Bromodifluoroacetates:

General procedure E:

KF (23 mg, 0.4 mmol) was added to a 15 mL screw-top vial, and dried in a vacuum oven for a minimum of 24 h. The vial was removed from the oven, sealed with a PTFE septum, and allowed to cool under a dry atmosphere of N_2. CuI (3.8 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), and 1,10-phenanthroline (phen, 3.6 mg, 0.020 mmol) or 2,2':6',2"-terpyridine (terpy, 4.6 mg, 0.020 mmol) were added to the vial. The system was resealed, and evacuated and backfilled with dry N_2. DMF (0.2 mL) was injected as solvent, and the mixture was placed in a 50 °C or 60 °C heating block. After 10 min, propargyl bromodifluoroactetate (0.20 mmol) was added to the vial, and heating was maintained for 14 or 24 h. The mixture was cooled to rt, diluted with EtOAc (4 mL), and α,α,α-trifluorotoluene (0.025 mL, 0.20 mmol) was injected as a standard. After thorough mixing, an aliquot was withdrawn, and analyzed by ^{19}F NMR spectroscopy. The aliquot was recombined with the reaction mixture, which was further diluted with EtOAc (20 mL). The mixture was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude material was subjected the silica gel chromatography to provide trifluoromethylallenes. The ratio of allene / alkyne products was determined by analysis of the ^1H NMR spectra of purified material.

General procedure F:

KF (23 mg, 0.4 mmol) was added to a 15 mL screw-top vial, and dried in a vacuum oven for a minimum of 24 h. The vial was removed from the oven, sealed with a PTFE septum, and allowed to cool under a dry atmosphere of N_2. Propargyl bromodifluoroacetate (0.2 mmol), CuI (3.8 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), and 1,10-phenanthroline (phen, 3.6 mg, 0.020 mmol) or 2,2':6',2"-terpyridine (terpy, 4.6 mg, 0.020 mmol) were added to the vial. The system was resealed, and evacuated and backfilled with dry N_2. DMF (0.2 mL) was injected as solvent, and the mixture was placed in a 50 °C or 60 °C heating block for 14 or 24 h. The mixture was cooled to rt, diluted with EtOAc (4 mL), and α,α,α-trifluorotoluene (0.025 mL, 0.20 mmol) was injected as a standard. After thorough mixing, an aliquot was withdrawn, and analyzed by ^{19}F NMR spectroscopy. The aliquot was recombined with the reaction mixture, which was further diluted with EtOAc (20 mL). The mixture was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude material was subjected the silica gel chromatography to afford trifluoromethylallenes. The ratio of allene / alkyne products was determined by analysis of the ^1H NMR spectra of purified material.



4.3a

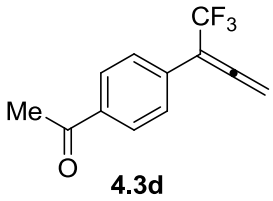
(1,1,1-Trifluorobuta-2,3-dien-2-yl)benzene[17]

General procedure E was followed using **4.1a** (0.29 g, 1.0 mmol), CuI (19 mg, 0.10 mmol), phen (18 mg, 0.020 mmol), NaO_2CCF_2Br (49 mg, 0.25 mmol), KF (0.12 g, 2.0

mmol), and DMF (1.0 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (0.13 g, 70%). Analysis of the ^{1}H NMR spectrum revealed a <1:100 ratio of **4.2a** : **4.3a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.8 Hz, 2 H), 7.45–7.39 (m, 2 H), 7.38–7.32 (m, 1 H), 5.57 (q, *J* = 3.4 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.43 (t, *J* = 3.7 Hz, 3 F).



4.3d

1-(4-(1,1,1-Trifluorobuta-2,3-dien-2-yl)phenyl)ethanone

General procedure E was followed using **4.1d** (66 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a yellow oil (31 mg, 69%). Analysis of the ^{1}H NMR spectrum revealed a 1:33 ratio of **4.2d** : **4.3d**.

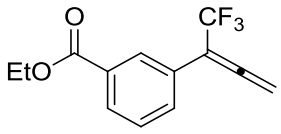
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99–7.94 (m, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 5.64 (q, *J* = 3.3 Hz, 2 H), 2.62 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 209.2 (q, *J* = 4.1 Hz), 197.5, 136.6, 134.1, 128.8, 127.2 (q, *J* = 1.7 Hz), 123.2 (q, *J* = 273.9 Hz), 101.63 (q, *J* = 34.9 Hz), 84.5, 26.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.41 (t, *J* = 3.4 Hz).

IR (film): 3066, 2358, 2341, 1969, 2341, 1969, 1934, 1685, 1605, 1433, 1359, 1307, 1267, 1124, 1107, 935, 869, 840, 717, 609 cm^{-1}.

HRMS (EI$^+$): mass calculated for $[M]^+$ ($C_{12}H_9F_3O$) requires *m/z* 226.0605, found *m/z* 226.0608 (1.3 ppm).



4.3e

Ethyl 3-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzoate

General procedure E was followed using **4.1e** (72 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a pale yellow oil (39 mg, 76%). Analysis of the ^{1}H NMR spectrum revealed a 1:33 ratio of **4.2e** : **4.3e**.

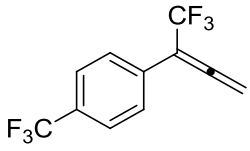
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16–8.08 (m, 1 H), 8.00 (dt, *J* = 7.8, 1.4 Hz, 1 H), 7.68–7.59 (m, 1 H), 7.46 (t, *J* = 7.8 Hz, 1 H), 5.61 (q, *J* = 3.4 Hz, 2 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.7 (q, *J* = 4.0 Hz), 166.2, 131.3, 131.2 (q, *J* = 1.4 Hz), 129.8, 129.4, 128.9, 128.4, 123.3 (q, *J* = 273.8 Hz), 101.4 (q, *J* = 34.9 Hz), 84.2, 61.4, 14.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.34 (t, *J* = 3.4 Hz, 3 F).

IR (film): 3068, 2985, 1973, 1938, 1720, 1606, 1583, 1446, 1367, 1309, 1174, 1124, 1024, 873, 757, 692, 651 cm^{-1}.

HRMS (EI$^+$): mass calculated for $[M]^+$ ($C_{13}H_{11}F_3O_2$) requires *m/z* 256.0711, found *m/z* 256.0716 (2.0 ppm).



4.3f

1-(1,1,1-Trifluorobuta-2,3-dien-2-yl)-4-(trifluoromethyl)benzene

General procedure E was followed using **4.1f** (71 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 49:1) afforded the title compound as a colorless oil (33 mg, 66%). Analysis of the ^{1}H NMR spectrum revealed a 1:40 ratio of **4.2f** : **4.3f**.

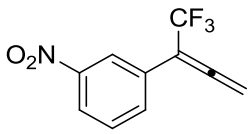
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 5.64 (q, *J* = 3.4 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 209.0 (q, *J* = 4.1 Hz), 133.1 (q, *J* = 1.6 Hz), 130.4 (q, *J* = 32.7 Hz), 127.4 (q, *J* = 1.6 Hz), 125.8 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.2 Hz), 123.1 (q, *J* = 274.8 Hz), 101.3 (q, *J* = 35.0 Hz), 84.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.50 (t, *J* = 3.5 Hz, 3 F), –63.79 (s, 3 F).

IR (film): 3076, 2930, 1971, 1933, 1622, 1435, 1410, 1331, 1308, 1267, 1173, 1130, 1105, 1068, 1018, 937, 868, 843, 735 cm^{-1}.

HRMS (EI$^+$): mass calculated for $[M]^+$ ($C_{11}H_6F_6$) requires *m/z* 252.0374, found *m/z* 252.0366 (3.2 ppm).



4.3g

1-Nitro-3-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene

General procedure E was followed using **4.1g** (67 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 9:1) afforded the title compound as a yellow oil (31 mg, 68%). Analysis of the ^{1}H NMR spectrum revealed a 1:29 ratio of **4.2g** : **4.3g**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1 H), 8.23–8.14 (m, 1 H), 7.83–7.73 (m, 1 H), 7.58 (t, *J* = 8.1 Hz, 1 H), 5.71 (q, *J* = 3.3 Hz, 2 H).

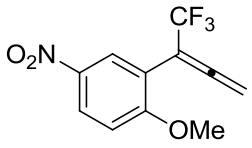
^{13}C NMR (101 MHz, $CDCl_3$): δ 208.9 (q, *J* = 4.0 Hz), 148.7, 132.7 (q, *J* = 1.6 Hz), 131.4, 129.9, 123.1, 123.0 (q, *J* = 273.9 Hz), 122.2 (q, *J* = 1.7 Hz), 100.8 (q, *J* = 35.5 Hz), 85.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.65 (t, *J* = 3.6 Hz, 3 F).

IR (film): 3078, 2995, 1974, 1930, 1531, 1350, 1309, 1182, 983, 871, 806, 707, 684 cm^{-1}.

HRMS (EI$^+$): mass calculated for $[M]^+$ ($C_{10}H_6F_3NO_2$) requires *m/z* 229.0351, found *m/z* 229.0322 (12.7 ppm).

MS (CI): mass calculated for $[M]^+$ ($C_{10}H_6F_3NO_2$) requires *m/z* 229.0, found *m/z* 229.0



4.3h

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

General procedure E was followed using **4.1h** (73 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 4:1) afforded the title compound as a yellow oil (38 mg, 74%). Analysis of the ^{1}H NMR spectrum revealed a 1:10 ratio of **4.2h** : **4.3h**.

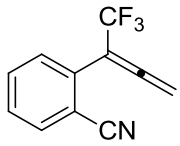
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (dd, *J* = 9.1, 2.8 Hz, 1 H), 8.23 (d, *J* = 2.8 Hz, 1 H), 7.01 (d, *J* = 9.1 Hz, 1 H), 5.42 (q, *J* = 3.4 Hz, 2 H), 3.97 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 209.4 (q, *J* = 3.6 Hz), 162.4, 141.3, 126.7, 126.5, 122.9 (q, *J* = 273.9 Hz), 119.9, 111.0, 95.8 (q, *J* = 37.2 Hz), 82.2, 56.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.07 (t, *J* = 3.6 Hz, 3 F).

IR (film): 3082, 2995, 2949, 2847, 1981, 1612, 1585, 1518, 1497, 1464, 1346, 1298, 1273, 1180, 1144, 1121, 1084, 1020, 968, 910, 868, 825, 754, 733, 694, 663, 636 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{11}H_9F_3NO_3$) requires *m/z* 260.0535, found *m/z* 260.0508 (2.7 mmu).



4.3i

2-(1,1,1-Trifluorobuta-2,3-dien-2-yl)benzonitrile

General procedure E was followed using **4.1i** (63 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / EtOAc 1:0 → 9:1) afforded the title compound as a colorless oil (27 mg, 64%). Analysis of the ^{1}H NMR spectrum revealed a <1:100 ratio of **4.2i** : **4.3i**.

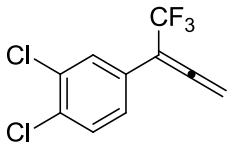
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77–7.73 (m, 1 H), 7.67–7.60 (m, 2 H), 7.52–7.47 (m, 1 H), 5.63 (q, *J* = 3.4 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.3 (q, *J* = 3.7 Hz), 134.0, 133.0, 132.9, 129.2, 129.1 (q, *J* = 1.4 Hz), 127.8 (q, *J* = 273.8 Hz), 117.2, 113.7, 98.2 (q, *J* = 36.7 Hz), 84.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.10 (t, *J* = 3.7 Hz, 3 F).

IR (film): 3074, 2995, 2928, 2854, 2230, 1979, 1936, 1597, 1487, 1448, 1421, 1308, 1259, 1182, 1122, 1101, 1041, 939, 868, 766, 748, 725, 654, 609, 582, 554, 509 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{11}H_7NF_3$) requires *m/z* 210.0531, found *m/z* 210.0509 (2.2 mmu).



4.3j

1,2-Dichloro-4-(1,1,1-trifluorobuta-2,3-dien-2-yl)benzene

General procedure E was followed using **4.1j** (72 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes) afforded the title compound as a colorless oil (41 mg, 80%). Analysis of the ^{1}H NMR spectrum revealed a 1:29 ratio of **4.2j** : **4.3j**.

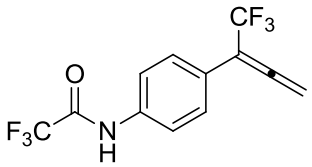
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 2.1 Hz, 1 H), 7.45 (d, *J* = 8.5 Hz, 1 H), 7.31–7.26 (m, 1 H), 5.63 (q, *J* = 3.3 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.6 (q, *J* = 3.9 Hz), 133.2, 132.6, 130.8, 129.4, 129.0 (q, *J* = 1.7 Hz), 126.3 (q, *J* = 1.7 Hz), 123.0 (q, *J* = 273.1 Hz), 100.6 (q, *J* = 35.3 Hz), 84.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.66 (t, *J* = 3.3 Hz, 3 F).

IR (film): 3070, 2927, 1973, 1930, 1226, 1475, 1309, 1255, 1178, 1126, 1031, 958, 869, 821, 723 cm^{-1}.

HRMS (EI$^+$): mass calculated for $[M]^+$ ($C_{10}H_5Cl_2F_3$) requires *m/z* 251.9720, found *m/z* 251.9725 (2.0 ppm).



4.3k

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

General procedure E was followed using **4.1k** (0.080 g, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup (wash with 1 N HCl before H_2O and brine washes) and chromatographic purification (hexanes / EtOAc 19:1 → 4:1) afforded the title compound as an amorphous tan solid (27 mg, 46%). Analysis of the ^{1}H NMR spectrum revealed an 1:8 ratio of **4.2k** : **4.3k**.

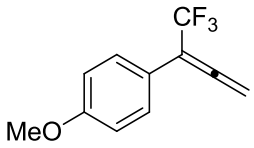
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (s, 1 H), 7.63–7.58 (m, 2 H), 7.51–7.45 (m, 2 H), 5.60 (q, *J* = 3.4 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.7 (q, *J* = 3.9 Hz), 154.9 (q, *J* = 37.5 Hz), 135.0, 133.1, 128.2 (d, *J* = 1.6 Hz), 123.3 (d, *J* = 273.9 Hz), 120.7, 115.7 (q, *J* = 288.8 Hz), 101.3 (q, *J* = 34.8 Hz), 84.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ –60.57 (t, *J* = 3.6 Hz, 3 F), –75.70 (s, 3 F).

IR (film): 3302, 2926, 1973, 1705, 1610, 1595, 1541, 1518, 1433, 1410, 1318, 1290, 1265, 1173, 1113, 966, 937, 912, 872, 837, 766, 729, 702, 660, 634, 600 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{12}H_7NOF_6$) requires *m/z* 295.0432, found *m/z* 295.0422 (3.4 ppm).



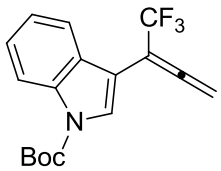
4.3l

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

General procedure E was followed using **4.1l** (64 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / DCM 19:1) afforded the title compound as a colorless oil (32 mg, 75%). Analysis of the ^{1}H NMR spectrum revealed a <1:100 ratio of **4.2l** : **4.3l**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.35 (m, 2 H), 6.95–6.89 (m, 2 H), 5.52 (q, *J* = 3.4 Hz, 2 H), 3.83 (s, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ [–61.65]–[–61.72] (m, 3 F).



4.3m

Tert-butyl 3-(1,1,1-trifluorobuta-2,3-dien-2-yl)-1H-indole-1-carboxylate

General procedure F was followed using **4.1m** (86 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / DCM 19:1 → 9:1)

afforded the title compound as a colorless oil (30 mg, 47%). Analysis of the ^{1}H NMR spectrum revealed a 1:100 ratio of **4.2m** : **4.3m**.

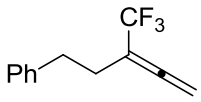
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.3 Hz, 1 H), 7.88 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.74 (s, 1 H), 7.38 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1 H), 7.27 (dt, *J* = 15.2, 0.9 Hz, 1 H), 5.70 (qd, *J* = 2.9, 0.9 Hz, 2 H), 1.70 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 208.9 (q, *J* = 3.7 Hz), 149.5, 135.5, 128.4, 125.2, 123.3 (q, *J* = 274.3 Hz), 124.2 (q, *J* = 2.6 Hz), 123.1, 119.9, 115.5, 108.0, 95.7 (q, *J* = 36.1 Hz), 84.6, 84.5, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ [–61.83]–[–61.87] (m, 3 F).

IR (film): 3165, 3055, 2982, 2934, 1971, 1940, 1736, 1562, 1452, 1375, 1310, 1290, 1244, 1148, 1117, 1084, 1041, 1024, 883, 854, 762, 746, 729, 692 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{17}H_{17}NO_2F_3$) requires *m/z* 324.1211, found *m/z* 324.1198 (4.0 ppm).



4.3n

(3-(Trifluoromethyl)penta-3,4-dien-1-yl)benzene

General procedure E was followed using **4.1n** (63 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), terpy (4.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (22 mg, 51%). Analysis of the ^{1}H NMR spectrum revealed a 1:9 ratio of **4.2n** : **4.3n**.

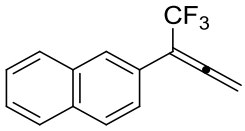
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (m, 2 H), 7.27–7.20 (m, 3 H), 5.19 (h, *J* = 3.5 Hz, 2 H), 2.86–2.75 (m, 2 H), 2.47 (ddt, *J* = 11.0, 7.2, 3.3 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.6 (q, *J* = 4.3 Hz), 140.7, 128.44, 128.41, 126.2, 123.8 (q, *J* = 273.1 Hz), 98.0 (q, *J* = 33.9 Hz), 82.4, 33.5, 27.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ –62.24 (s, 3 F).

IR (film): 3088, 3065, 3030, 2928, 2860, 1985, 1954, 1605, 1497, 1454, 1333, 1263, 1202, 1155, 1119, 1082, 1055, 1030, 980, 864, 744, 700 cm^{-1}.

MS (CI): mass calculated for $[M]^+$ ($C_{12}H_{11}F_3$) requires *m/z* 212.1, found *m/z* 212.1.



4.3o

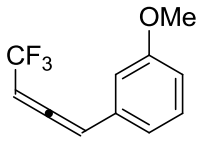
2-(1,1,1-Trifluorobuta-2,3-dien-2-yl)naphthalene[18]

KF (813 mg, 14.0 mmol) and a stir bar were added to a 25 mL round-bottom flask, and placed in a 200 °C vacuum-oven. After 24 h, the flask was equipped with a 3-way flushing adaptor, and allowed to cool under an atmosphere of dry N_2. The flask was charged with CuI (133 mg, 0.700 mmol), phen (126 mg, 0.700 mmol), and NaO_2CCF_2Br (345 mg, 1.75 mmol). The system was evacuated and backfilled with dry N_2 (3x), and remained under a positive pressure of N_2 during the course of the reaction. DMF (7.00 mL) was injected, and the flask was immersed in a 50 °C oil bath (Note: evolution of CO_2). After 10 min, **4.1o** (2.37 g, 7.00 mmol) was injected, and the mixture was stirred for 14 h. The reaction was allowed to cool to rt, and diluted with EtOAc (100 mL). The mixture was washed with 1 N HCl (100 mL), water (100 mL), and brine (100 mL). The

organic phase was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Chromatographic purification (hexanes / EtOAc 19:1) afforded the title compound as an amorphous yellow solid (1.33 g, 81%) Analysis of the ^{1}H NMR spectrum revealed a 1:40 ratio of **4.2o** : **4.3o**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1 H), 7.89–7.80 (m, 3 H), 7.54 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.53–7.48 (m, 2 H), 5.63 (q, *J* = 3.3 Hz, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.21 (d, *J* = 4.1 Hz, 3 F).



4.3p

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

General procedure E was followed using **4.1p** (64 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (pentane / Et_2O 49:1 → 19:1) afforded the title compound as a colorless oil (35 mg, 82%). Alkyne **4.2p** was not observed by ^{1}H or ^{19}F NMR spectroscopy.

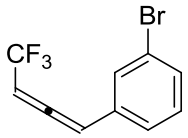
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.26 (m, 1 H), 6.92 (dt, *J* = 7.8, 1.2 Hz, 1 H), 6.88–6.83 (m, 2 H), 6.65 (dq, *J* = 6.4, 3.8 Hz, 1 H), 5.89 (p, *J* = 5.9 Hz, 1 H), 3.83 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.1 (q, *J* = 5.8 Hz), 160.1, 132.2 (q, *J* = 1.7 Hz), 130.1, 122.5 (q, *J* = 271.1 Hz), 120.3, 114.4, 112.9, 101.4, 89.8 (q, *J* = 39.2 Hz), 55.4.

^{19}F NMR (471 MHz, $CDCl_3$): δ [–61.15]–[–61.21] (m, 3 F).

IR (film): 3007, 2962, 2943, 2839, 1969, 1599, 1583, 1493, 1470, 1441, 1414, 1398, 1306, 1286, 1263, 1225, 1130, 1047, 885, 872, 841, 785, 754, 735, 689, 648, 636 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{11}H_{10}F_3O$) requires *m/z* 215.0684, found *m/z* 215.0675 (4.2 ppm).



4.3q

1-Bromo-3-(4,4,4-trifluorobuta-1,2-dien-1-yl)benzene

General procedure E was followed using **4.1q** (74 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / EtOAc 49:1 → 19:1) afforded the title compound as a colorless oil (39 mg, 74%). Alkyne **4.2q** was not observed by ^1H or ^{19}F NMR spectroscopy.

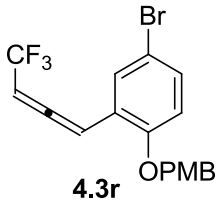
^1H NMR (500 MHz, $CDCl_3$): δ 7.46–7.42 (m, 2 H), 7.26–7.22 (m, 2 H), 6.62 (dq, *J* = 6.4, 3.8 Hz, 1 H), 5.94 (p, *J* = 5.9 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.1 (q, *J* = 5.7 Hz), 133.1 (d, *J* = 1.7 Hz), 131.7, 130.6, 130.4, 126.2, 123.2, 122.3 (q, *J* = 271.2 Hz), 100.4, 90.3 (q, *J* = 39.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ [–61.34]–[–61.42] (m, 3 F).

IR (film): 3069, 2957, 1967, 1705, 1593, 1572, 1475, 1429, 1416, 1371, 1348, 1259, 1192, 1163, 1132, 1074, 1018, 997, 883, 856, 787, 750, 694, 673 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{10}H_6F_3Br$) requires *m/z* 261.9605, found *m/z* 261.9589 (1.6 mmu).



4.3r

4-Bromo-1-((4-methoxybenzyl)oxy)-2-(4,4,4-trifluorobuta-1,2-dien-1-yl)benzene

General procedure E was followed using **4.1r** (101 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / DCM 4:1) afforded the title compound as a colorless oil (32 mg, 40%). Alkyne **4.2r** was not observed by ^{1}H or ^{19}F NMR spectroscopy.

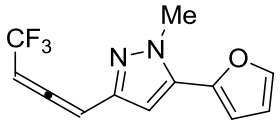
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 2.5 Hz, 1 H), 7.36–7.31 (m, 3 H), 6.99 (dq, *J* = 6.6, 4.0 Hz, 1 H), 6.96–6.91 (m, 2 H), 6.84 (d, *J* = 8.8 Hz, 1 H), 5.82 (p, *J* = 5.9 Hz, 1 H), 5.02 (s, 2 H), 3.84 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.5 (q, *J* = 5.8 Hz), 159.6, 154.7, 132.3, 131.1, 129.3, 128.0, 122.4 (q, *J* = 271.0 Hz), 121.9 (q, *J* = 1.7 Hz), 114.3, 114.1, 113.3, 94.9, 89.2 (q, *J* = 39.1 Hz), 70.6, 55.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ [–61.23]–[–61.31] (m, 3 F).

IR (film): 3016, 2957, 2935, 2837, 1967, 1612, 1587, 1516, 1491, 1466, 1416, 1404, 1379, 1304, 1246, 1175, 1130, 1036, 1001, 887, 864, 824, 806, 690, 646 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M–H]^+$ ($C_{18}H_{13}O_2F_3Br$) requires *m/z* 397.0051, found *m/z* 397.0039 (3.0 ppm).



4.3s

5-(Furan-2-yl)-1-methyl-3-(4,4,4-trifluorobuta-1,2-dien-1-yl)-1H-pyrazole

General procedure E was followed using **4.1s** (72 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / DCM 4:1) afforded the title compound as a colorless oil (36 mg, 70%). Alkyne **4.2s** was not observed by ^{1}H or ^{19}F NMR spectroscopy.

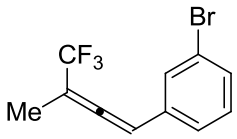
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 1.9, 0.8 Hz, 1 H), 6.75 (dq, *J* = 6.6, 3.8 Hz, 1 H), 6.59 (dd, *J* = 3.4, 0.8 Hz, 1 H), 6.52 (dd, *J* = 3.4, 1.8 Hz, 1 H), 6.49 (s, 1 H), 5.86 (dq, *J* = 5.8, 6.5 Hz, 1 H), 4.04 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 207.8 (q, *J* = 5.8 Hz), 144.4, 143.1, 142.4 (q, *J* = 1.9 Hz), 135.8, 122.3 (q, *J* = 271.0 Hz), 111.7, 109.2, 103.6, 94.1, 89.3 (q, *J* = 39.2 Hz), 38.9.

^{19}F NMR (471 MHz, $CDCl_3$): δ [–61.31]–[–61.35] (m, 3 F).

IR (film): 3126, 3013, 2955, 1975, 1531, 1472, 1427, 1394, 1367, 1294, 1269, 1252, 1221, 1128, 1007, 903, 885, 841, 797, 741, 710, 687, 592, 571 cm^{-1}.

HRMS (ESI^+): mass calculated for $[M+H]^+$ ($C_{12}H_{10}F_3N_2O$) requires *m/z* 255.0745, found *m/z* 255.0737 (3.1 ppm).



4.3t

1-Bromo-3-(4,4,4-trifluoro-3-methylbuta-1,2-dien-1-yl)benzene

General procedure E was followed using **4.1t** (76 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 50 °C for 14 h. Workup and chromatographic purification (hexanes / EtOAc 49:1) afforded the title compound as a colorless oil (39 mg, 70%). Alkyne **4.2t** was not observed by ^{1}H or ^{19}F NMR spectroscopy.

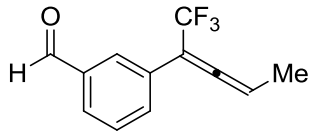
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43–7.39 (m, 2 H), 7.25–7.20 (m, 2 H), 6.47 (hept, *J* = 3.1 Hz, 1 H), 1.99 (d, *J* = 3.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.2 (q, *J* = 4.0 Hz), 134.4, 131.3, 130.5, 130.3, 126.1, 123.5 (q, *J* = 273.9 Hz), 123.1, 99.1, 98.6 (q, *J* = 35.4 Hz), 13.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ –66.59 (d, *J* = 3.2 Hz, 3 F).

IR (film): 3063, 3001, 2962, 2932, 2862, 1971, 1742, 1703, 1593, 1568, 1477, 1464, 1429, 1381, 1302, 1267, 1211, 1190, 1153, 1122, 1090, 1072, 1036, 997, 976, 947, 903, 883, 862, 845, 825, 779, 760, 744, 683, 671, 646, 615 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{11}H_8F_3Br$) requires *m/z* 275.9761, found *m/z* 275.9781 (2.0 mmu).



4.3u

3-(1,1,1-Trifluoropenta-2,3-dien-2-yl)benzaldehyde

General procedure E was followed using **4.1u** (66 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 60 °C for 24 h. Workup and chromatographic purification (hexanes / EtOAc 49:1 → 9:1) afforded the title compound as a yellow oil (19 mg, 43%). Analysis of the ^{1}H NMR spectrum revealed a 1:25 ratio of **4.2u** : **4.3u**.

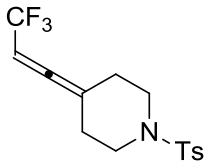
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.04 (s, 1 H), 7.94–7.91 (m, 1 H), 7.83 (dt, *J* = 7.7, 1.4 Hz, 1 H), 7.70 (ddt, *J* = 7.9, 2.0, 1.0 Hz, 1 H), 7.55 (t, *J* = 7.7 Hz, 1 H), 6.02 (qd, *J* = 7.4, 3.7 Hz, 1 H), 1.93 (d, *J* = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 205.4 (q, *J* = 4.0 Hz), 192.0, 136.9, 132.8 (t, *J* = 1.6 Hz), 131.6, 129.5, 129.2, 128.4, 123.3 (q, *J* = 273.9 Hz), 100.5 (q, *J* = 35.0 Hz), 95.9, 13.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.53 (d, *J* = 3.1 Hz, 3 F).

IR (film): 3067, 2961, 2930, 2853, 2822, 2729, 1961, 1707, 1601, 1583, 1485, 1443, 1398, 1373, 1310, 1246, 1194, 1157, 1121, 1070, 1034, 982, 968, 916, 837, 800, 733, 692, 681, 660, 646, 590, 538 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M+H]^+$ ($C_{12}H_{10}OF_3$) requires *m/z* 227.0684, found *m/z* 227.0671 (1.3 mmu).



4.3v

1-Tosyl-4-(3,3,3-trifluoroprop-1-en-1-ylidene)piperidine

General procedure F was followed using **4.1v** (87 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), terpy (4.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 60 °C for 24 h. Workup (DCM used in place of EtOAc for extraction) and chromatographic purification (DCM) afforded the title compound as a colorless solid (41 mg, 62%). Alkyne **4.2v** was not observed by ^{1}H or ^{19}F NMR spectroscopy.

m.p.: 102–103 °C.

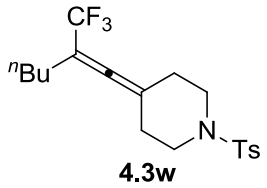
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.63 (m, 2 H), 7.37–7.31 (m, 2 H), 5.35 (qp, *J* = 6.4, 2.2 Hz, 1 H), 3.24 (dt, *J* = 11.3, 5.6 Hz, 2 H), 3.11–3.03 (m, 2 H), 2.45 (s, 3 H), 2.42 (ddt, *J* = 7.0, 3.8, 1.4 Hz, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.2 (q, *J* = 5.8 Hz), 144.0, 133.4, 130.0, 127.7, 122.6 (q, *J* = 270.5 Hz), 105.2, 85.3 (q, *J* = 39.1 Hz), 46.7, 29.5 (q, *J* = 1.3 Hz), 21.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.72 (d, *J* = 6.0 Hz, 3 F).

IR (film): 3032, 2962, 2918, 2849, 1985, 1597, 1464, 1437, 1354, 1339, 1306, 1277, 1250, 1198, 1167, 1122, 1038, 1018, 976, 924, 843, 816, 725, 689, 654, 627, 563 cm^{-1}.

HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{15}H_{16}F_3NO_2SNa$) requires *m/z* 354.0752, found *m/z* 354.0760 (2.3 ppm).



4.3w

1-Tosyl-4-(2-(trifluoromethyl)hex-1-en-1-ylidene)piperidine

General procedure F was followed using **4.1w** (0.20 g, 0.40 mmol), CuI (7.6 mg, 0.040 mmol), phen (7.2 mg, 0.040 mmol), NaO_2CCF_2Br (0.020 g, 0.10 mmol), KF (46 mg, 0.80 mmol), and DMF (0.40 mL) as solvent. The reaction was heated at 60 °C for 24 h. Workup (DCM used in place of EtOAc for extraction) and chromatographic purification (DCM) afforded the title compound as a colorless solid (0.13 g, 81%). Alkyne **4.2w** was not observed by ^{1}H or ^{19}F NMR spectroscopy.

m.p.: 73–74 °C.

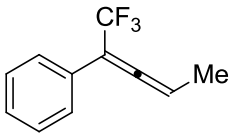
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 3.25 (dt, *J* = 11.2, 5.4 Hz, 2 H), 3.04 (dt, *J* = 11.7, 5.9 Hz, 2 H), 2.46 (s, 3 H), 2.39 (t, *J* = 5.7 Hz, 4 H), 2.09 (t, *J* = 7.0 Hz, 2 H), 1.42 – 1.24 (m, 4 H), 0.85 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 197.1 (q, *J* = 4.4 Hz), 143.9, 133.5, 129.9, 127.7, 123.8 (q, *J* = 273.5 Hz), 105.1, 98.3 (q, *J* = 33.5 Hz), 47.0, 30.0, 29.6, 26.1, 22.0, 21.7, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –65.39 (s, 3 F).

IR (film): 3030, 2959, 2930, 2860, 1979, 1597, 1495, 1466, 1456, 1441, 1427, 1356, 1339, 1290, 1248, 1211, 1198, 1167, 1117, 1103, 1040, 1018, 980, 970, 933, 922, 816, 800, 719, 689, 677, 654, 635 cm^{-1}.

HRMS (ESI^+): mass calculated for $[M+Na]^+$ ($C_{19}H_{24}F_3NO_2SNa$) requires *m/z* 410.1378, found *m/z* 410.1367 (2.7 ppm).



4.3x

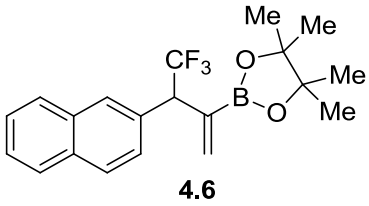
(1,1,1-Trifluoropenta-2,3-dien-2-yl)benzene[17]

General procedure E was followed using **4.1x** (61 mg, 0.20 mmol), CuI (3.8 mg, 0.020 mmol), phen (3.6 mg, 0.020 mmol), NaO_2CCF_2Br (9.8 mg, 0.050 mmol), KF (23 mg, 0.40 mmol), and DMF (0.20 mL) as solvent. After activation, the reaction was heated at 60 °C for 24 h. Workup and chromatographic purification (pentane) afforded the title compound as a colorless oil (17 mg, 42%). Analysis of the ^{1}H NMR spectrum revealed a <1:100 ratio of **4.2x** : **4.3x**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.42 (m, 2 H), 7.40–7.34 (m, 2 H), 7.34–7.28 (m, 1 H), 5.93 (qq, *J* = 6.9, 3.2 Hz, 1 H), 1.89 (d, *J* = 7.3 Hz, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.46 (d, *J* = 3.1 Hz, 3 F).

Functionalization Reactions of Trifluoromethylallenes:



4.6

4,4,5,5-Tetramethyl-2-(4,4,4-trifluoro-3-(naphthalen-2-yl)but-1-en-2-yl)-1,3,2-dioxaborolane

In a N_2 filled glovebox, a 15 mL screw-top vial was charged with CuCl (1.0 mg, 0.010 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (4.3 mg, 0.010 mmol), NaO^tBu (7.7 mg, 0.080 mmol) and THF (1.0 mL), and the solution was stirred for 1 h.

Bis(pinacolato)diboron (56 mg, 0.22 mmol) was added, and the mixture was stirred for 30 min. Allene **4.3o** (47 mg, 0.20 mmol) and MeOH (49 µL, 1.2 mmol) were added, and the vial was sealed and removed from the glovebox and stirred for 14 h. The mixture was filtered through a pad of SiO_2, and the pad was rinsed with Et_2O (3 x 4 mL). The solvent was removed *in vacuo* to provide a brown oil. Chromatographic purification (hexanes / EtOAc 1:0 → 19:1) afforded the title compound as a colorless solid (59 mg, 82%).

m.p.: 84–86.

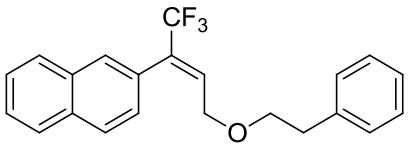
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88–7.79 (m, 4 H), 7.53–7.44 (m, 3 H), 6.20 (s, 1 H), 6.07 (s, 1 H), 4.57 (q, *J* = 9.8 Hz, 1 H), 1.19 (s, 6 H), 1.09 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 135.5, 133.3, 132.9, 132.2, 132.2, 129.1, 128.2, 128.1, 127.7, 127.6, 126.5 (q, *J* = 281.3 Hz), 126.3, 126.2, 84.1, 52.6 (q, *J* = 26.8 Hz), 24.8, 24.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ –66.62 (d, *J* = 9.7 Hz).

IR (film): 3059, 2978, 2930, 1701, 1622, 1601, 1437, 1381, 1373, 1362, 1337, 1321, 1258, 1213, 1140, 1097, 964, 872, 856, 843, 816, 746, 723 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{20}H_{22}O_2F_3B$) requires *m/z* 362.1665, found *m/z* 362.1667 (0.6 ppm).



4.7

(*E*)-2-(1,1,1-Trifluoro-4-phenethoxybut-2-en-2-yl)naphthalene

In a N_2 filled glovebox, a 15 mL screw-top vial was charged with chloro[1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene]gold(I) (12 mg, 0.020 mmol), AgOTf (5.2 mg, 0.020 mmol), and PhMe (0.20 mL). The mixture was stirred for 5 min, after which a solution of allene **4.3o** (47 mg, 0.20 mmol) and 2-phenylethanol (26 µL, 0.22 mmol) in PhMe (0.30 mL) was injected. The vial was sealed and removed from the glovebox. After stirring for 36 h at rt, the solvent was removed *in vacuo*. Chromatographic purification (hexanes / DCM 1:0 → 4:1) afforded the title compound as a colorless oil (56 mg, 78%).

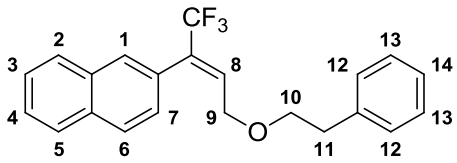
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92–7.83 (m, 3 H), 7.72 (s, 1 H), 7.59–7.51 (m, 2 H), 7.35 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.32–7.26 (m, 2 H), 7.24–7.21 (m, 1 H), 7.21–7.17 (m, 2 H), 6.64 (tq, *J* = 5.9, 1.5 Hz, 1 H), 4.02 (dq, *J* = 6.1, 2.0 Hz, 2 H), 3.59 (t, *J* = 7.1 Hz, 2 H), 2.86 (t, *J* = 7.1 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 138.7, 133.7 (q, *J* = 5.4 Hz), 133.3, 133.1 (q, *J* = 30.2 Hz), 133.0, 129.1, 129.0, 129.0, 128.5, 128.4, 128.3, 127.9, 127.0, 126.7, 126.7, 126.4, 123.3 (q, *J* = 273.4 Hz), 71.9, 67.2, 36.4.

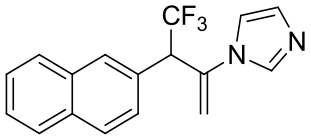
^{19}F NMR (376 MHz, $CDCl_3$): δ –66.81 (m, 3 F).

IR (film): 3061, 3021, 2935, 2920, 2862, 1601, 1504, 1497, 1477, 1454, 1350, 1331, 1296, 1244, 1177, 1163, 1121, 999, 968, 926, 899, 860, 820, 750, 719, 698 cm^{-1}.

HRMS (APCI–hexane/PhMe): mass calculated for $[M]^+$ ($C_{22}H_{19}OF_3$) requires *m/z* 356.1388, found *m/z* 356.1374 (3.9 ppm).



position	^{1}H NMR			NOESY
	δ	multiplicity	*J* (Hz)	correlations
1	7.72	s	–	2, 9
2	7.87–7.83	m	–	1, 3
3	7.59–7.51	m	–	2, 4
4	7.59–7.51	m	–	3, 5
5	7.92–7.83	m	–	4, 6
6	7.92–7.83	m	–	5, 7
7	7.35	dd	8.5, 1.7	6, 9
8	6.64	tq	5.9, 1.5	9, 10
9	4.02	dq	6.1, 2.0	1, 7, 8, 10, 11
10	3.59	t	7.1	8, 9, 11, 12
11	2.86	t	7.1	9, 10, 12
12	7.21–7.17	m	–	10, 11, 13
13	7.32–7.26	m	–	12, 14
14	7.24–7.21	m	–	13



4.9

1-(4,4,4-Trifluoro-3-(naphthalen-2-yl)but-1-en-2-yl)-1H-imidazole

In a N_2 filled glovebox, a 15 mL screw-top vial was charged with allylpalladium(II) chloride dimer (1.8 mg, 0.0050 mmol), 1,1'-bis(diphenylphosphino)ferrocene (5.5 mg, 0.010 mmol), and THF (0.50 mL). The mixture was stirred for 5 min, after which allene **4.3o** (47 mg, 0.20 mmol) and imidazole (16 mg, 0.24 mmol) were added. The vial was

sealed, removed from the glovebox, and placed in a 80 °C oil bath. After 24 h, the mixture was allowed to cool to rt and the solvent was removed *in vacuo*. Chromatographic purification (DCM / MeOH 1:0 → 19:1) afforded the title compound as an amorphous brown solid (41 mg, 67%).

^{1}H NMR (400 MHz, C_6D_6): δ 7.56–7.44 (m, 4 H), 7.27 (s, 1 H), 7.23–7.17 (m, 2 H), 7.14–7.08 (m, 1 H), 7.01 (s, 1 H), 6.38 (t, *J* = 1.3 Hz, 1 H), 5.08 (m, 1 H), 4.86 (m, 1 H), 4.07 (q, *J* = 8.9 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 137.3, 136.1, 133.5, 133.3, 130.2, 129.3, 129.2, 128.4, 128.2, 127.9, 127.2, 127.0, 126.0, 124.9 (q, *J* = 280.4 Hz), 118.0, 111.2 (q, *J* = 2.1 Hz), 54.8 (q, *J* = 28.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ –67.34 (d, *J* = 8.6 Hz).

IR (film): 3113, 3057, 3024, 2918, 1653, 1601, 1510, 1487, 1373, 1348, 1315, 1256, 1163, 1126, 1107, 1072, 1005, 903, 858, 818, 748, 689, 658 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{14}F_3N_2$) requires *m/z* 303.1109, found *m/z* 303.1101 (2.6 ppm).

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