Communication

# Selective Defluoroallylation of Trifluoromethylarenes

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# Selective Defluoroallylation of Trifluoromethylarenes

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*Supporting Information Placeholder*

**ABSTRACT:** We report a fluoride-initiated coupling reaction between trifluoromethylarenes and allylsilanes to access allylated α,α-difluorobenzylic compounds. This method's utility is demonstrated through a 30 mmol scale reaction, a sequential allylation/derivatization protocol and multiple examples of site-selective trifluoromethylarene allylation. Initial mechanistic studies suggest a base-induced single electron transfer pathway is responsible for the high efficiency and selectivity of this novel C–F substitution process.

The α,α-difluorobenzylic substructure is becoming an increasingly studied and valued motif in pharmaceutical and agrochemical applications.[1] In addition to the general benefits that benzylic fluorination can provide in medicinal chemistry, such as enhanced bioavailability, metabolic stability and lipophilicity, α,α-difluorobenzylic structures also serve as less-oxidizable bioisosteres of aryl ethers.[2,3] As interest in this substructure has increased, so too has the need for more efficient and versatile methods for its synthesis. Recent efforts have sought to develop alternatives to carbonyl deoxyfluorination methodology that relies on stoichiometric use of highly reactive reagents (e.g. diethylaminosulfur trifluoride).[4] For example, benzylic difluorination reactions using electrophilic fluorine reagents have been reported.[5] Meanwhile, substantial developments have been made using aryldifluoromethyl- or difluoroalkyl-based coupling partners to assemble α,α-difluorobenzylic derivatives, primarily through cross-coupling or radical-based approaches.[6-8]

An attractive alternative approach to α,α-difluorobenzylic compounds would be the direct coupling of reagents that do not require preparation of a difluorinated precursor. In this regard, we report the discovery and development of a coupling reaction between allylsilanes and trifluoromethylarenes (Figure 1a). Initial observations suggest this reaction proceeds through a base-induced single electron transfer (SET) pathway, resulting in high monoselectivity to provide synthetically versatile allylated products.

The substitution of a single C–F bond in trifluoromethylarenes represents a rapid and modular route to α,α-difluorobenzylic compounds.[9] The potential benefits of such a process has attracted significant attention, although the high C–F bond strength (~115 kcal/mol for $PhCF_3$) limits the activation strategies available for substitution.[10] As each substitution occurs, the strength of the remaining C–F bonds continuously decreases (99 kcal/mol for $PhCFH_2$), making monoselective substitution an exceedingly difficult process.[11,12]

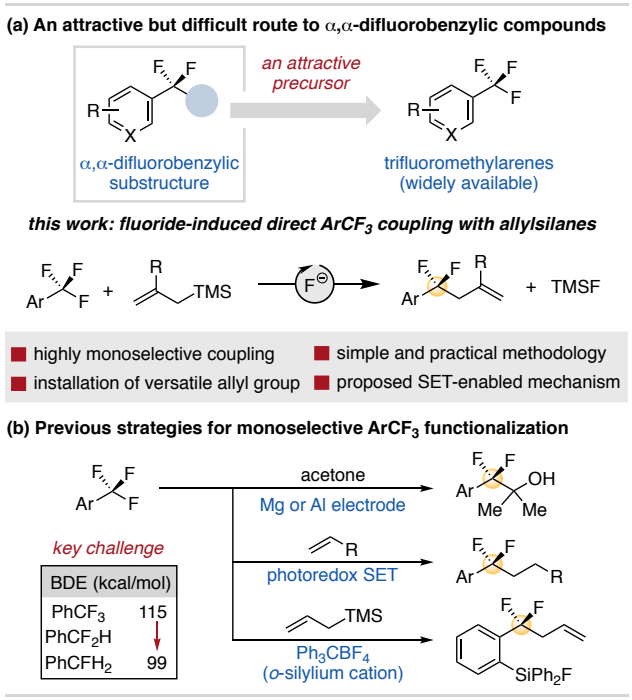


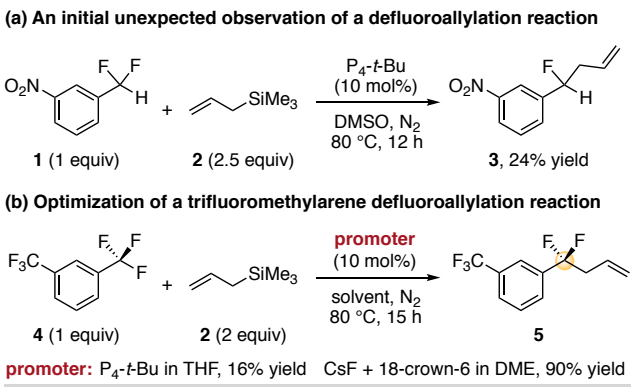

**Figure 1.** Motivation and background for the direct functionalization of trifluoromethylarenes.

There are three reported strategies for achieving monoselective C–C bond forming reactions of trifluoromethylarenes (Figure 1b). First, metal or electrochemical reductions have been used to generate aryldifluoromethyl anions that react with electrophiles, such as acetone.[13] Second, photoredox-catalyzed trifluoromethylarene reduction to access aryldifluoromethyl radicals was recently discovered; addition of this intermediate to *N*-aryl acrylamides was reported by Gschwind and König, while the addition to unactivated alkenes was disclosed by Jui.[14,15] Third, Yoshida and Hosoya

reported a method that involves fluoride transfer to an *ortho*-silylium cation, resulting in an aryldifluoromethyl cation that reacts with nucleophilic species.[16]

Our lab has been interested in using strong Brønsted bases as catalysts for new deprotonative functionalization reactions.[17] While investigating difluoromethylarene deprotonation, we observed a defluoroallylation reaction when 1-(difluoromethyl)-3-nitrobenzene (**1**) was mixed with allyltrimethylsilane (**2**) in the presence of the organic superbase $P_4$-*t*-Bu (Scheme 1a).[18] Given that $P_4$-*t*-Bu can act as a strong Lewis base, we reasoned that this reaction may have been promoted via activation of allyltrimethylsilane.[19,20] If this mechanism were operative, we hypothesized that defluoroallylation of trifluoromethylarenes may also occur to deliver allylated α,α-difluorobenzylic products. To examine this proposal, we used 1,3-bis(trifluoromethyl)benzene (**4**) as a model substrate for defluoroallylation (Scheme 1b).[21] Using $P_4$-*t*-Bu in THF, we initially observed a 16% defluoroallylation yield of product **5**. Further optimization led to 90% yield of **5** using 18-crown-6-ligated CsF (10 mol%) as an inexpensive and efficient promoter in 1,2-dimethoxyethane (DME). We note that the defluoroallylation yield decreases when allyl(methoxy)dimethylsilane (75% yield) or allyl(dimethyl)phenylsilane (67% yield) are used as coupling partners, and that the reaction must be conducted under inert atmosphere. Details regarding solvent, temperature and fluoride source effects are provided in the Supporting Information.

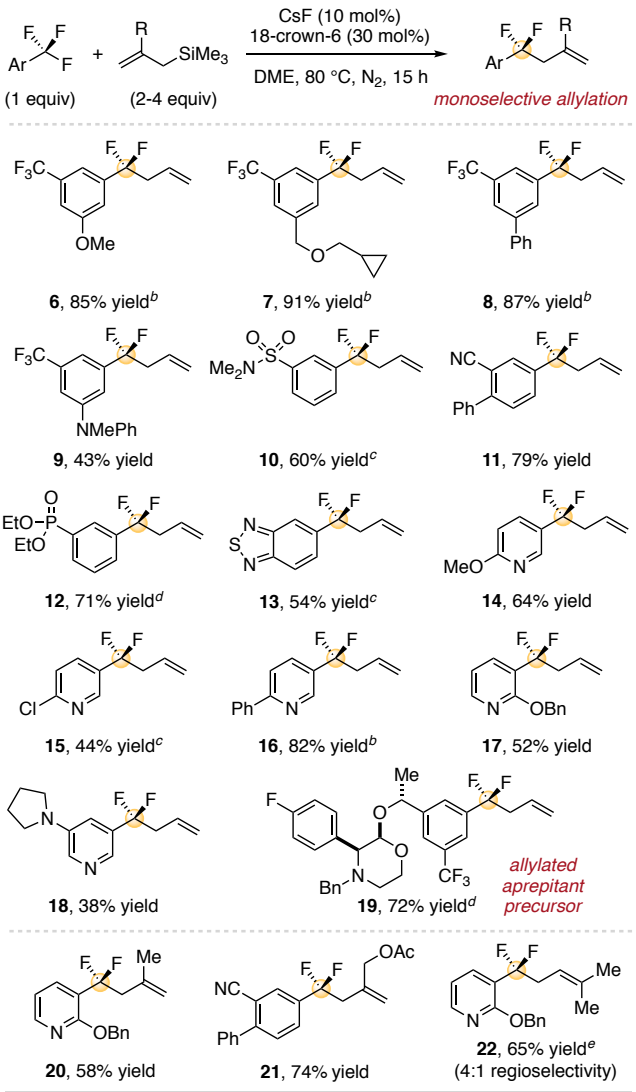
**Scheme 1. Discovery of a trifluoromethylarene defluoroallylation reaction.**[a]




[a]Yields determined by $^1$H NMR spectroscopy.

Table 1 shows a series of trifluoromethylarenes that underwent monoselective allylation under the optimized reaction conditions.[22] We note that some allylated products were sensitive to purification[23] and these products were isolated after *in situ* alkene hydrogenation or bromination (denoted as footnotes *b* and *c* in Table 1, respectively). A series of 1,3-bis(trifluoromethyl)arenes underwent allylation of one trifluoromethyl group in high yield (**6**-**9**). Other electron-deficient trifluoromethylarenes featuring sulfonamide (**10**), cyano (**11**) and phosphonate (**12**) substituents also provided high yields. Heterocyclic substrates were similarly effective, including a benzo[*c*]-1,2,5-thiadiazole (**13**) and 3-(trifluoromethyl)pyridine variants featuring methoxy (**14**), phenyl (**16**), benzyloxy (**17**) and pyrrolidino (**18**) substituents. Notably, 2-chloro-5-(trifluoromethyl)-pyridine (**15**) underwent defluoroallylation while avoiding chloride displacement by fluoride. A 1,3-bis(trifluoromethyl)aryl-containing substructure of the drug aprepitant was also allylated in 72% yield (**19**).

**Table 1. Substrate scope for trifluoromethylarene allylation.**[a]

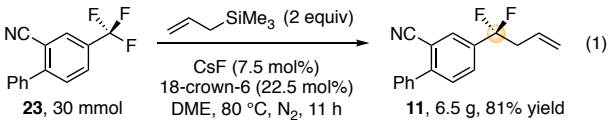



[a]Yields are of purified product; [b]Isolated yield of saturated product following *in situ* alkene hydrogenation using Schwartz's reagent; [c]Product isolated as dibrominated adduct; [d]48 h reaction time; [e]DMSO as solvent; see Supporting Information for details.

Use of 2-substituted allyltrimethylsilanes yielded disubstituted alkene products **20** and **21** in good yield. Meanwhile, unsymmetrical allylsilanes led to regioisomeric mixtures of products; for example, 3,3-dimethylallyltrimethylsilane led

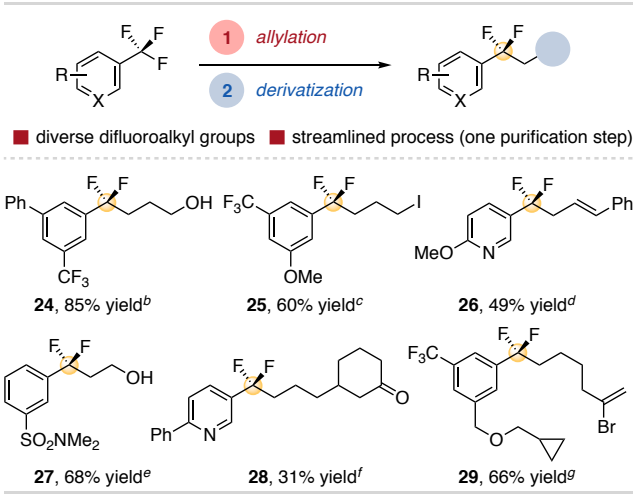
to 65% substitution yield favoring the trisubstituted alkene in a 4:1 ratio to the terminal alkene (**22**).[24]

To demonstrate the utility of this method, we first performed the allylation of trifluoromethylarene **23** on a preparative scale (30 mmol) to provide 6.5 g of product **11** (81% yield, equation 1).




Next, we developed a sequential allylation/derivatization protocol as a modular approach to arenes with diverse difluoroalkyl substituents. This process involved only a single isolation step and the overall yields with respect to the trifluoromethylarene reactant are shown in Scheme 2. Standard olefin manipulations provided terminal alcohol and alkyl iodide products (**24**, **25** and **27**), while a Heck-coupling reaction yielded a phenyl-substituted allylated product (**26**). Alkene hydrozirconation followed by C–C bond forming reactions provided ketone- (**28**) and alkene-containing (**29**) products.[25] Many further applications of this derivatization strategy can be envisioned.

**Scheme 2. Demonstration of one-pot allylation/derivatization processes.**[a]




[a]Isolated yield starting from trifluoromethylarene using defluoroallylation conditions from Table 1, followed by: [b]9-BBN, THF, rt; $H_2O_2$, NaOH; [c]$(C_5H_5)_2ZrHCl$, DCM, rt; $I_2$; [d]PhI, $Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, DMF, 100 °C; [e]$O_3$, MeOH, -78 °C; $NaBH_4$; [f]$(C_5H_5)_2ZrHCl$, THF, rt; CuCN, 2-cyclohexen-1-one; [g]$(C_5H_5)_2ZrHCl$, THF, rt; CuCN, 2,3-dibromopropene; see Supporting Information for full details.

The following observations and precedents suggest an allylation mechanism involving a SET pathway (Figure 2a). First, the scope of effective trifluoromethylarene substrates in Table 1 share electronic similarities to those reported by Jui in 2018[14b], in which photoredox-catalyzed SET to a trifluoromethylarene leads to mesolytic cleavage, generating an α,α-difluorobenzylic radical.[26,27] Second, C–Si σ-bonds are well-known to activate adjacent π-electrons toward single electron oxidation, an effect enhanced by Lewis base coordination.[28-30] Third, fluoride-initiated allylation reactions involving allyltrimethylsilane have been proposed to proceed through pentacoordinate and hexacoordinate silicate intermediates, as well as discrete allyl anion species.[20,31] Based on this analysis, we speculate that an anionic allylic intermediate participates in SET to the trifluoromethylarene, generating an α,α-difluorobenzylic radical that reacts with an allyl radical equivalent through either a recombination or a chain process.[32,33] It is likely that the fluoride anion expelled from the trifluoromethylarene can activate another equivalent of allyltrimethylsilane. The absence of multiallylation products is consistent with a SET mechanism as reduction of the monodefluoroallylation product is more difficult than the trifluoromethylarene.[26]

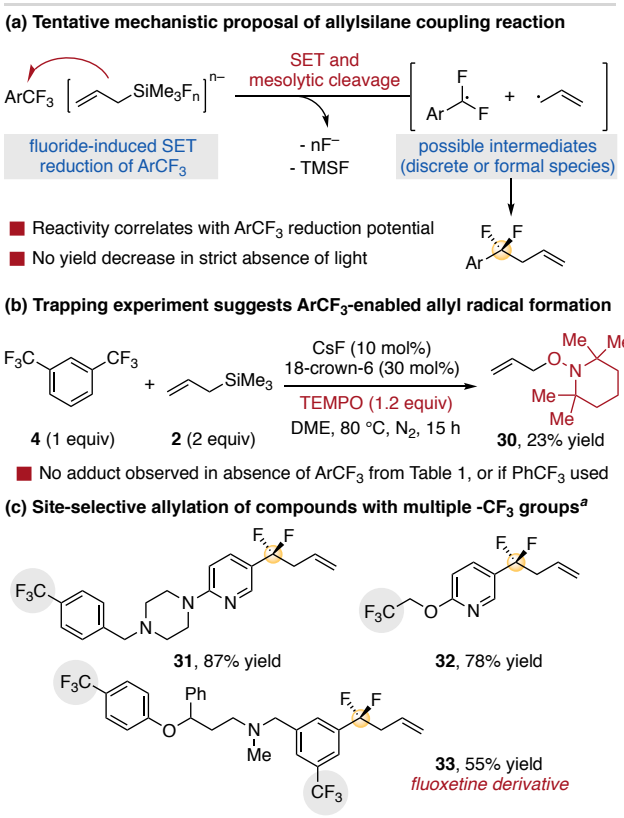



**Figure 2.** Proposed reaction pathway and experimental studies that led to site-selective defluoroallylation reactions. [a]Isolated yields using conditions shown in Table 1; see Supporting Information for details.

When 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to a standard allylation reaction of 1,3-bis(trifluoromethyl)benzene (**4**), a 23% yield of allylated-TEMPO adduct **30** was observed (Figure 2b).[34] Control experiments showed that this adduct is not formed in the absence of a trifluoromethylarene from Table 1.[35] These observations are consistent with an allyl radical species that is

generated only in the presence of a suitable trifluoromethylarene substrate. We have performed further control studies that demonstrate light is not required for defluoroallylation to occur. The exact nature of the intermediates involved in this reaction and how they ultimately couple to each other remains the subject of ongoing studies.

Based on our current mechanistic hypothesis, we reasoned that site-selective defluoroallylation could be accomplished on substrates that contain multiple trifluoromethyl groups. Thus, complex structures with differentiated trifluoromethyl groups on multiple arenes (**31** and **33**) were selectively allylated in high yields (Figure 2c). Selectivity for trifluoromethylarene allylation was also observed over alkyl-substituted trifluoromethyl groups (**32**).

We expect this methodology to provide an attractive route to diverse α,α-difluorobenzylic compounds given the overall selectivity, practicality and scope of the defluoroallylation reaction. Further mechanistic studies are ongoing to improve this method and generalize this approach to other novel coupling reactions.

## 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).

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### Notes

The authors declare no competing financial interest.

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(22) To test for double defluoroallylation, the model product **5** was resubjected to the reaction conditions shown in Table 1; after 8 h, over 95% mass balance of unreacted **5** was accounted for and no discernable double allylated product was observed.

(23) For certain substrates, we observed fluoride elimination during chromatographic isolation of the allylated product; this process was minimized after alkene saturation or dibromination.

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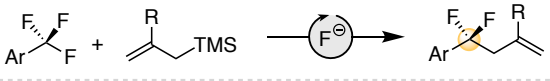
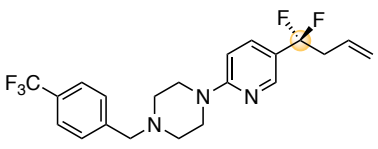
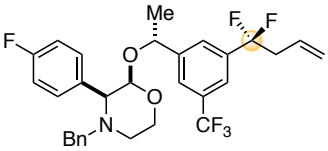
***a fluoride-initiated monoselective coupling reaction***




87% yield




72% yield