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Photochemical C-F Activation Enables Defluorinative Alkylation of Trifluoroacetates and -Acetamides

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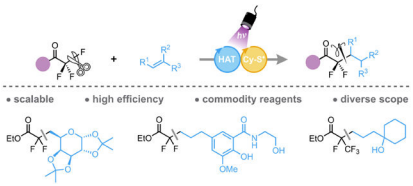
Abstract

The installation of *gem*-difluoromethylene groups into organic structures remains a daunting synthetic challenge despite their attractive structural, physical, and biochemical properties. A very efficient retrosynthetic approach would be the functionalization of a single C-F bond from a trifluoromethyl group. Recent advances in this line of attack have enabled the C-F activation of trifluoromethylarenes, but limit the accessible motifs to only benzylic *gem*-difluorinated scaffolds. In contrast, the C-F activation of trifluoroacetates would enable their use as a bifunctional *gem*-difluoromethylene synthon. Herein, we report a photochemically-mediated method for the defluorinative alkylation of a commodity feedstock: ethyl trifluoroacetate. A novel mechanistic approach was identified using our previously developed diaryl ketone HAT catalyst to enable the hydroalkylation of a diverse suite of alkenes. Furthermore, electrochemical studies revealed that more challenging radical precursors, namely trifluoroacetamides, could also be functionalized via synergistic Lewis acid/photochemical activation. Finally, this method enabled a concise synthetic approach to novel *gem*-difluoro analogs of FDA-approved pharmaceutical compounds

Graphical Abstract:



Keywords

Photochemistry; Carbon-Fluorine bond activation; Radical Chain

The emplacement of fluorine within organic substructures is among the more widely studied subsets of chemistry because of the numerous applications of fluorinated compounds.

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The Supporting Information including all experimental details, reaction optimization data, spectral characterization of novel compounds and cyclic voltammetry data is available free of charge on the ACS Publications website.

The *gem*-difluoromethylene unit is a particularly intriguing bioisosteric motif utilized in drug-discovery programs because of the exceptional pharmacokinetic (PK) properties, hydrogen bonding abilities, and enzymatic stability imparted by C-F bonds.[1–6] However, incorporation of this unique fluorinated linkage, especially in a late-stage fashion, remains a significant synthetic challenge because of the dearth of protocols currently available for the construction of CF_2 groups. A select range of methods for the incorporation of *gem*-difluoromethylene groups has been developed, most of which rely on specialized fluorinated functional groups and/or highly reactive fluorinating reagents (e.g., DAST or Selectfluor).[7–21] The shortcomings of the aforementioned methods emphasize the urgent need for mild, general methods for *gem*-difluoromethylene installation from commodity starting materials.

The selective activation of a single C-F bond in a trifluoromethyl (CF_3) group presents a significantly more attractive approach given the diverse array of readily available CF_3-containing structures, but also poses a formidable synthetic challenge. Recent efforts have been made in this area, with most protocols focusing on the activation of a CF_3-arene.[22–30] Although novel, the benzylic *gem*-difluoromethylene products have minimal utility as synthetic intermediates, limiting the possibility for further elaboration to diverse chemical structures. In contrast, the C-F activation of α-trifluoromethyl carbonyl compounds, especially trifluoroacetates, would enable their use as bifunctional lynchpins in the synthesis of complex CF_2-containing compounds (Figure 1). Following a defluorinative functionalization, the resulting *gem*-difluoro ester/carboxylates would offer several potential downstream transformations, allowing chemists to construct highly decorated fluorine-containing molecular scaffolds. The activation of a commodity, bench-stable starting material, such as ethyl trifluoroacetate ($0.06/mmol), has unquestionable advantages over niche materials such as bromo- or iododifluoroacetates ($2.58–7.15/mmol), which were previously the standard bifunctional feedstocks for such strategies. This concept is not without precedent, as a defluorinative alkylation (DFA) of α-trifluoromethyl carbonyl compounds via boryl radical activation was recently disclosed by Wang and Houk.[31] The boryl radical addition triggers a spin-center shift (SCS),[32] producing *gem*-difluoro *α*-carbonyl radicals (**1b**) that undergo Giese addition onto activated styrene derivatives. Although novel, the harsh and potentially dangerous conditions (super-stoichiometric *tert*-butyl peroxide at 120°C in MeCN) detract from the practicality of this method. Additionally, this report focused on trifluoroacetamides, including only a small subset of the more synthetically useful trifluoroacetates. Given these limitations, we sought to identify an alternate mode of catalysis for the DFA of trifluoroacetates via photochemical activation. The envisioned method would overcome the unresolved challenges in *gem*-difluoromethylene construction by transforming commodity starting materials under mild, scalable conditions.

According to calculations by Wang and Houk, the defluorinative SCS barrier for trifluoroacetates (**1a** → **1b**) was significantly high, contributing to the diminished DFA yields. Preliminary studies by Janata and Giese demonstrated that SCS fragmentation is generally much faster for charged species than their neutral counterparts.[33, 34] Therefore, we reasoned that the corresponding trifluoroacetate radical anion (**2a**), generated via single

electron reduction, would undergo a faster defluorinative SCS compared to the neutral intermediate **1a**, which was generated via boryl radical addition. Given the challenging reduction potential of alkyl trifluoroacetates (−2.0 V vs SCE), we turned to a recently discovered method utilizing $CO_2^{\bullet-}$ as a potent single electron reductant (−2.2 V vs SCE).[35, 36] We began our optimization studies (see SI for full details) by identifying ethyl trifluoroacetate (**3**) as a readily available commodity CF_3 radical precursor. Attempts to use photoredox catalysts to access the $CO_2^{\bullet-}$ reductant as previously described[35, 36] only furnished the desired DFA product in poor yields with a complex mixture of byproducts (see SI). We therefore envisioned an alternative mechanism relying on a photoactive hydrogen atom transfer (HAT) catalyst to activate the formate salt. Gratify-ingly, utilization of our previously developed diaryl ketone HAT catalyst (**5**)[37] accomplished the desired defluorinative alkylation of ethyl trifluoroacetate in quantitative yield. Examination of a suite of related diaryl ketone catalysts revealed that ketones substituted with one electron-withdrawing and one electron-donating aryl group performed the best. Such diaryl ketones exhibit low excited state energies because of captodative stabilization of the triplet ketyl diradical, making them particularly effective for photochemical HAT.[37] In addition to improved reactivity, this HAT catalyst tolerated a more diverse set of functional groups compared to the typical photocatalysts previously employed. Furthermore, we discovered that the structure of the thiol had a significant impact on the DFA yield. We reasoned that the thiol was critical to the mechanism as it engages in HAT with the radical Giese adduct as well as the formate, sustaining the proposed radical chain. Therefore, the optimal bond dissociation enthalpy should, in theory, fall between that of the newly formed C-H bond in the product (97–99 kcal/mol)[38] and the formyl C-H bond (88 kcal/mol).[38] A significant decrease in yield was observed when using aryl- (S-H BDE = ~80 kcal/mol)[38] rather than alkyl thiols (S-H BDE = 87–89 kcal/mol),[38] likely because the aryl S-H bond dissociation enthalpies are below that of the formyl C-H bond, resulting in inefficient HAT. Lower loadings (1–4 equivalents) of ethyl trifluoroacetate resulted in incomplete consumption of the olefin. Sodium outperformed any other alkaline earth metal or organic counterions of the formate salt. Consistent with literature precedent,[35,36] this reaction functioned best in strongly polar, aprotic solvents. Control studies confirmed the necessity of diaryl ketone catalyst **5**, thiol, and light for efficient reactivity (see SI). Additional experiments revealed that the loading of benzophenone **5** could be dropped to as low as 1 mol % with only a minimal decrease in yield given the same irradiation time, enabling practical DFA on multi-gram scale (see SI). Ultimately, these studies demonstrate that this novel strategy of diaryl ketone-mediated HAT is uniquely suited to facilitate the reduction of trifluoroacetates via $CO_2^{\bullet-}$ in the desired DFA.

As we set out to examine the scope of the DFA of ethyl trifluoroacetate, we found that a wide variety of alkenes bearing complex functional groups could be incorporated (Table 1). Unactivated terminal alkenes, which are unreactive under typical photoredox conditions,[39] produced the desired product in good to excellent yield. Remarkably, alkenes bearing alcohols, amines, amides, anhydrides, boronate esters, epoxides, and electron-rich heterocycles offered minimal to no off-target reactivity, demonstrating the excellent functional group tolerance of this reaction. Products **9**, **10**, and **14** were furnished from alkenes bearing alpha-heteroatomic, allylic C-H bonds without undesired activation at

these homolytically labile positions. A suite of alkene-containing natural products was also incorporated, including limonene oxide to afford **19**, demonstrating the applicability of this method to the synthesis of complex molecular architectures and sensitive functional groups. Compound **21**, derived from (−)-carvone, demonstrates the chemoselectivity for radical addition to an electron-rich alkene over an electron-poor enone. A range of internal alkenes also underwent DFA with excellent regioselectivity (**25–27**), remarkably including access to anhydride **26**. The fragmentation of the bridged-bicyclobutane observed in production of **27**, derived from (−)-nopol, confirms the radical nature of this process. In addition to unactivated alkenes, the scope was extended to electron-rich substrates including enamines, enamides, and enols (**28–37**). An enol ether derived from (D)-galactose underwent the DFA with excellent diastereoselectivity. Surprisingly, product **34** was isolated without any cleavage of the silyl ether despite the generation of stoichiometric fluoride byproducts. Unfortunately, styrene derivatives were unable to be incorporated into this DFA protocol.

We then sought to expand the protocol to other α-fluoroesters, enabling the construction of unique fluoroalkyl groups. A diverse range of alkenes were engaged in hydroalkylation with ethyl difluoroacetate, producing α-monofluoro esters. Ethyl difluoroacetate exhibited sluggish reactivity compared to ethyl trifluoroacetate, likely because of a more challenging reduction potential (−2.9 V vs SCE). However, at increased loadings and extended reaction times compounds **38–40**, **42** and **44** were obtained in good to excellent yield. Ethyl pentafluoropropionate (−2.6 V vs SCE) underwent a single, regioselective defluorinative alkylation with a similar range of alkenes (**41**, **43**, **45**), requiring no alteration of our standard reaction conditions. To our knowledge, such perfluoroesters have yet to be successfully engaged in defluorinative alkylation protocols.[31] These results demonstrate the excellent chemoselectivity and broad applicability of this method for the facile preparation of complex, synthetically challenging fluoroalkyl groups.

To demonstrate this method as a general protocol for DFA of trifluoromethyl carbonyl species, we sought to expand the scope of radical precursors to trifluoroacetamides, but initially only trace consumption of starting materials was observed. Cyclic voltammetry studies of trifluoroacetamide **46** (−2.2 V vs SCE) rationalized the inability of $CO_2^{\bullet-}$ to effect DFA under our original conditions. However, examination of a suite of Lewis acids revealed that a catalytic loading of $Zn(OTf)_2$ restored reactivity for *N*-aryl trifluoroacetamides by lowering the reduction potential by 0.5 V. Under these conditions, a set of unactivated, activated, and internal alkenes underwent DFA with super-stoichiometric loading of trifluoroacetamide **46** (Table 2). The reaction displayed minimal degradation of the excess trifluoroacetamide, and typically >90% of the remaining starting material was recovered by crystallization prior to chromatography.

Given the efficiency of the developed protocol, we probed its scalability (Scheme 1). Using 4-phenyl-1-butene as a model alkene, the reaction scale was increased 20- and 100-fold in batch with only a minimal decrease in yield. Importantly, no specialized glassware, equipment, or irradiation source was required, and the reaction was completed within the same time frame as in the small-scale reactions. We also demonstrated how increased scale allowed more efficient purification methods to be used, such as vacuum distillation, dramatically decreasing the process mass intensity (PMI)[40] for this transformation. In

particular, pinacol boronate **14** could not be isolated on 0.5 mmol because it decomposed when exposed to SiO_2 chromatography, but was successfully isolated by distillation on 25 mmol scale. The ease of scalability and cost-effectiveness of this photochemical transformation make it a remarkably practical method for the multi-gram preparation of *gem*-difluoromethylene compounds.

To showcase the applicability of this DFA method toward medicinal chemistry, we prepared three novel *gem*-difluoro precursor derivatives of FDA-approved small molecule APIs via concise syntheses (Scheme 2). The advantages of this photochemical DFA of unactivated alkenes (**53**, **55** and **57**) are evident when juxtaposed with classical approaches using bromo- or iododifluoroacetates, which necessitate unsustainable noble metal catalysis.[41] In addition to accessing the illustrated targets, incorporation of the *gem*-difluoroester motif renders these DFA products as excellent synthetic intermediates, enabling rapid exploration of chemical space for structure-activity relationship (SAR) studies. We anticipate that this method will enable the preparation of many novel *gem*-difluoro-containing scaffolds in medicinal chemistry that would have previously been infeasible.

Given previous literature precedent,[35] we propose that the developed DFA mechanism operates via a highly efficient radical chain process, mediated by both diaryl ketone and thiol HAT events (Figure 2). Photoexcitation of the diaryl ketone catalyst (**I**) accesses the triplet state diradical (**II**) that undergoes HAT from **IV**, generating **V**. Intermediate **V** accomplishes a single electron reduction of the α-trifluorocarbonyl substrate **VI**, producing the corresponding radical anion (**VII**) and CO_2 as a byproduct. Intermediate **VII** then undergoes an efficient defluorinative spin-center shift to produce the desired *gem*-difluoro radical (**VIII**), which engages in a Giese addition with an alkene. The Giese adduct (**IX**) is then quenched via HAT from a thiol (**XII**), generating a thiyl radical (**XI**) and the hydroalkylated product **X**. Thiyl radical **XI** then takes part in a single electron transfer with **III**, returning the diaryl ketone to its neutral ground state (**I**). Alternatively, this thiyl radical (**XI**) could perform HAT from **IV**, initiating a radical chain. Quantum yield experiments ($\phi = 4.9$) are in good agreement with a radical chain process as is suggested by previous mechanistic studies by Jui.[35] Examination of bond dissociation enthalpies (O-H in **III** = 102 kcal/mol;[37] C-H in **IV** = 87 kcal/mol[35]) and relative radical philicities suggest that the rate of HAT between **II** and formate **IV** is much faster than between **II** and **XII**. Therefore, we believe the diaryl ketone catalyst is not only critical in the initiation of this mechanism, but likely sustains the radical chain throughout the course of the reaction.

The method developed addresses a pressing need in the synthesis of fluorinated small molecules. The incorporation of *gem*difluoromethylene groups, a previously daunting synthetic challenge, is now readily accomplished by photochemical DFA. A novel HAT-initiated approach to radical chain reduction via $CO_2^{\bullet-}$ has been identified, facilitating the hydroalkylation of unactivated and electronically rich alkenes. This protocol serves as an exceptionally efficient and functionally tolerant strategy to prepare complex α,α-difluorocarbonyl derivatives, making it a prime candidate for the late-stage functionalization of complex molecules. The cost effectiveness of all reagents and starting materials, combined with the simple reaction set up and short irradiation time, make this reaction applicable to multi-gram scale preparation of fluorinated motifs in organic synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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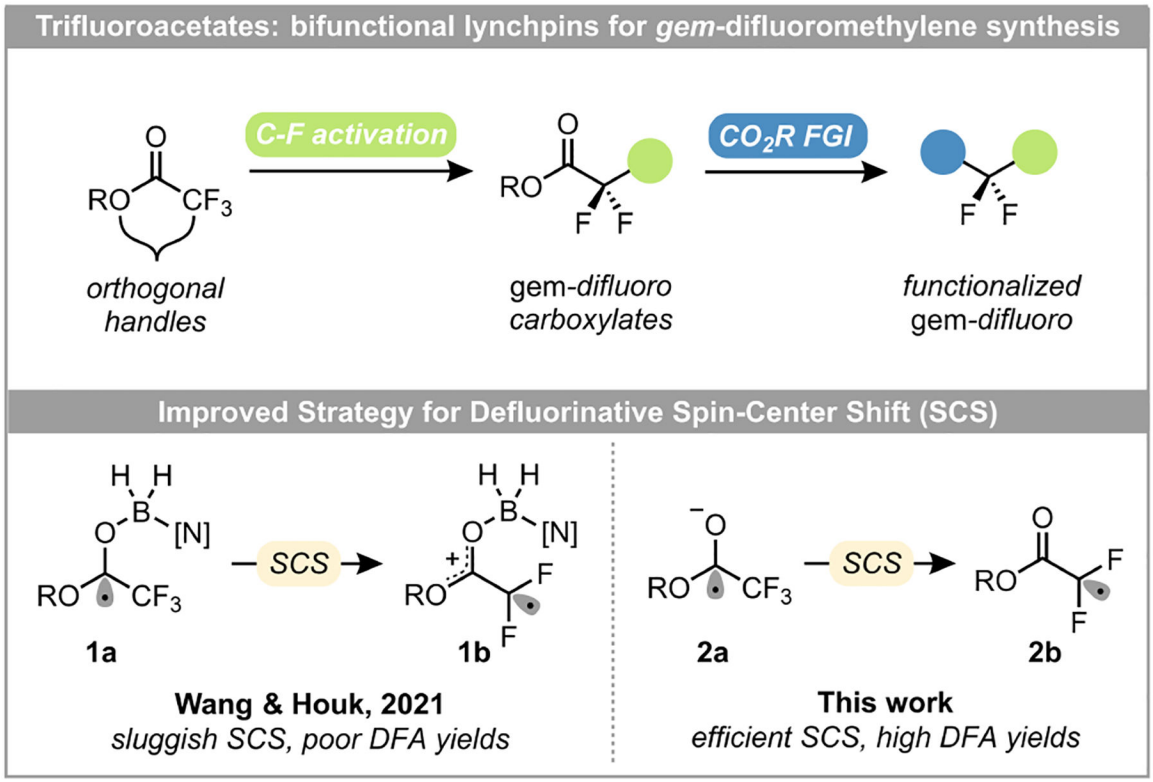


Figure 1.
Defluorinative functionalization strategies ([N] = *N,N*-dimethyl-4-aminopyridine)

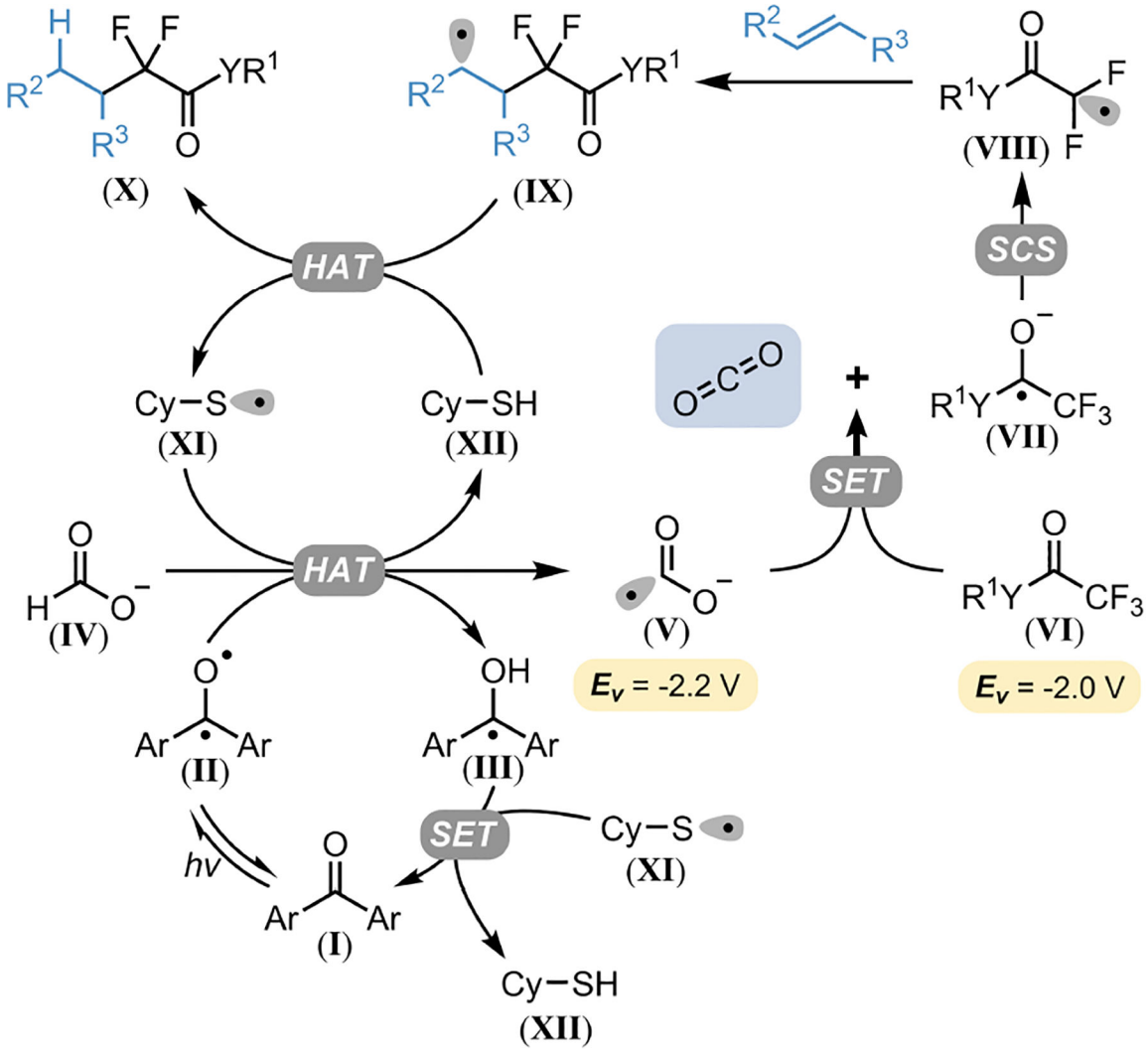
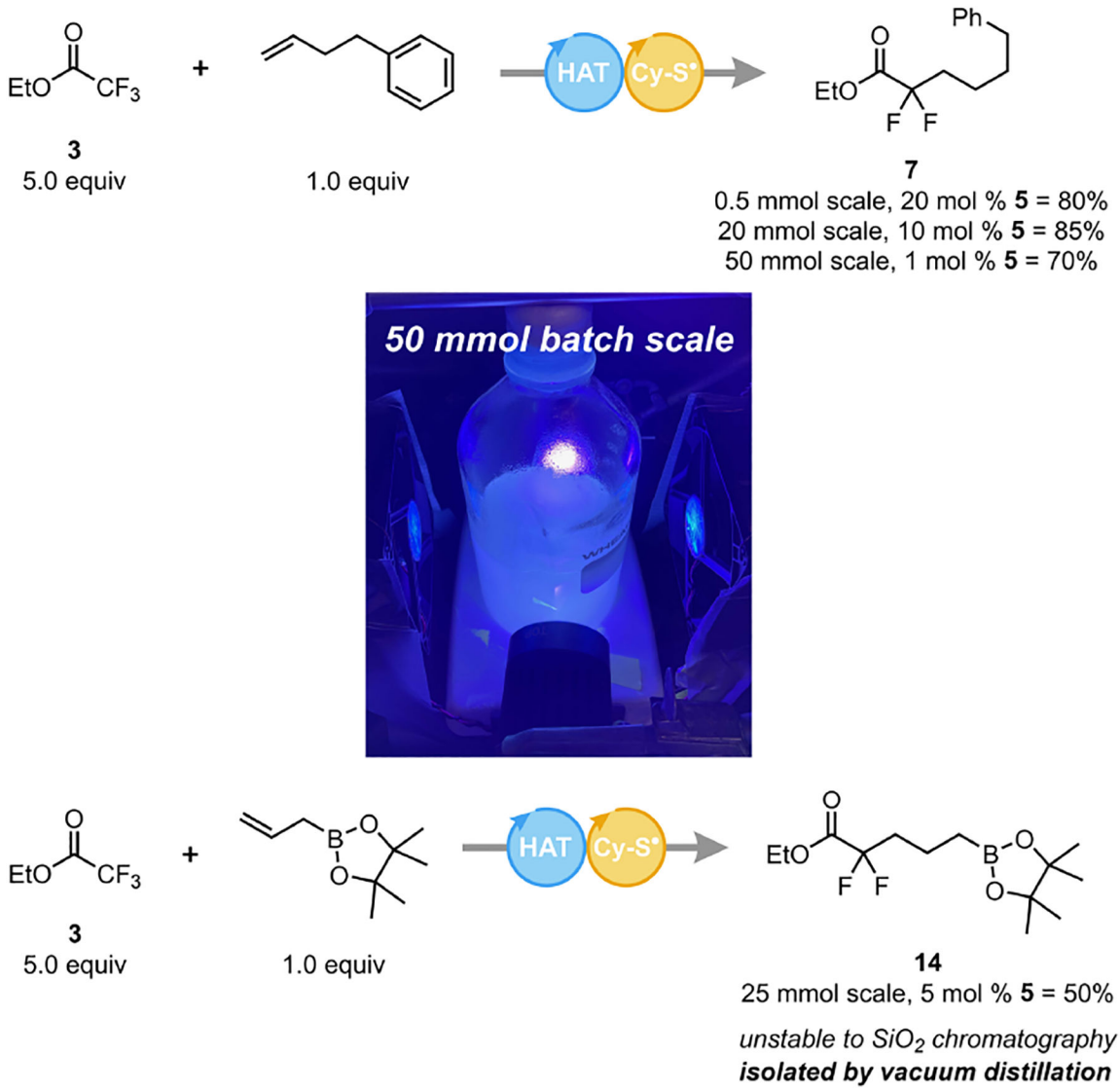


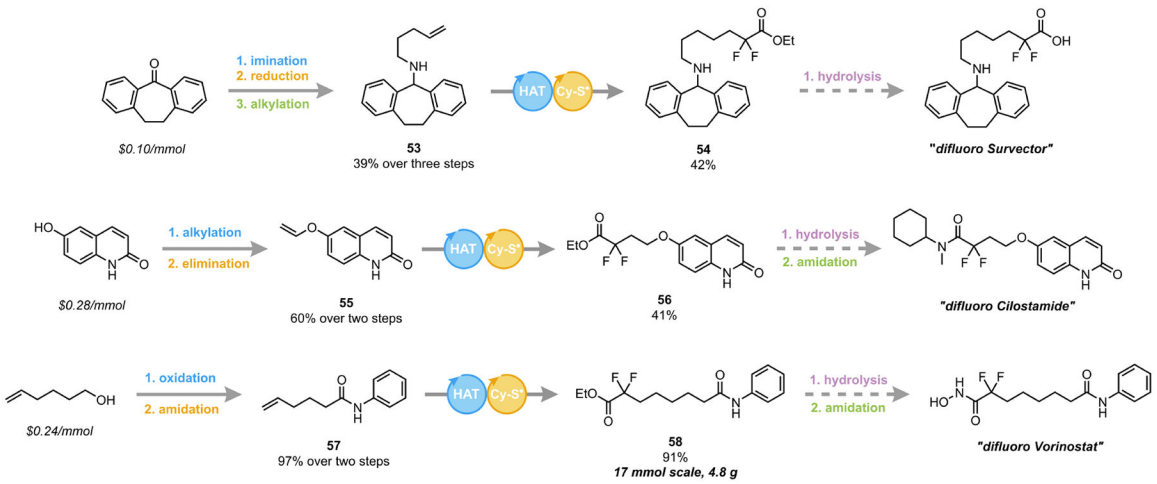
Figure 2.
Proposed Mechanism for Photochemical DFA of α-Trifluorocarbonyl Compounds



Scheme 1.

Multi-gram DFA of Ethyl Trifluoroacetate

Standard DFA conditions as in Table 1 using either 10, 5 or 1 mol % benzophenone **5**. See SI for further details



Scheme 2.

Synthesis of *gem*-difluoro analogs of select APIs

See SI for alkene preparation details. Standard DFA conditions as in Table 1

Table 1.

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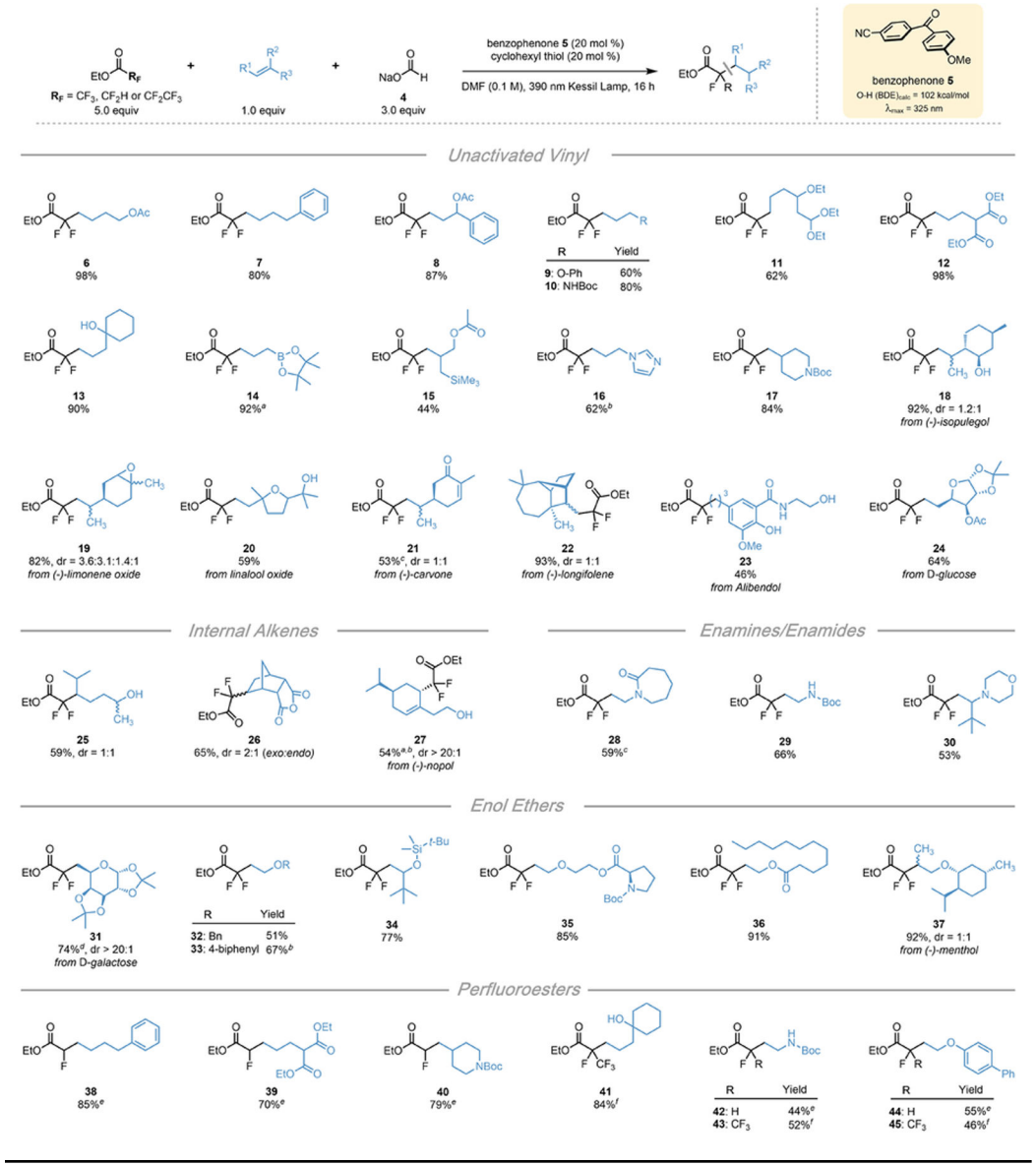
Scope of Alkenes in the DFA of Perfluorinated Esters



All values indicate the yield of the isolated product. Unless otherwise noted: alkene (1 equiv, 0.5 mmol), ethyl trifluoroacetate (5 equiv, 2.5 mmol), sodium formate (3 equiv, 1.5 mmol) benzophenone **5** (20 mol %, 0.10 mmol), cyclohexanethiol (20 mol %, 0.10 mmol), DMF (0.1 M), 16 h, irradiating with a 390 nm PR160 Kessil lamp.

[a]H NMR yield of crude reaction.

[b]Using 5 equiv of sodium formate and 10 equiv of ethyl trifluoroacetate.

[c]Using 10 equiv of ethyl trifluoroacetate.

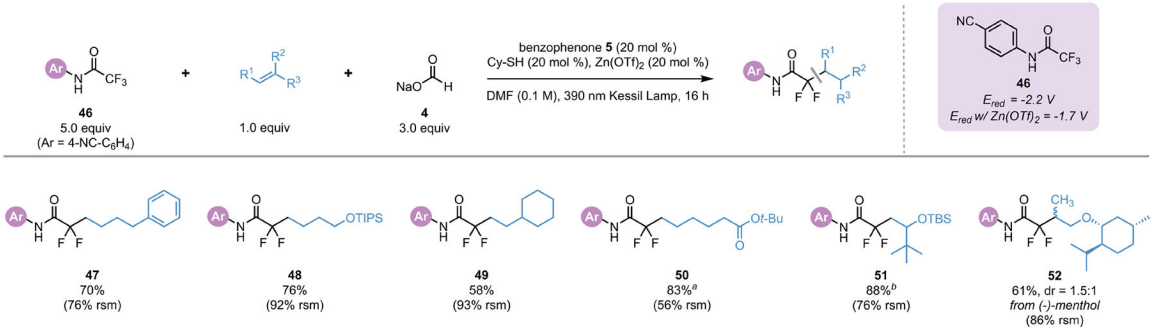
[d]Isolated as the corresponding carboxylic acid.

[e]Using ethyl difluoroacetate (10 equiv, 5.0 mmol) in place of ethyl trifluoroacetate with 48 h reaction time.

[f]Using ethyl pentafluoropropionate (5 equiv, 2.5 mmol) in place of ethyl trifluoroacetate.

Table 2.

Scope of Alkenes in the DFA of *N*-Aryl Trifluoroacetamides



All values indicate the yield of the isolated product. Unless otherwise noted: alkene (1 equiv, 1.0 mmol), *N*-(4-cyanophenyl)-trifluoroacetamide (5 equiv, 5.0 mmol), sodium formate (3 equiv, 3.0 mmol) benzophenone **5** (20 mol %, 0.20 mmol), cyclohexanethiol (20 mol %, 0.20 mmol), Zn(OTf)2 (20 mol %, 0.20 mmol), DMF (0.1 M), 16 h, irradiating with a 390 nm PR160 Kessil lamp. RSM = percent recovered *N*-(4-cyanophenyl)-trifluoroacetamide (**46**) based on 4 equiv.

[a] Isolated as the corresponding carboxylic acid.

[b] Using "recycled" **46** recovered by precipitation protocol from previous DFA reactions.