Communication

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Catalytic Defluoroalkylation of Trifluoromethylaromatics with Unactivated Alkenes

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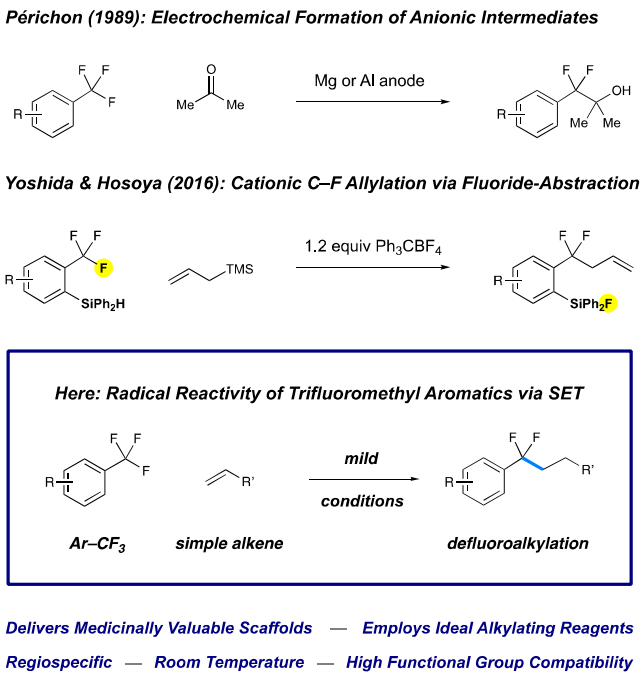
Supporting Information Placeholder

ABSTRACT: We describe a new catalytic approach to selective functionalization of the strong C–F bonds in trifluoromethylaromatic (Ar–CF_3) systems. In this approach, single electron reduction of Ar–CF_3 substrates (using a photoredox catalyst) results in difluorobenzylic radical formation through a C–F cleavage mechanism. These radicals undergo efficient intermolecular coupling with simple alkenes in a defluoroalkylation process where radical termination is accomplished by a polarity reversal catalyst. This mild catalytic protocol engages a wide range of substrates to give medicinally relevant fluorinated substructures with complete regiocontrol.

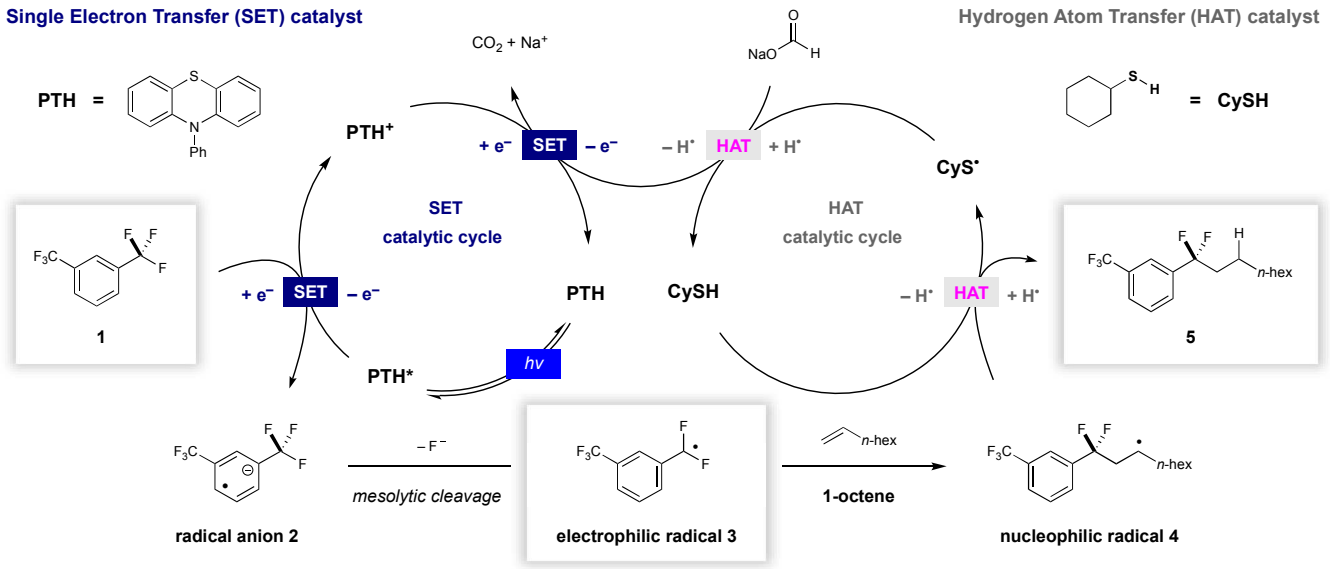
The selective functionalization of strong chemical bonds is an important goal in chemical synthesis. While tremendous progress has been made in the manipulation of aryl and alkenyl C–F bonds,[1–4] selective functionalization of aromatic trifluoromethyl groups remains challenging. Cleavage of the C–F bonds in Ar–CF_3 substrates can be accomplished using electrochemistry,[5,6] reducing metals,[7–9] transition metal complexes,[10–14] or main-group Lewis acids.[14,15] Although these approaches are diverse in nature, they are united in their propensities to perform exhaustive defluorination of the trifluoromethyl unit; in part because C–F bond strength decreases as defluorination proceeds.[16] In this context, the selective exchange of a single C–F bond for a C–C bond would be valuable because it would allow for structural diversification while retaining benzylic fluorination. Toward this aim, there are two general approaches (illustrated in Figure 1) that operate through complementary ionic intermediates. Périchon detailed electrochemical conditions for α,α-difluorobenzylic anion formation and subsequent trapping with carbonyl-based electrophiles.[17] More recently, Yoshida and Hosoya described a cationic intermolecular coupling of trifluoromethyl arenes with allyl silanes.[18] Because this system operates through intramolecular fluoride abstraction, it is limited to substrates that contain an *ortho*-silyl group. We were interested in developing a different approach to Ar–CF_3 activation, where single electron reduction could be generally utilized in the formation and reaction of α,α-difluorobenzylic radicals. We hypothesized that the use of highly reducing photoredox catalysts[19,20] would grant access to this pathway, and that the resulting radical species could be employed in a number of catalytic processes.[21] Here, we describe the ability of this approach to perform intermolecular defluorinative coupling of trifluoromethyl arenes with simple, unactivated alkenes (Figure 1).

Figure 1. Strategies for defluorinative C–C bond-formation in trifluoromethylaromatics.



In medicinal chemistry, the introduction of benzylic difluorination is a powerful strategy for tuning the properties of a given small molecule. Synthetic approaches to this motif include deoxyfluorination of ketones with the indiscriminately reactive reagent diaminosulfur trifluoride (DAST),[22] benzylic C–H

Figure 2. Proposed Mechanism for This Dual Catalytic Defluoroalkylation Process.



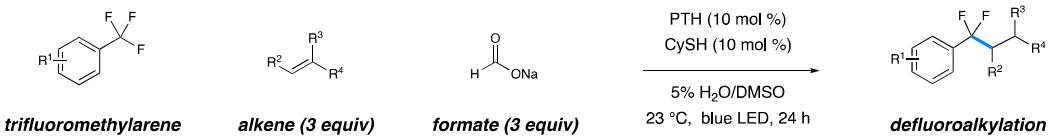
difluorination,[23] and Stephenson's photocatalytic Smiles rearrangement.[24] In addition, Minisci radical arylation[25] and transition metal-catalyzed cross-coupling[26] strategies have effectively produced this valuable substructure in a modular manner. However, regioselectivity in radical arylation is largely substrate-controlled,[27] and both of these strategies require preparation of a different fluoroalkyl coupling partner for each difluorobenzylic target. In contrast, defluoroalkylation of Ar–CF_3 substrates would permit flexible variation of both the aromatic and alkyl fragments, where a vast array of simple olefins would function as alkyl sources. Because radical addition to simple olefins is a regioselective process that occurs with high fidelity in the presence of many functional groups, we anticipated that this system would be useful for the synthesis of a wide range of complex fluorinated organics.

Our proposed mechanistic approach to Ar–CF_3 defluoroalkylation is shown in Figure 2, where two different catalysts would operate in concert to accomplish the transfer of electrons and hydrogen atoms. Under irradiation by a commercial blue LED, excitation of the organic photoredox catalyst *N*-phenylphenothiazine (**PTH**), first introduced by Read de Alaniz and Hawker, would generate the highly reducing excited state **PTH*** ($E_{1/2}$* = –2.10 V vs. SCE).[28] Single electron transfer (SET) to 1,3-bistrifluoromethylbenzene **1** ($E^0_{1/2}$ = –2.07 V vs. SCE)[29] would deliver the key radical anion **2**, as well as the oxidized ground state catalytic species **PTH**$^+$. This electron transfer event was studied using Stern-Volmer experiments where quenching of the excited catalyst (**PTH***) was only observed in the presence of **1** (none of the other reactants or reagents quenched **PTH***). Radical anion **2** would undergo mesolytic cleavage to expel fluoride, consequently delivering electrophilic radical **3**. Intermolecular radical addition to 1-octene would afford nucleophilic radical **4**, which would be polarity matched for hydrogen atom transfer (HAT) from the electrophilic polarity reversal catalyst,[30] cyclohexane thiol (**CySH**, BDE = 86.8 kCal/mol).[31] This step would concurrently deliver the desired defluoroalkylation product **5** and the thiyl species **CyS**$^\bullet$. Regeneration of both catalysts by sodium formate (through HAT and SET)[32] would close both catalytic cycles, liberating carbon dioxide and sodium fluoride as the only stoichiometric byproducts. An alternative radical chain mechanism involving formate radical anion as propagating reductant is also consistent with our observations.

This novel dual catalytic approach to Ar–CF_3 activation is attractive, in part, because it employs inexpensive, readily accessible organic catalysts (no precious metals are required) and consumes light and formate as stoichiometric reagents. The optimal conditions for this process utilize the trifluoromethyl arene as limiting reagent with excess alkene and sodium formate (3.0 equivalents each), and 10 mol% of each catalyst at room temperature in aqueous DMSO (5% H_2O (v/v)). Control experiments indicated that both catalysts are required for effective reaction of the otherwise inert starting materials, as are light and sodium formate (see SI for details).

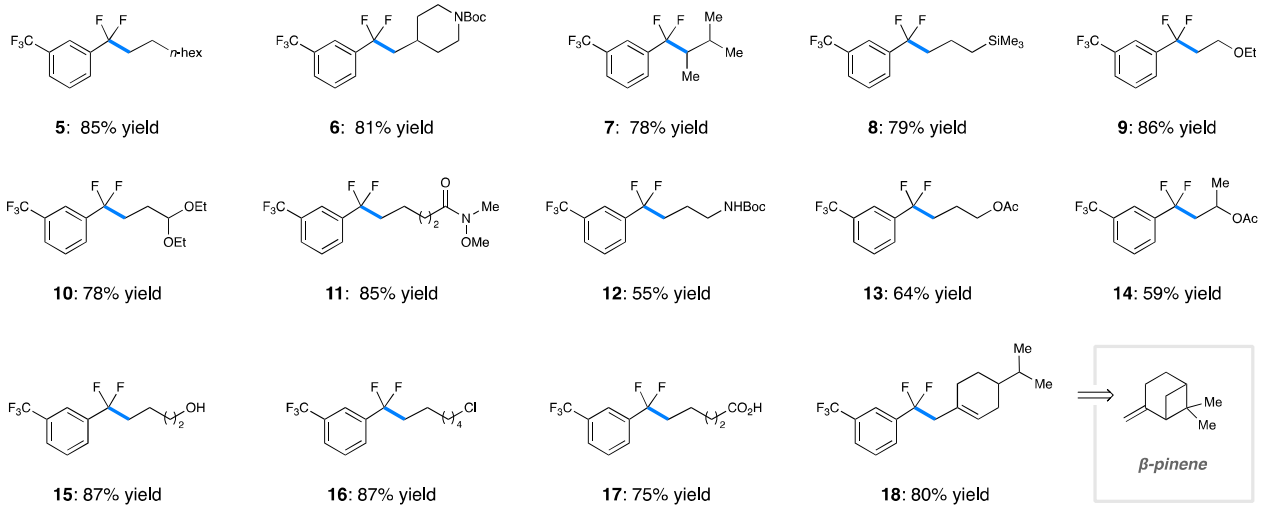
As illustrated in Table 1, this light-driven system effectively couples a wide range of unactivated alkene structures with the bis(trifluoromethyl)aromatic **1** to give the corresponding defluoroalkylation products. Transformation of monosubstituted, 1,1-disubstituted, and trisubstituted alkenes gave rise to compounds **5**–**7** in good yield (78–85%) with complete regiocontrol. More nucleophilic olefins like allyltrimethylsilane, ethyl vinyl ether, and isopropenyl acetate smoothly participated

Table 1. Dual Catalytic Defluoroalkylation: Substrate Scope[a]



trifluoromethylarene *alkene (3 equiv)* *formate (3 equiv)* *defluoroalkylation*

alkenes

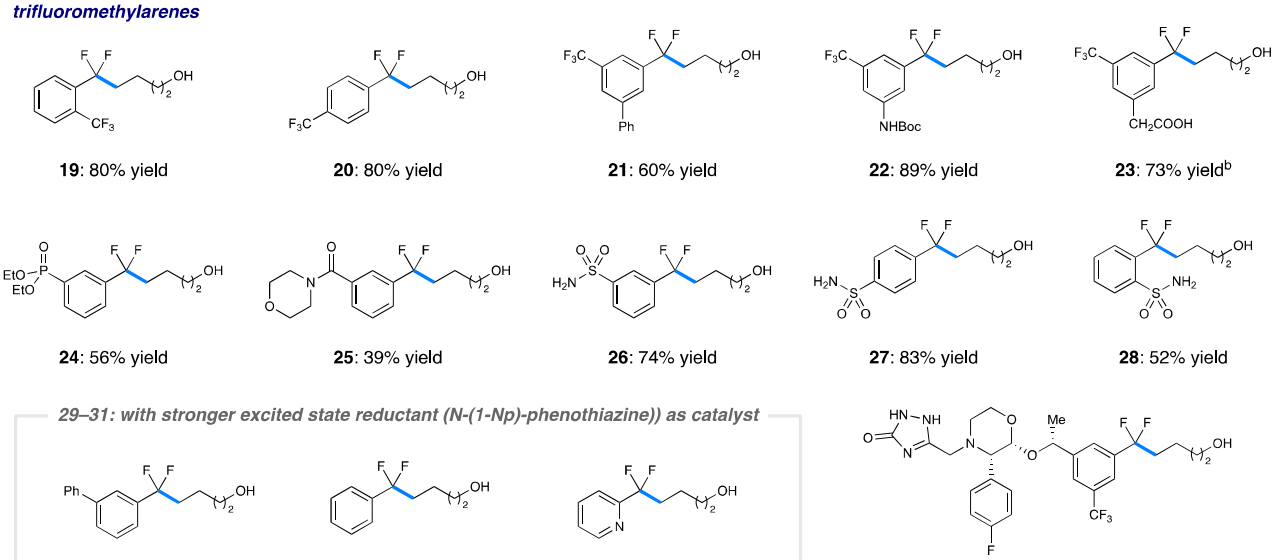


5: 85% yield **6**: 81% yield **7**: 78% yield **8**: 79% yield **9**: 86% yield

10: 78% yield **11**: 85% yield **12**: 55% yield **13**: 64% yield **14**: 59% yield

15: 87% yield **16**: 87% yield **17**: 75% yield **18**: 80% yield *β-pinene*

trifluoromethylarenes



19: 80% yield **20**: 80% yield **21**: 60% yield **22**: 89% yield **23**: 73% yield[b]

24: 56% yield **25**: 39% yield **26**: 74% yield **27**: 83% yield **28**: 52% yield

29–31: with stronger excited state reductant (N-(1-Np)-phenothiazine)) as catalyst

29: 60% yield[c] **30**: 11% yield[c] **31**: 47% yield[c]

32: 85% yield from aprepitant[d]

[a]Reaction conditions: Ar–CF_3 (0.5 mmol), alkene (1.5 mmol), PTH (10 mol%), CySH (10 mol%), HCO_2Na (1.5–2.0 mmol), 5% (v/v) H_2O/DMSO (5.0 mL), blue LED, 23 °C, 24 h, isolated yields shown. [b]Reaction was conducted for 48 h. [c]*N*-(1-Np)-phenothiazine (10 mol%) was used in place of PTH. [d]Reaction was conducted on 0.1 mmol scale

here (**8**, **9**, **14**: 59–86% yield). This method accepts olefinic coupling partners that contain many important functional groups, including acetals, Weinreb amides, carbamates, esters, alcohols, alkyl chlorides, and carboxylic acids (**10**–**17**; 55–87% yield). Radical addition to the bicyclic terpene β-pinene is accompanied by ring opening to afford the functionalized cyclohexene **18** (80% yield), which is consistent with the proposed radical nature of this defluorination. Critically, substrate activation under this model is guided by reduction potential rather than C–F bond strength. Because single electron reduction of these defluoroalkylation ($ArCF_2R$) products is more difficult than reduction of the corresponding starting material ($ArCF_3$) species,[6] selective activation of only one C–F bond was observed in all cases.

We then applied this system to the reductive defluoroalkylation of other electron-deficient Ar–CF_3 systems, using 3-buten-1-ol as the coupling partner. Bis(trifluoromethyl)benzenes are good substrates in this process, regardless of the relative locations of the CF_3 groups (**19** and **20** were both formed in 80% yield). Evaluation of a small series of 5-substituted 1,3-bis(trifluoromethyl)benzene substrates indicated that this aromatic scaffold could be altered without significant loss of chemical efficiency (**21**–**23**: 60–89% yield). Trifluoromethylaromatics that bear nonfluorinated electron-withdrawing groups also undergo regioselective olefin addition to give the diethylarylphosphonate **24** (56% yield), morpholine amide **25** (39% yield) or sulfonamides **26**–**28** (52–83% yield).

A main limitation of this process lies in the requisite electronic properties of the trifluoromethylaromatic. Aryl substrates that have stronger electron-withdrawing groups (e.g. alkyl esters) undergo alkene coupling along with further reduction to give the corresponding alkylaromatics. On the other hand, Aryl substrates devoid of additional activating elements are poorly reactive under standard conditions. However, use of the more highly-reducing photoredox catalyst *N*-(1-naphthyl)phenothiazine (E = –2.23 V vs. SCE)[33] enabled formation of products **29**–**31**, albeit in diminished yields. Finally, the antiemetic drug, Aprepitant, could be effectively functionalized using this protocol, directly delivering **32** in 85% yield without affecting the other functional groups in the molecule.

In summary, we have described a catalytic system that accomplishes selective cleavage of a single C–F bond in trifluoromethylaromatic substrates. We demonstrate that this approach delivers novel radical intermediates and that these intermediates effectively couple with a broad collection of unactivated alkene subtypes. These conditions are mild, tolerant of many valuable functional groups, and provide the desired products with complete selectivity for the linear isomers. This protocol, driven by the action of two organic small molecule catalysts, can be employed in the activation of different trifluoromethyl aromatic substructures. Mechanistic studies and the application of this strategy to the synthesis of other high value product classes are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures and spectral data are available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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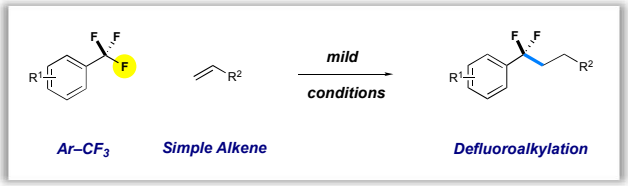
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