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Selective C–F Functionalization of Unactivated Trifluoromethylarenes

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Abstract

Fluorinated organic molecules are pervasive within the pharmaceutical and agrochemical industries due to the range of structural and physicochemical properties that fluorine imparts. Currently, the most abundant methods for the synthesis of the aryl–CF₂ functionality have relied on the deoxyfluorination of ketones and aldehydes using expensive and poorly atom economical reagents. Here, we report a general method for the synthesis of aryl–CF₂R and aryl–CF₂H compounds through activation of the corresponding trifluoromethyl arene precursors. This strategy is enabled by an endergonic electron transfer event that provides access to arene radical anions that lie outside of the catalyst reduction potential. Fragmentation of these reactive intermediates delivers difluorobenzyl radicals that can be intercepted by abundant alkene feedstocks or a hydrogen atom to provide a diverse array of difluoalkylaromatics.

Graphical Abstract

INTRODUCTION

The trifluoromethylaromatic (Ar–CF₃) motif is routinely utilized in drug and agrochemical design, because its incorporation can significantly alter the properties of a given biologically active small molecule.^{1–4} Accordingly, a number of methods have been reported over the past decade that enable the efficient construction of Ar–CF₃ compounds.^{5–10} Although trifluoromethyl units are traditionally unreactive, we recently became interested in selective manipulation of these compounds through a radical anion-based mechanism for carbon-

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Supporting Information

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Experimental procedures, spectral data, and computational data (PDF)

The authors declare no competing financial interest.

fluorine (C–F) bond cleavage. We envisioned that the resulting radical intermediates could serve as precursors to a number of valuable fluorinated scaffolds, including difluoroalkyl aromatics (isosteres for aryl ethers and aryl ketones)¹¹ and difluoromethyl arenes (lipophilic hydrogen bond donors).^{12–16} These difluorobenzyl arrays have emerged as important components of bioactive small molecules (two of which are shown in Figure 1). The direct molecular editing of trifluoromethylaromatics in this way would offer a valuable complement to technologies that grant access to these difluorinated motifs through construction of the C_{Aryl}–CF₂R/H bond.^{17–23}

Although reductive activation of the C–F bonds in this substrate class can be accomplished using a range of approaches (e.g., electrochemical reduction,^{24,25} low-valent metals,^{26–28} or frustrated Lewis pairs^{29,30}), preventing exhaustive defluorination (thereby bypassing valuable di- and monofluorinated intermediates) remains a significant synthetic problem. This is because, in part, C–F bond strength decreases as defluorination proceeds.³¹ Troupel³² and Lalic³³ reported two different systems for interception of anionic difluorobenzyl species through trapping with carbonyl-based electrophiles. In addition, Prakash reported a Mg⁰-based system for hydrodefluorination (HDF) of bis(trifluoromethyl)-benzene derivatives.²⁶ Yoshida and Hosoya recently described an intermolecular coupling of trifluoromethyl arenes that contain ortho-silyl groups with allyl silanes, which operates through a cationic mechanism.³⁴ While these systems allow for selective defluorofunctionalization of specific substrate classes, a general approach to Ar–CF₃ functionalization remains elusive.

Our strategy is mechanistically founded on recent work from our group³⁵ and König's,³⁶ where the use of highly reducing photoredox catalysts resulted in partial defluorination of activated trifluoromethylaromatic substrates (Figure 2), under irradiation with visible light. In our method, single electron transfer (SET) from an organic photoredox catalyst to the aryl substrate is followed by C–F cleavage to deliver difluorobenzyl radicals that display unique reactivity profiles. This system, ultimately propelled by oxidation of formate to CO₂, effectively performs monodefluoroalkylation reactions with a wide range of unactivated olefins as alkyl sources. However, the utility of both of these systems is limited by the requirement for electronic activation of the substrates. More specifically, successful reaction has only been demonstrated for trifluoromethylaromatics that contain auxiliary electron-withdrawing groups (e.g., –CF₃, –CN, –SO₂NH₂). Here, we describe the development of conditions that overcome this limitation, thus enabling controlled C–F functionalization of unactivated trifluoromethylaromatics. We show that these difluorobenzyl radical intermediates can be utilized selectively in both alkylation and reduction processes.

RESULTS AND DISCUSSION

We began our study by examining the reaction of benzotrifluoride (Ph–CF₃) with 3-buten-1-ol to afford the defluoroalkylation (DFA) product **1** (shown in Scheme 1). After slight modification of our initially reported conditions, we evaluated a series of photoredox catalysts, a selection of which is shown in Scheme 1. While *N*-phenylphenothiazine (PTH, **P1**) was ineffective at room temperature, the use of **P2–P4** afforded the desired product to varying degrees (up to 31% yield after 24 h). Increasing reaction temperature resulted in

significantly improved yields of the desired linear alkylation product. The most effective catalyst (**P3**, developed by Miyake for organic atom-transfer radical polymerization)³⁷ has been reported to be highly absorbent in the visible spectrum ($\lambda_{\text{max}} = 388 \text{ nm}$, $\epsilon_{\text{max}} = 26\,635 \text{ M}^{-1} \text{ cm}^{-1}$) with a 98% intersystem crossing (ISC) efficiency to a long-lived triplet excited state that is strongly reducing ($E_{1/2}^* = \text{desired products } 1.70 \text{ V vs standard calomel electrode (SCE)}$).³⁸ The use of **P3** (2 mol %) at 100 °C resulted in 89% yield of **1**, as determined by NMR. Interestingly, for the organic SET catalysts (**P1**, **P3**, **P4**), reaction progress is not strongly correlated with reduction potential of the catalyst. Rather, conversion at higher temperatures is more closely related to excited-state lifetime. This effect is most pronounced through the use of **P4** in this process, because it is significantly less reducing than **P1** but equally effective at high temperature.

As shown in Table 1, a collection of unactivated trifluoromethylaromatics could be engaged under these conditions. In addition to carbon and oxygen-substituted substrates, arylamine derivatives reacted smoothly to afford the desired products **2–10** in 44–92% yield. The benzylic carbinol was cleanly retained, giving alkylation product **11** in 82% yield. Pyridine substrates with trifluoromethyl groups at the 2- and 3-positions gave rise to **12–15** in 41–78% yield. These reactions were most effectively performed at room temperature, because the difluoroalkylpyridine products can be further reductively defluorinated. In fact, 4-trifluoromethylpyridine currently remains outside the scope of these processes; attempted alkylation reactions largely resulted in picoline production with only trace amounts of the desired product. Likewise, while this protocol is effective in activating electron-deficient aromatics (such as those described in our previous report³⁵), the elevated temperature and more effective catalyst typically resulted in further defluorination of these substrates. The functionalization of marketed pharmaceuticals could also be performed under these conditions to afford derivatives **16–18** in 61%–73% yield, demonstrating that basic functions, alcohols, and internal alkenes are well-tolerated.

Although these conditions are able to accomplish challenging redox events, we found that thioethers, sulfoxides, and sulfones alike were preserved throughout the course of the reaction without any observable alteration of the sulfur oxidation states (**19–21**, 59–64% yield). To probe the chemoselective nature of heterolytic C–X cleavage within a single π -system, we examined the reactivity of a series of 4-halogenated benzotrifluorides. From the corresponding radical anions, cleavage of the aryl C–I, C–Br, and C–Cl bonds (bond dissociation energy (BDE) = 71.6, 80.3, and 95.5 kcal/mol, respectively; see Supporting Information for details) occurred in preference to the stronger benzylic C(sp³)–F bond (BDE = 118.1 kcal/mol), resulting in mixtures of protodehalogenation and aryl radical alkylation products.³⁹ In contrast, the aryl C–F bond (BDE = 127.5 kcal/mol) was completely preserved, affording **22** in 48% yield (where the mass balance was comprised of unreacted starting material). In addition to aryl halides, alkyl halides currently lie outside the scope of this process, where either reductive dehalogenation or substitution with formate are primary pathways of these substrates.

In line with our previous report, the olefin scope for coupling with unactivated trifluoromethylaromatics is broad, giving a range of difluoroalkylated benzene derivatives from benzotrifluoride. The use of benzotrifluoride as a precursor to difluoroalkyl benzene

derivatives is attractive, because it is abundantly available at low cost (~\$7/mol) when compared to conventional reagents that accomplish deoxyfluorination of aryl ketones (e.g., diethylaminosulfur trifluoride (DAST) or Fluolead).⁴⁰ While the standard conditions (5 equiv of olefin with limiting Ar–CF₃ substrate) were effective here (see Table 1 and Supporting Information for examples), we found that using a cosolvent quantity (50 equiv) of benzonitrile could be conveniently employed for coupling of simple olefins with acetate, acetal, or Weinreb amide groups (Table 2: **23–25**, 64–78% yield). Other nucleophilic olefins including the vinyl ether, acetate, amides, and vinyl carbazole were also effective coupling partners under this protocol (**26–30**, 55–95%). β -Substitution of aliphatic olefins was also well-tolerated (**31**, 94% yield). Although these conditions operate at elevated temperature, decomposition through saponification or hydrolysis pathways was not observed. Ethylene, propylene, isobutylene, and 2-methyl-2-butene are attractive two-, three-, four-, and five-carbon synthons that are produced on large scale from hydrocarbon cracking. Performing our reductive DFA method on Ph–CF₃ under 25 psi of ethylene provided the desired product (**33**) in 65% yield (based on formate as limiting reagent). This result was replicated with propylene (**34**, 68% yield), isobutylene (**35**, 87% yield), and 2-methyl-2-butene (**36**, 46% yield).

To further illustrate the value of this photocatalytic DFA in medicinal chemistry, we applied it in the formal syntheses of bioactive difluoroalkylaromatic molecules (as indicated in Scheme 2). The patent routes proceed through difluorobenzyl arene intermediates **37**, **40**, and **44**, all of which were synthesized via deoxyfluorination of the corresponding carbonyl compounds. The reported preparation of growth hormone secretagogue **38** involves construction of a 1,3-dithiolane intermediate from **39** and 1,2-ethanedithiol. Subsequent desulfurative fluorination with nitrosonium cation and Olah's reagent delivered the geminal difluoride motif. Ester reduction provided primary alcohol **37** in 45% yield over three steps.⁴¹ With this catalytic approach, reaction of Ph–CF₃ (50 equiv) with allyl alcohol provided the same intermediate in a single step (63% yield). The reported synthesis of **41**, an Retinoid-related orphan receptor gamma (ROR γ) modulator, also involves a dithiolation/desulfurative fluorination sequence using ketone **43** as starting material. Palladium-catalyzed enolate coupling and carboxylic acid deprotection afforded **40** in 4% yield over four steps.⁴² Under our conditions, commercial trifluoromethyl arene **42** reacted with ethylene gas (25 psi) to afford the same intermediate, after ester saponification, in 63% overall yield. In the reported synthesis of amine **44**, a precursor to β 2 adrenergic receptor agonist **45**, DAST was employed for direct deoxyfluorination of benzylic ketone **47**. Phenethylamine **44** was then delivered via sequential alcohol deprotection, Mitsunobu etherification, and reduction (4% yield over five steps).⁴³ Our alternative route to this intermediate involves reacting trifluorotoluene (50 equiv) with vinyl ether **46** on 12 mmol scale (1 mol % **P3**) to give the corresponding defluoroalkylation product in 92% yield (4 g). Acidic cleavage of the *tert*-butyloxycarbonyl (Boc) group gave **44** in 91% over two steps. While deoxyfluorination remains an effective tool for difluoroalkylaromatic production, these examples illustrate the potential of this catalytic protocol to streamline the preparation of medicinally relevant Ar–CF₂R building blocks.

Scheme 3 shows our proposed mechanism for this transformation, where excitation of **P3** with visible light (through irradiation with commercial blue light-emitting diodes (LEDs)) delivers the excited-state reductant **P3***. Reversible single-electron transfer to the trifluoromethylarene substrate gives rise to the corresponding radical anion and the ground-state catalyst radical cation. Formation of the key difluorobenzyl radical intermediate is then accomplished via thermodynamically driven mesolytic C–F cleavage event. Regioselective intermolecular addition to the olefin substrate provides an alkyl radical adduct that undergoes polarity matched hydrogen atom transfer (HAT) with thiophenol to furnish the defluoroalkylation products. Regeneration of both the thiol and photoredox catalysts occurs with formate as stoichiometric reductant producing a metal fluoride salt and CO₂ as byproducts.

The findings that are described in this paper were enabled by the discovery that **P3** has the ability to engage unactivated trifluoromethylaromatics. This is mechanistically interesting because, in comparison to our initial report in this area (using **P1** and activated Ar–CF₃ substrates), this substrate set is more difficult to reduce, and the most effective catalyst (**P3**) is not as strongly reducing. Within this context, we propose that the reversible SET events that are operational here are endergonic in the forward direction. Consistent with this proposal are Stern–Volmer excited-state quenching studies, which revealed that quenching of **P3*** with benzotrifluoride occurs to a minute extent ($K_{SV} = 0.02$; none of the other reaction components quench the excited state). Although the concentration of radical anion intermediate is low under these conditions, fluoride expulsion provides a thermodynamic driving force for radical formation. Indeed, the calculated thermodynamic profile (details given in the Supporting Information) indicates that C–F bond elongation from benzotrifluoride radical anion is essentially barrierless (<3 kcal/mol). Taken together, these results indicate that, although substrate reduction is a critical step within this pathway, mesolytic cleavage acts as the primary determinant in radical formation.

We questioned whether the radical intermediates that are accessible under this paradigm could be generally utilized in the formation of other bonds. Of particular interest to us was the idea that interception of this species with a hydrogen atom would grant access to the corresponding difluoromethyl arene (Ar–CF₂H). Selective HDF of trifluoromethylaromatics in this manner would offer a novel approach to this high-value motif.

Summarized in Scheme 3 are existing strategies for trifluoromethylaromatic HDF. In 2016, Lalic reported a system that utilizes catalytic amounts of both palladium and copper in conjunction with triphenylsilane and potassium *tert*-butoxide to defluorinate a series of 4-trifluoromethyl biaryl compounds, generating presumed nucleophilic addition products to dimethylformamide (DMF).³³ Reaction of these intermediates with *tert*-butanol resulted in selective production of the corresponding difluoromethylaromatics. Prakash described that Mg⁰ can be utilized in HDF processes of various bis(trifluoromethyl)benzene derivatives with varying selectivity for the corresponding reduction products.²⁶ While appealing for its operational simplicity, this protocol is limited to bis(trifluoromethyl)benzene substrates, as benzotrifluoride was reported to be unreactive, and more electron-poor systems underwent exhaustive defluorination (complete reduction of trifluoromethylaromatics to the corresponding toluene derivatives). Exhaustive defluorination is the major outcome within

the trifluoromethylaromatic HDF literature, where electrochemical reduction,²⁵ alkali metal reduction,^{26–28} or Lewis acids^{29,30} have been reported to activate these strong C–F bonds.

To evaluate the feasibility of the proposed HDF pathway, we reacted 2-trifluoromethylacetanilide with **P3** and a range of reductants in dimethyl sulfoxide (DMSO) under irradiation with blue LEDs. These studies (optimization details are given in the Supporting Information) revealed that formate reductants are uniquely effective for HDF and that there is a pronounced effect of the formate counterion on reactivity. The optimized conditions (indicated in Table 3) again involve the use of **P3** (2 mol %) along with cesium formate (3 equiv) at 50 °C, which delivered the desired difluoromethylaromatic **48** in 75% isolated yield without detectable overreduction products. Similarly, the isomeric trifluoromethyl-bearing acetanilides were good substrates for this transformation, affording the corresponding products **49** and **50** in 55–70% yield. Additionally, the outlined conditions efficiently engaged compounds bearing only alkyl substituents in the *para*- (**51**, 64% yield), *meta*- (**52**, 48% yield), and *ortho*- (**53**, 50% yield), a significant advance over previously reported technologies. Other oxygen- or nitrogen-substituted substrates could be reductively defluorinated with high selectivity for the Ar–CF₂H products (**54–56**, 45–65% yield).

Hydrodefluorination of 2-, 3-, and 4-trifluoromethyl substituted pyridines **57–59** was also successful under this protocol, giving the desired products in acceptable (42–50%) yield. Much like we observed under DFA conditions, yields of pyridine-based substrates were bolstered by substitution of electron-donating groups at the 2-position (**60–62**, 57–64% yield). Although this substrate set underwent HDF in moderate yield, these results demonstrate that significant structural diversity is tolerated by this protocol including acidic protons, heterocycles, and other reducible groups.

CONCLUSIONS

In summary, we have developed a robust method for the defluoroalkylation and hydrodefluorination of unactivated trifluorotoluene derivatives using the combination of two organocatalysts (no metal is required), inexpensive formate salts, and visible light. The use of Miyake's phenoxazine, **P3**, was key in the development and generality of these methods. The reductive radical process, driven by the selective cleavage of a single benzylic C–F bond, can be employed to access a diverse range of Ar–CF₂R and Ar–CF₂H substrates. Mechanistic studies and the development of additional applications of difluorobenzylic radicals are underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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program goal: production of high-value motifs from $Ar-CF_3$

Figure 1.
Molecular editing of $Ar-CF_3$ groups via catalytic C-F functionalization.

König: Cascade Radical Addition/Cyclization with Methacrylamides **Jui: Dual Catalytic Defluoroalkylation with Simple Alkenes**

Previous Work: Auxiliary EWG is required

This Work: Unactivated Ar-CF₃ substrates;

HAT to radical intermediate for Ar-CF₂H

Figure 2.
Radical C-F functionalization of Ar-CF₃ substrates via photoredox catalysis.

Scheme 1. Activation of Stable C–F Bonds by Single-Electron Transfer using Photoredox Catalysis^a

^aReaction conditions: benzotrifluoride (0.25 mmol), 3-buten-1-ol (1.25 mmol), photoredox catalyst (**P1**: 10 mol %; **P2–P4**: 2 mol %), potassium formate (0.75 mmol), thiophenol (10 mol %), DMSO (2.5 mL), blue light, 24 h. Yields determined by ¹⁹F NMR analysis with internal standard.

Scheme 2.

Catalytic Defluoroalkylation in the Synthesis of Medicinal Building Blocks

Scheme 3.
Catalytic or Direct HAT Mechanisms for Defluorofunctionalization of Trifluoromethyl Arenes

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Table 1.

Catalytic Defluoroalkylation: Scope of Unactivated Trifluoromethylaromatic Substrates^a

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^aReaction conditions: Ar-CF₃ substrate (0.5 mmol), 3-buten-1-ol (2.5 mmol), **P3** (2 mol %), potassium formate (1.5 mmol), thiophenol (10 mol %), DMSO (5.0 mL), blue light, 100 °C, 24 h, isolated yields given.

^bReaction conducted with 2.5 mmol of potassium formate.

^cReaction conducted at 23 °C.

^dReaction conducted with 5.0 mmol of olefin.

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Table 2.

Scope of Olefinic Coupling Partner for Photocatalytic Difluoroalkylaromatic Synthesis^a

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^g Reaction conditions: benzotrifluoride (3 mL), alkene (0.5 mmol), **P3** (2 mol %), potassium formate (2.5 mmol), thiophenol (10 mol %), DMSO (5.0 mL), blue light, 100 °C, 24 h; isolated yields given.

^h Reaction conducted with potassium formate as limiting reagent, yields determined by ¹⁹F NMR analysis with an internal standard.

Table 3.

Substrate Scope for Hydrodefluorination^a

^aReaction conditions: Ar-CF₃ substrate (0.5 mmol), cesium formate (1.5 mmol), Miyake phenoxazine **P3** (2 mol %), DMSO (5.0 mL), blue light, 50 °C, 24 h; isolated yields given; parentheses indicate the ratios of Ar-CF₂H to Ar-CFH₂ products, as determined by NMR analysis of the crude reaction mixtures.

^bReaction run at 23 °C

^cYield determined by ¹⁹F NMR with an internal standard.