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A Base-Promoted Reductive Coupling Platform for the Divergent Defluorofunctionalization of Trifluoromethylarenes

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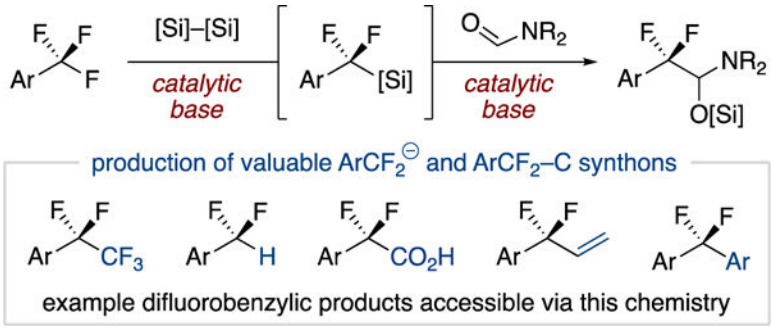
Abstract

We report a trifluoromethylarene reductive coupling method that dramatically expands the scope of difluorobenzylic substructures accessible *via* C–F bond functionalization. Catalytic quantities of a Lewis base, in conjunction with a disilane reagent in formamide solvent, leads to the replacement of a single trifluoromethyl fluorine atom with a silylated hemiaminal functional group. The reaction proceeds through a difluorobenzyl silane intermediate that can also be isolated. Together, these defluorinated products are shown to provide rapid access to over 20 unique difluoroalkylarene scaffolds.

Graphical Abstract



The α,α-difluorobenzylic substructure ($ArCF_2R$) is often studied in pharmaceutical and agrochemical research as a means to modulate bioavailability and metabolic stability, amongst other potential benefits of fluorine incorporation.[1] A key feature of an aromatic difluoroalkyl substituent is the structural modularity possible *via* the R group, allowing further optimization of a compound's desired properties. The challenge of exploring this chemical space lies in the lack of general methods to access derivatives from a single precursor, typically requiring the synthesis of a unique reagent for each target of interest.[2] For example, carbonyl deoxyfluorination[3,4] and cross-coupling[5] reactions are commonly

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ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization data for all compounds (PDF).

used to access such motifs, but these routes first require access to the carbonyl or RCF_2X coupling partner, respectively.[6] Therefore, a method that can access valuable α,α-difluorobenzylic frameworks in a diversifiable fashion could greatly accelerate investigation of this substructure.[7]

The C–F functionalization of trifluoromethylarenes is an ideal route to α,α-difluorobenzylic compounds due to the wide availability of trifluoromethylarenes and their prevalence in late-stage settings.[8] The impact of such methodology hinges on the ability to access α,α-difluorobenzylic derivatives that reflect the structural diversity found in bioactive compounds (Figure 1).[9] A major challenge for the single C–F substitution of a trifluoromethyl group is the fact that the C–F bonds become weaker as defluorination proceeds[10], typically resulting in overfunctionalization.[11] Early efforts to address this challenge using electrochemical[12] and metal[13] reducing conditions are either limited to simple trifluoromethylbenzenes or are unselective. Recent reports by König, Jui, and Gouverneur use photoredox catalysis to achieve monoselective C–F reduction and hydroalkylation on a wide range of trifluoromethylarenes.[14] An alternative strategy reported by Young employs frustrated Lewis pairs to form C–F substituted pyridinium and phosphonium salts, primarily used as electrophilic difluorobenzylic reagents.[15,16] Despite these impressive advancements, there is still the need for a unified method that accesses a greater breadth of α,α-difluorobenzylic substructures from trifluoromethylarenes.

Our group recently reported a fluoride-initiated protocol for the selective defluoroallylation of trifluoromethylarenes using allyltrimethylsilane coupling partners (Figure 2a).[17,18] While practical, this reaction can only access difluoroalkyl substituents that map onto the allyl coupling fragment. To address this limitation, we herein report the development of a base-initiated, silane-mediated, reductive coupling platform of trifluoromethylarenes (Figure 2b). This method expands the C–F transformations accessible from trifluoromethylarenes by providing a versatile silylated hemiaminal synthon that possesses the reactivity of both an aldehyde and an iminium ion. The identification of a difluorobenzyl silane as the key intermediate for the reductive coupling reaction also allowed for its isolation and use as a general difluorobenzylic pronucleophile.

This work began with the goal of discovering a single silane reagent that couples with trifluoromethylarenes to generate synthetically versatile difluorobenzylic products. While investigating disilane[19] coupling partners, we observed that catalytic activation of commercially available tris(trimethylsilyl)silane (TTMSS) with Lewis basic salts in DMF generates silylated hemiaminal adduct **2** (Scheme 1). Given that a silylated hemiaminal could potentially serve as a branching point for a wealth of derivatization reactions, we sought to further optimize this reaction. Notably, similar silylated hemiacetal and hemiaminal adducts were proposed as intermediates in Lalic's dual Pd/Cu-catalyzed selective trifluoromethylarene reduction protocol that is conducted with triphenylsilane in DMF.[20] Strong Lewis bases, such as fluoride and alkoxide salts, provide low yields of **2**, while carboxylate salts lead to significantly higher yields (entries 1–3). Ultimately, we found 18-crown-6-ligated cesium formate to be the optimal catalyst system (76% yield, entry 4). The reaction proceeds in slightly lower yield without 18-crown-6 (63%, entry 5) or using tetrabutylammonium acetate (69%, entry 6). Other commercial disilanes are less effective

at promoting this reaction (entries 7 and 8). Unfortunately, all attempts to isolate product **2** *via* chromatography resulted in decomposition. Evaluation of other formamides led to the identification of 4-formylmorpholine (4FM) in NMP (1:1 mixture) as a satisfactory substitute for DMF, providing chromatographically stable **3** in 66% isolated yield (Scheme 1b, entry 10). Benzotrifluoride can also be used as a cosolvent (entry 11) and, for some substrates, results in improved yields (*vide infra*).

Table 1 shows representative trifluoromethylarenes that are amenable to the base-promoted coupling reaction. 1,3-Bis(trifluoromethyl)arenes are effective substrates, including when scaled to 10 mmol (**3**) or with free phenolic O–H (**4**) and terminal alkene (**5**) functional groups. Sulfonamide (**6,** characterized by X-ray crystallography) and phosphonate ester (**7**) aryl substituents also sufficiently activate the trifluoromethylarene towards functionalization. Heteroaryl and drug-like trifluoromethylarenes are also effective, including 2-, 3- and 4-trifluoromethylpyridines (**8–11**), a benzylated aprepitant precursor (**12**) and a fluoxetine-trifluoromethylpyrimidine derivative (**13**) that selectively couples at the electron-deficient heteroarene. Under the current reaction conditions, trifluoromethylbenzenes that lack an electron-withdrawing group do not react, while substrates with electrophilic functional groups (e.g. ketone) undergo competitive side reactions with the silane.[21]

We expected these silylated hemiaminal products to be versatile synthetic intermediates based on their resemblance to reported trifluoromethyl formamide adducts.[22] The diversity of difluorobenzylic frameworks accessible from the silylated hemiaminal unit is demonstrated in Scheme 2, with sixteen transformations shown starting from product **3** (prepared on multigram scale). These reactions employ common reagents and require one purification step, with detailed procedures described in the Supporting Information (Section VII, pages S14–25). Numerous reactions can be conducted directly with the silylated hemiaminal (Scheme 2a), including cleavage to a deuterated difluoromethylarene (**14**), condensation to an oxime (**15**), condensation-dehydration to a nitrile (**16**), a Petasis-type styrenylation process (**17**), oxidation to an amide (**18**), reduction to a tertiary amine (**19**), and a Mannich-type addition reaction (**20**). Conversion of **3** into a hemiacetal is facile with catalytic acid in ethanol without the need for isolation.[23,24] From this intermediate, many transformations are possible (Scheme 2b), including reduction (**21**), reductive amination (**22**), Wittig (**23**, **24**), heterocycle condensation (**25**), Henry (**26**), oxidation (**27**), cyanide addition (**28**) and silylation (**29**) reactions.

An additional application of this method is its use for late-stage C–F functionalization *via* sequenced reductive coupling and derivatization. A series of pharmaceutical derivatives and drug-like structures are shown in Scheme 3 that underwent defluorofunctionalization using one total purification step. This includes trifluoromethylaryl derivatives of apriprazole (**30** and **31**), fluoxetine (**34**) and bepotastine (**35**), as well as an aprepitant precursor (**32** and **33**) and a trifluoromethylquinoline substrate (**36**). These examples demonstrate the ability to modify trifluoromethyl substituents of bioactive compounds, as well as the ability to carry the typically inert trifluoromethyl group through multistep syntheses before derivatization.

Insight into the mechanism of this reductive coupling process first came while varying the reaction conditions. We observed the product identity to be dependent on the solvent

used; in NMP, the major product is difluorobenzylsilane **37**, and in MeCN, the major product is difluoromethylarene **38** (Figure 3a).[25] We reasoned that formation of the benzylsilane (**37**) and subsequent *in situ* base-promoted desilylation could explain the solvent dependence.[26] Subjection of benzylsilane **37** to cesium formate in MeCN or DMF provides difluoromethylarene **38** or silylated hemiaminal **2**, respectively (Figure 3b).[27] A profile of the model reaction in DMF shows the concurrent formation of benzylsilane **37** and the silylated hemiaminal **2**, and once the trifluoromethylarene has been consumed, the remaining benzylsilane is converted to the silylated hemiaminal (Figure 3c). These observations support defluorosilylation as the key process en route to the formamide addition product **2**. Each reaction of this sequence generates an anion (fluoride or oxyanion) that could regenerate the formate anion or propagate silane activation *via* an anionic chain process, explaining why only catalytic quantities of formate salt are required (Figure 3d).[28]

Defluorosilylation likely occurs *via* initial formation of a silicate[29] or silyl anion from TTMSS[30,31], and we have obtained evidence that both TMS and $HSi(TMS)_2$ anions may be generated under the reaction conditions.[32,33] As silyl anions are known to be potent reductants[34], bases[35] and halophilic nucleophiles[36], numerous mechanistic pathways for defluorosilylation seem plausible. Interestingly, when TTMSS is replaced with other disilane reagents (e.g. Si_2Me_6 or $Si(TMS)_4$) for the model reaction, consumption of the trifluoromethylarene is observed but with little formation of the hemiaminal product.[37] These comparisons indicate TTMSS strikes the right balance of Lewis acidity and capability of silyl anion generation to mediate the selective reductive coupling reaction. Details of these control studies and a discussion of possible pathways for the initiation of this reaction are provided in the Supporting Information. Investigations are underway to gain more insight into the defluorosilylation process and to identify disilanes that can activate a wider scope of trifluoromethylarenes.[38,39]

The discovery of a defluorosilylation pathway provides an opportunity to expand the scope of accessible C–F coupling products. Use of the α,α-difluorobenzylsilane as a masked carbanion can access derivatives that are challenging to prepare from the hemiaminal intermediates.[26] The model defluorosilylation product **37** was first isolated from a reaction conducted in NMP on a 5 mmol scale in 40% yield. From **37**, our recently reported fluoride-promoted protocol for benzylsilane cross-coupling to aryl nitriles can be used to generate defluoroarylation products (Scheme 4a).[40] This route provides an alternative to Zhang's recently developed light-promoted Pd-catalyzed trifluoromethylarene C–F arylation method.[41]

We also sought to show how defluorosilylation could serve as an entry to assembling difluoroalkylarene libraries with minor structural differences (Scheme 4b). Fluoride-activation of **37** promotes facile substitution with alkyl iodides, providing the defluoromethylation product (**41**), its isotopologues (**42** and **43**), and the ethyl derivative (**44**). Substitution using Togni reagent II[42] provides pentafluoroethyl product **45**, thus accomplishing a net extension of a trifluoromethyl substituent into a pentafluoroethyl group.

In summary, this reductive coupling platform expands the scope of α,α-difluorobenzylic substructures accessible from trifluoromethylarenes to better reflect the structural diversity

found in bioactive compounds (Figure 1). The reaction leverages the continuous generation of anionic intermediates to propogate a disilane-mediated defluorosilylation and formamide addition sequence. This ensemble allows a trifluoromethyl C–F bond to formally serve as a masked nucleophile, thus delivering new difluoroalkylarene synthetic linchpins.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(27). Because the yield of **38** is low under the “standard conditions” for the experiment shown in Figure 3b, we conducted additional control experiments that could mimic the conditions typical of the defluorofunctionalization reactions in Figure 3a. Thus, use of catalytic CsF as a base, which is formed as an intermediate under the defluorosilylation reaction conditions, promotes the desilylation reactions shown in Figure 3b in high yield. These results are shown as footnote a in Figure 3 and described in the Supporting Information.

(28). Mixing fluoride salts with trimethylsilylated carboxylates (RCO2TMS) rapidly releases the carboxylate anion and forms fluorotrimethylsilane. This observation, and the fact that use of fluoride as an initiator for the model reaction (Scheme 1, entry 1) leads to low yields, leads us to hypothesize that cesium formate is continuously generated under the reaction conditions and is acting as a true catalyst.

(29). For reviews on base activation of organosilanes, see: (a) Chuit C; Corriu RJP; Reye C; Young JC Reactivity of penta- and hexacoordinate silicon compounds and their role as reaction intermediates. Chem. Rev 1993, 93, 1371–1448.(b)Reich HJ Mechanism of C–Si Bond Cleavage Using Lewis Bases (n → σ*). In Lewis Base Catalysis in Organic Synthesis, Vol. 1; Wiley-VCH, 2016; pp 233–280.(c)García-Domínguez A; Leach AG; Llyod-Jones GC *In Situ* Studies of Arylboronic Acids/Esters and R_3SiCF_3 Reagents: Kinetics, Speciation, and Dysfunction at the Carbanion–Ate Interface. Acc. Chem. Res 2022, 55, 1324–1336. [PubMed: 35435655]

(30). For reviews on silyl anion generation and reactivity, see: (a) Lickiss P D; Smith, C. M. Silicone derivatives of the metals of groups 1 and 2. Coord. Chem. Rev 1995, 145, 75–124.(b)Tamao K; Kawachi A Silyl Anions. In Advances in Organometallic Chemistry, Vol. 38; Academic Press, 1995, 38, pp 1–58.(c)Marschner C Chapter 7 – Silicon-Centered Anions. In Organosilicon Compounds, Vol. 1; Academic Press, 2017, pp 295–360.

(31). For reviews on the use of TTMSS, see: (a) Giese B; Dickhaut J; Chatgilialoglu C; Wu X; Zhang Z Tris(trimethylsilyl)silane. In Encyclopedia of Reagents for Organic Synthesis; Wiley, 2022. Updated January 28, 2022. DOI: 10.1002/047084289X.rt420.pub3.(b)Chatgilialoglu C; Ferreri C; Landais Y; Timokhin VI Thirty Years of $(TMS)_3SiH$: A Milestone in Radical-Based Synthetic Chemistry. Chem. Rev 2018, 118, 6516–6572. [PubMed: 29938502]

(32). It is well known that Lewis base activation of tetrakis(trimethylsilyl)silane ($Si(TMS)_4$) can generate the $Si(TMS)_3$ anion; see ref 30c. Similarly, it has been observed that Lewis base activation of TTMSS can generate the $HSi(TMS)_2$ anion; see: (a) Marschner C A New and Easy Route to Polysilanylpotassium Compounds. Eur. J. Inorg. Chem 1998, 221–226.

(33). As control experiments, we subjected TTMSS and cesium formate in DMF at rt to various electrophiles in place of trifluoromethylarenes. We observed substitution products that most likely arise from generation of both the TMS and $HSi(TMS)_2$ anions; see Supporting Information for full details. Thus, we cannot rule out the generation of either silyl anion under the standard reaction conditions.

(34). (a) Sakurai H; Akane O; Umino H; Kira M Silyl anions. IV. New convenient method of producing radical anions involving one-electron transfer from trimethylsilylsodium. J. Am. Chem. Soc 1973, 95, 955–956.(b)Hideki S; Mitsuo K; Hiroshi U Silyl Anions VII. Electron Transfer From Trimethylsilylpotassium To Benzophenone And Naphthalene. Generation Of Anion Radicals In Nonpolar Solvents Such As n-Hexane. Chem. Lett 1977, 6, 1265–1268. (c)Smith AJ; Young A; Rohrbach S; O'Connor EF; Allison M; Wang H-S; Poole DL; Tuttle T; Murphy JA Electron-Transfer and Hydride-Transfer Pathways in the Stoltz–Grubbs Reducing System (KO*t*Bu/Et_3SiH). Angew. Chem. Int. Ed 2017, 56, 13747–13751.

(35). For pK_a values of organosilanes, see: Fu Y; Liu L; Li R-Q; Liu L; Guo Q-X First-Principal Predictions of Absolute pK_a's of Organic Acids in Dimethyl Sulfoxide Solution. J. Am. Chem. Soc 2003, 126, 814–822.

(36). For representative halophilic substitution processes involving silyl anions, see: (a) Shippey MA; Dervan PB Trimethylsilyl Anions. Direct Synthesis of Trimethylsilylbenzenes. J. Org. Chem. 1977, 42, 2654–2655.(b)Uematsu R; Yamamoto E; Maeda S; Ito H; Taketsugo T Reaction Mechansim of the Anomalous Formal Nucleophilic Borylation of Organic Halides with Silylborane: Combined Theoretical and Experimental Studies. J. Am. Chem. Soc 2015, 137, 4090–4099. [PubMed: 25773395]

(37). Use of other disilanes in place of TTMSS results in low yields of **2** and/or poor mass balance of **1**; these studies are described in the Supporting Information. The disilane must be capable of being activated by the Lewis base to promote defluorosilylation. The inability of hexamethyldisilane, which can only generate the TMS anion, to promote the reaction in high yield suggests that the role of TTMSS constitutes more than just the generation of a TMS anion.

(38). TTMSS is known to readily generate the $Si(TMS)_3$ radical and engage in radical-based reactions (see ref 31). However, replacement of H in TTMSS with other substituents (e.g. alkyl or amino groups) still results in some yield of **2** for the model reaction, suggesting the Si–H bond is not critical for the reaction mechanism. Furthermore, replacement of cesium formate with radical initiators (e.g. AIBN and benzoyl peroxide) results in no reductive coupling reaction. As another control, a reaction conducted with catalytic TTMSS and stoichiometric $Si(TMS)_4$ provided only low yields of product. Additionally, our optimization studies show that acetate bases perform similarly to formate bases, indicating that formate does not act as a reductant or radical anion precursor in this reaction; see: Hendy CM; Smith GC; Xu Z; Lian T; Jui NT Radical Chain Reduction via Carbon Dioxide Radical Anion ($CO2^{\bullet-}$). J. Am. Chem. Soc 2021, 143, 8987–8992. [PubMed: 34102836]

(39). For base-promoted defluorosilylation of aryl and alkyl fluorides, see: Liu X-W; Zarate C; Martin R Base-Mediated Defluorosilylation of $C(sp^2)$–F and $C(sp^3)$–F Bonds. Angew. Chem. Int. Ed 2019, 58, 2064–2068.

(40). (a) Reidl TW; Bandar JS Lewis Basic Salt-Promoted Organosilane Coupling Reactions with Aromatic Electrophiles. J. Am. Chem. Soc 2021, 143, 11939–11945. [PubMed: 34314159] (b) see also ref 26b.

(41). (a) Luo Y-C; Tong F-F; Zhang Y; He C-Y; Zhang X Visible-Light-Induced Palladium-Catalyzed Selective Defluoroarylation of Trifluoromethylarenes with Arylboronic Acids. J. Am. Chem. Soc 2021, 143, 139741–13979. (b) For several examples of formal defluoroarylation using aryl boronic acid coupling partners *via* Young's frustrated Lewis pair approach, see ref 15b.

(42). Charpentier J; Früh N; Togni A Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. Chem. Rev 2015, 115, 650–682 [PubMed: 25152082]

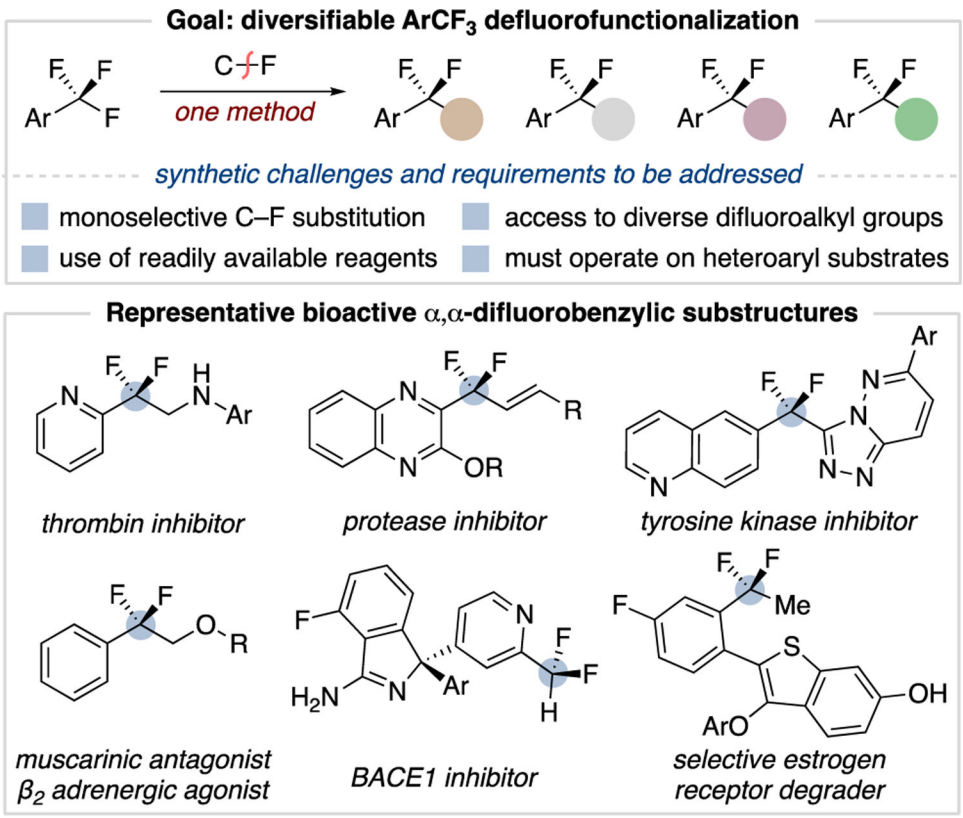


Figure 1.
Goals for defluorofunctionalization methodology.

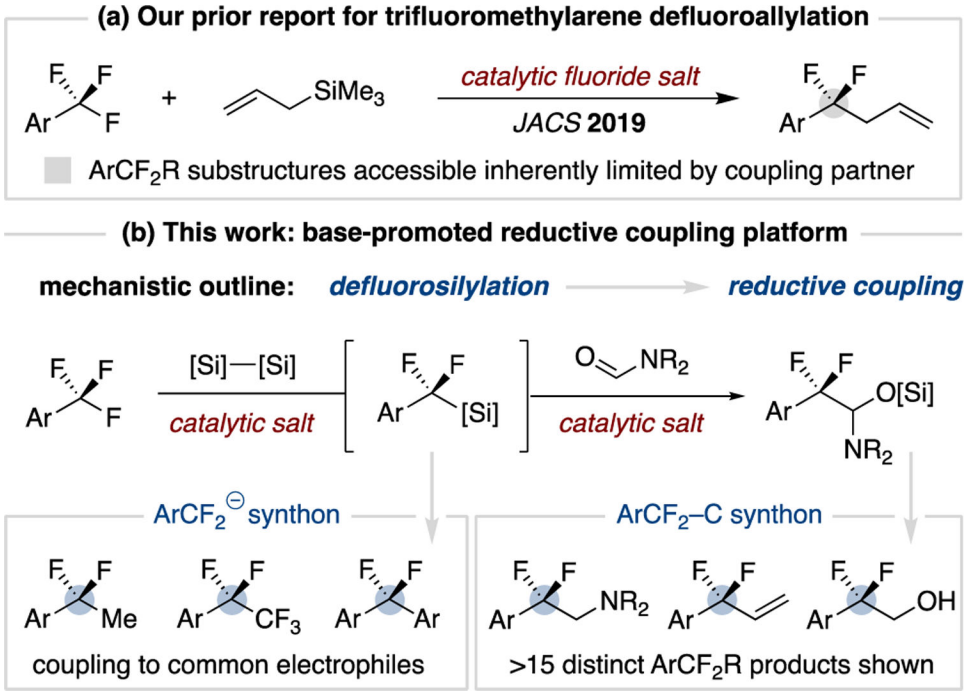


Figure 2.
Overview of base-promoted $ArCF_3$ functionalization.

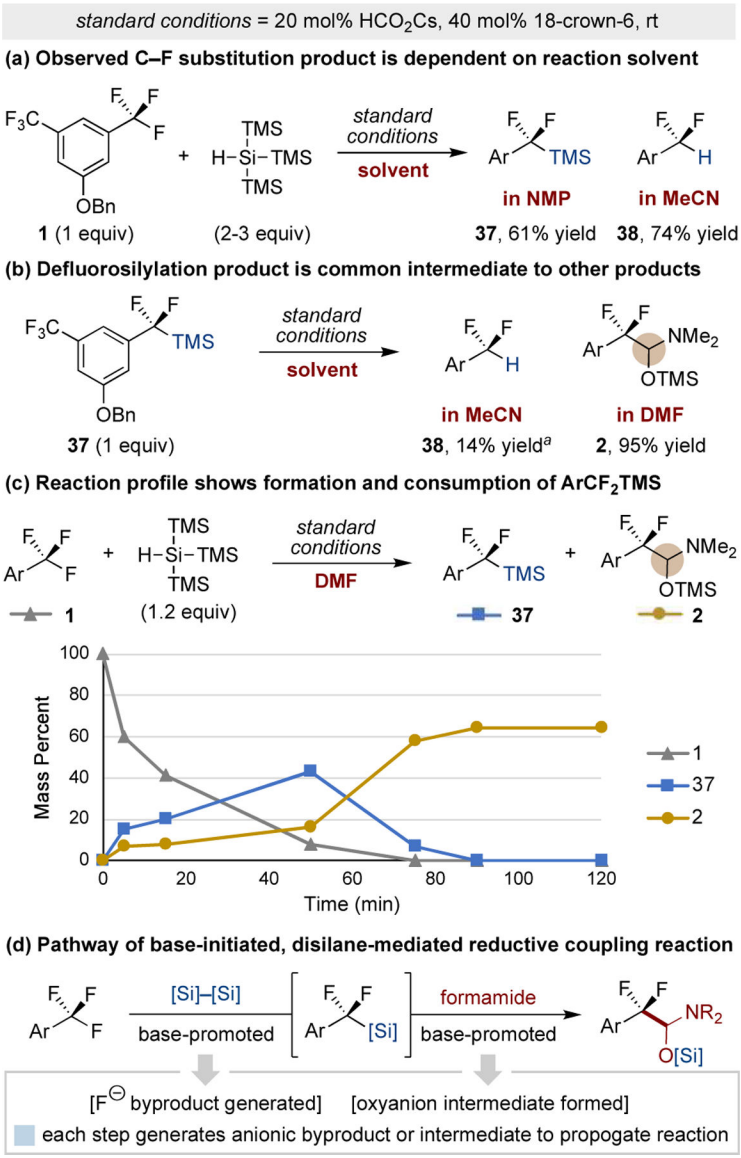
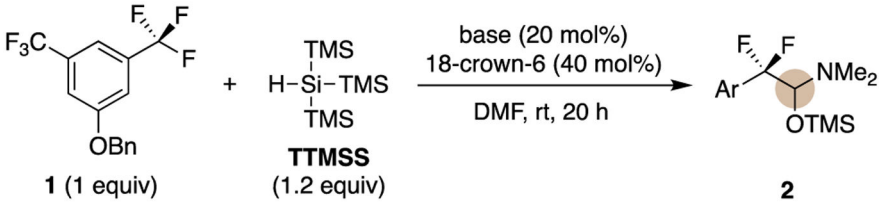


Figure 3.

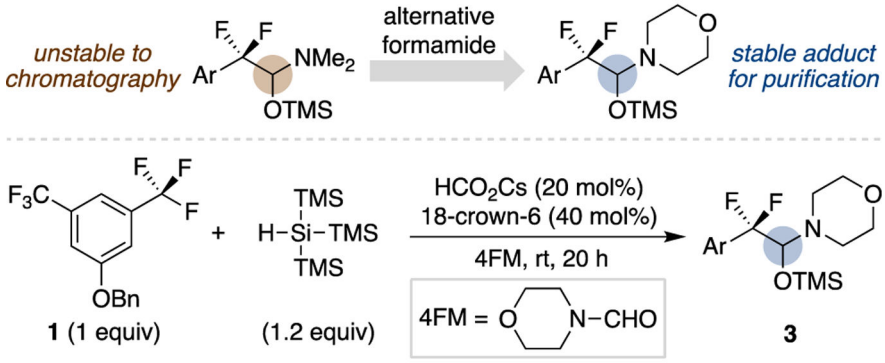
Studies and observations into reaction mechanism. Yields determined by ^{1}H or ^{19}F NMR spectroscopy. [a] Under alternative conditions, the yield of **38** is 86% if the reaction is conducted at 80 °C and 80% if CsF is used at rt in place of HCO_2Cs.

(a) Discovery and optimization of $ArCF_3$ reductive C–F coupling to DMF



Entry	Base	Variation to above conditions	Yield (2)[a]
1	CsF	-	5%
2	KOMe	-	30%
3	HCO_2K	-	42%
4	HCO_2Cs	-	76% (0%)[b]
5	HCO_2Cs	no 18-crown-6	63%
6	Bu_4NOAc	no 18-crown-6	69%
7	HCO_2Cs	Si_2Me_6 instead of TTMSS	0%
8	HCO_2Cs	$Si(TMS)_4$ instead of TTMSS	7%

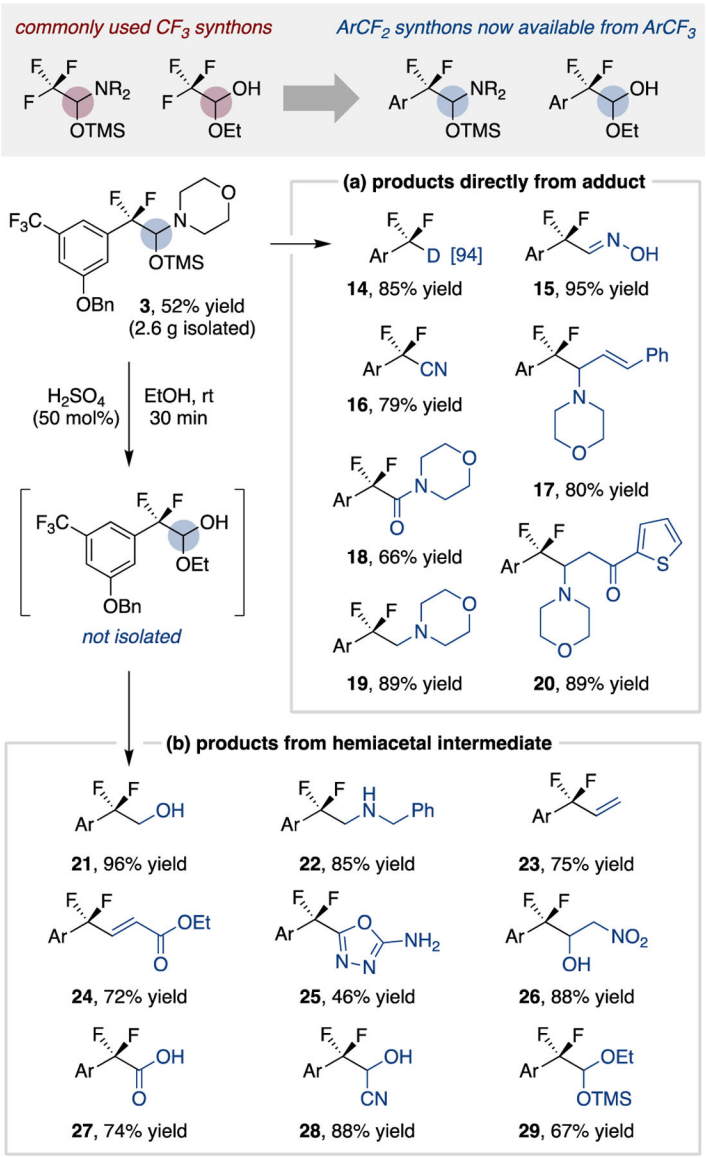
(b) Identification of a chromatography-stable silylated hemiaminal adduct



Entry	Variation to above conditions	Yield (3)[a]
9	-	38%
10	4FM/NMP (1:1) as solvent	69% (66%)[b]
11	4FM/$PhCF_3$ (1:1) as solvent	68%

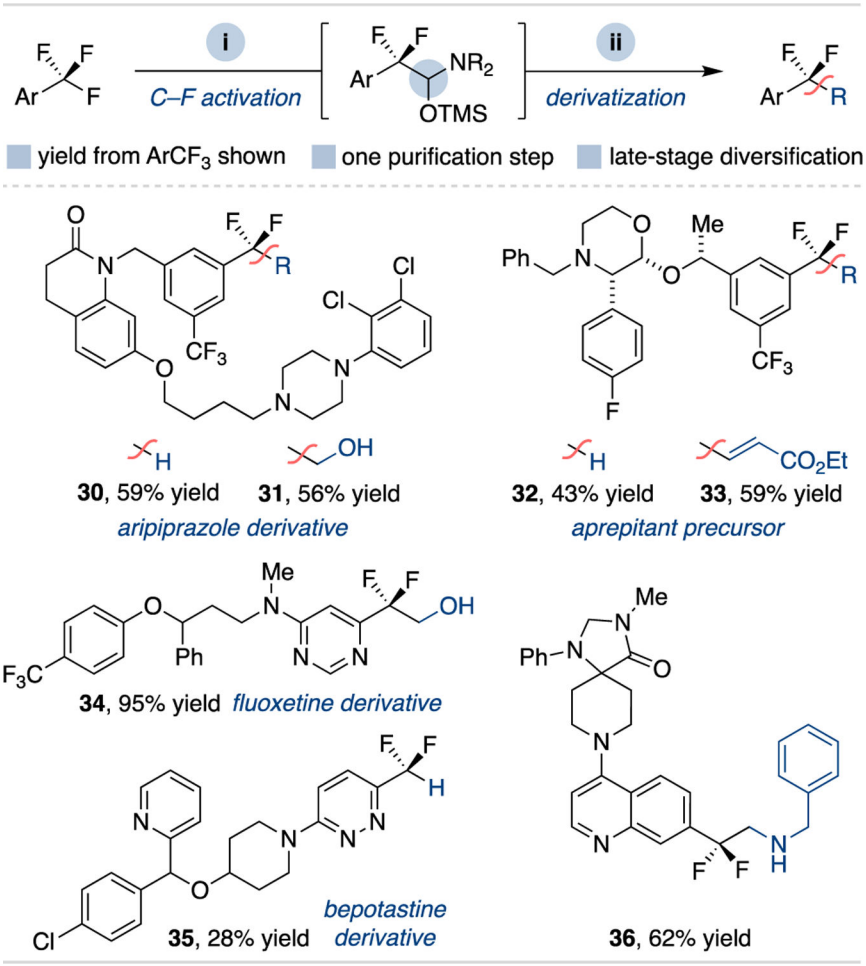
Scheme 1. Development of $ArCF_3$ reductive coupling reaction.

[a] Yields determined by ^1H NMR spectroscopy. [b] Yields in parentheses are isolated yields by column chromatography.



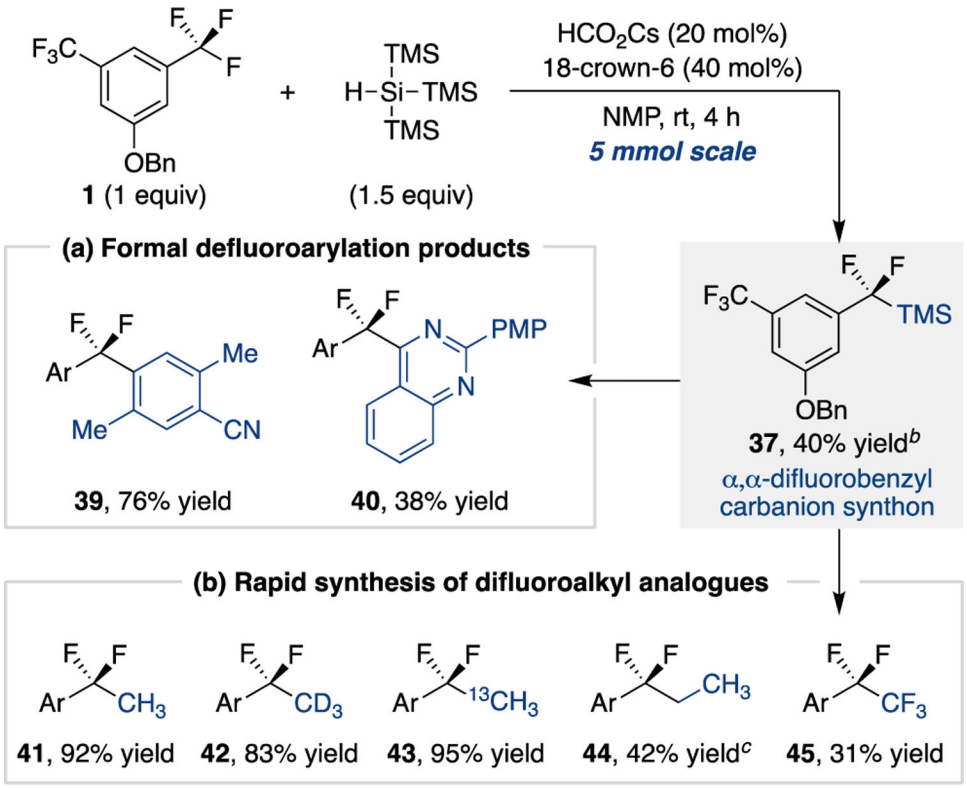
Scheme 2. Synthetic utility of hemiaminal adduct.[a]

[a] Isolated product yields; see Supporting Information for full synthetic details for each derivatization reaction.



Scheme 3. Divergent late-stage $ArCF_3$ C–F functionalization.[a]

[a] Isolated product yields starting from trifluoromethylarene; see Supporting Information for full synthetic details for each entry.

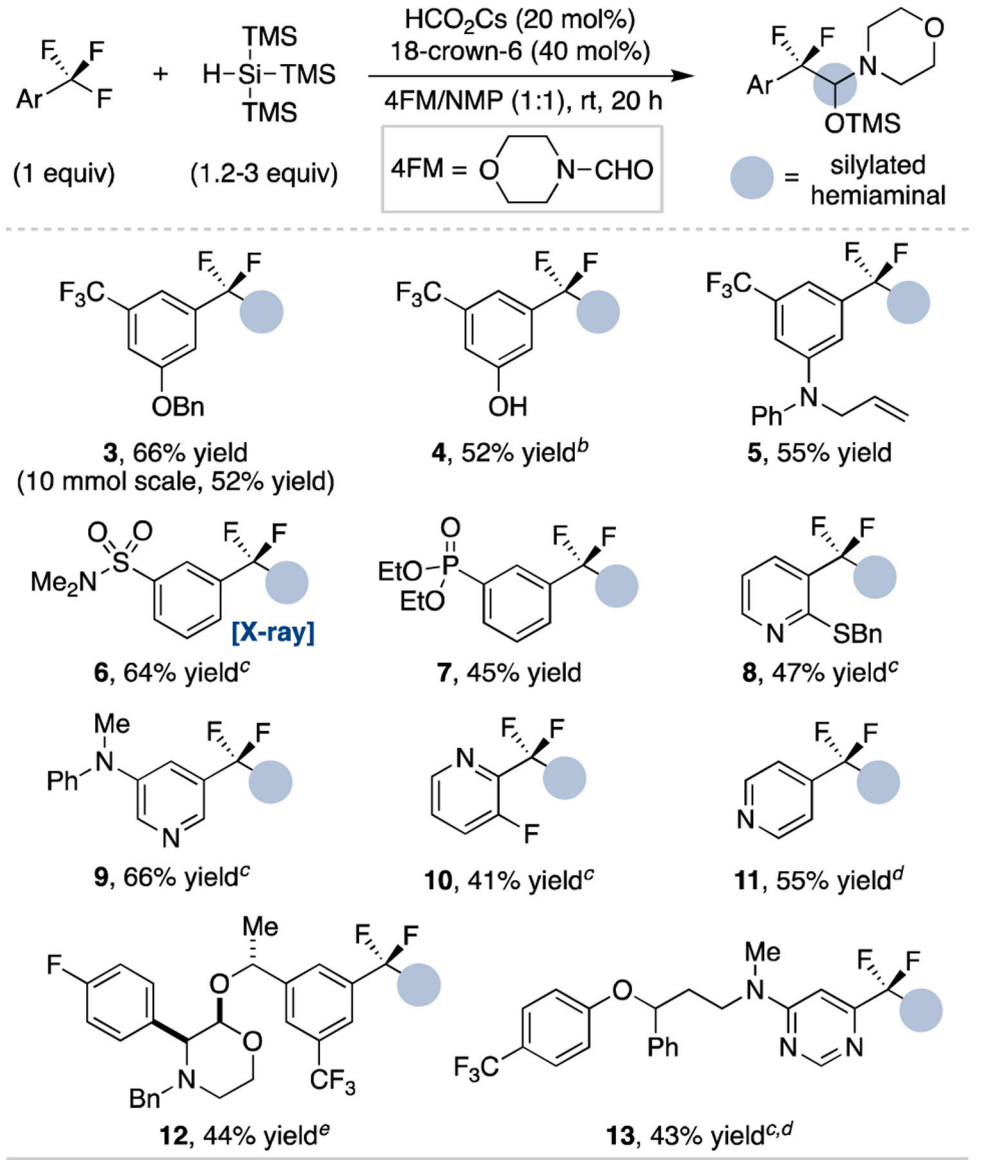


Scheme 4. Isolation and utility of α,α-difluorobenzylsilane.[a]

[a] Isolated product yields; see Supporting Information for full synthetic details for each entry. [b] 53% ^{19}F NMR yield; isolated yield reduced due to coelution with protodesilylated compound **38**. [c] 76% ^{1}H NMR yield; isolated yield reduced due to coelution with protodesilylation side product.

Table 1.

Substrate Scope of Trifluoromethylarenes.[a]



[a]Yields are of purified product on a 0.25–1 mmol scale; see Supporting Information for full details.

[b]Isolated as adduct with NEt_3.

[c]$PhCF_3$ used in place of NMP.

[d]Reaction conducted at 80 °C.

[e]Additional base (20 mol%) and TTMSS (1.2 equiv) added after 16 h.