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Organophotoredox Hydrodefluorination of Trifluoromethylarenes with Translational Applicability to Drug Discovery

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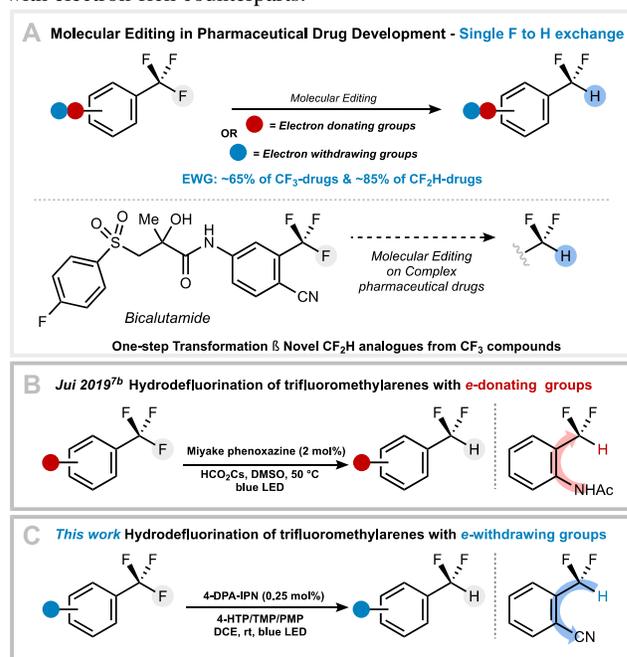
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Supporting Information Placeholder

ABSTRACT: Molecular editing such as insertion, deletion and single atom exchange in highly functionalized compounds is an aspirational goal for all chemists. Here, we disclose a photoredox protocol for the replacement of a single fluorine atom with hydrogen in a range of electron-deficient trifluoromethylarenes including complex drug molecules. A robustness screening experiment shows that this reductive defluorination tolerates a range of functional groups and heterocycles commonly found in bioactive molecules. Preliminary mechanistic studies allude to a catalytic cycle whereby the excited state of the organophotocatalyst is reductively quenched by the hydrogen atom donor, and returned in its original oxidation state by the trifluoromethylarene.

Fluorine-containing molecules have found applications in material science, the pharmaceutical and agrochemical sector because of the thermodynamic and kinetic stability of C–F σ -bonds.¹ However, this stability has led to the accumulation of organofluorine compounds, a concern of increasing importance for the environment.² As a result, the field of C–F functionalization is as active as C–F bond construction, and a number of stoichiometric and catalytic protocols have emerged involving both C(sp³)–F and C(sp²)–F bonds.³ Molecular editing enabling precision hydrodefluorination (HDF) of trifluoromethylarenes into difluoromethylarenes for applications in drug discovery remains a highly challenging endeavor because the bond dissociation energy (BDE) of C–F bonds decreases as fluorine substitution takes place (Scheme 1A).^{4a} Pioneering studies have reported strategies employing boron, silylium or phosphine adducts,⁵ and (transition) metals, but uncontrolled defluorination could not be avoided for many of these processes.⁶ Recently, Jui and co-workers considered photoredox catalysis, and demonstrated that reversible single electron transfer (SET) enables selective reductive defluorination of trifluoromethylarenes *via* arene radical anions that undergo fluoride expulsion. Hydrodefluorination was accomplished with

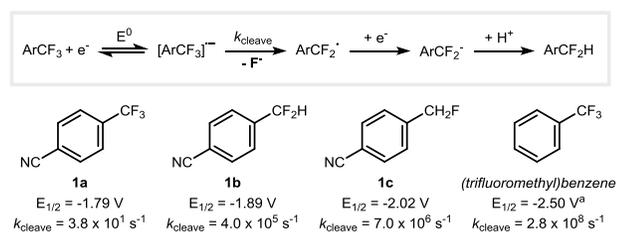
cesium formate and the Miyake phenoxazine photocatalyst under blue light activation (Scheme 1B).^{7b} This elegant protocol is applicable to unactivated trifluoromethylarenes adorned with electron donating groups. Despite these significant advances in the field, HDF of highly activated trifluoromethylarenes featuring electron withdrawing groups (EWG) to access difluoromethylarenes has not been accomplished. This is astonishing because the majority of tri- and difluoromethylated drugs feature the CF₃ or CF₂H group on electron poor arenes due to their higher resistance to oxidation and defluorination in comparison with electron-rich counterparts.⁸



Scheme 1. Hydrodefluorination of trifluoromethylarenes in the context of drug discovery.

More generally, the difluoromethyl group (CF₂H) is increasingly important in pharmaceutical research because it is a lipophilic hydrogen bond donor, and a bioisostere for thiol, alcohol, or amine groups.^{9,10} In the quest for a transformation that can expand translational potential in drug discovery, we invented a HDF process for electron-deficient trifluoromethylarenes applying photoredox catalysis (Scheme 1C).

Detailed mechanistic studies reported in 1997 by Savéant, Thiébaud and co-workers provided useful information on the electrochemical reductive cleavage of C–F bonds for 4-cyanofluorotoluenes **1a–c** and trifluoromethylbenzene.^{4a} The process involves fluoride expulsion from an anion radical, followed by reduction of the resulting neutral radical, and rapid protonation. As expected, the standard reduction potential for the formation of the anion radical decreases from **1a** to **1c**, although these are closely spaced, while the instability of the primary radical anion towards fluoride mesolytic cleavage increases. Facile exhaustive defluorination is observed experimentally, the challenge at hand for this category of highly activated substrates (Scheme 2).

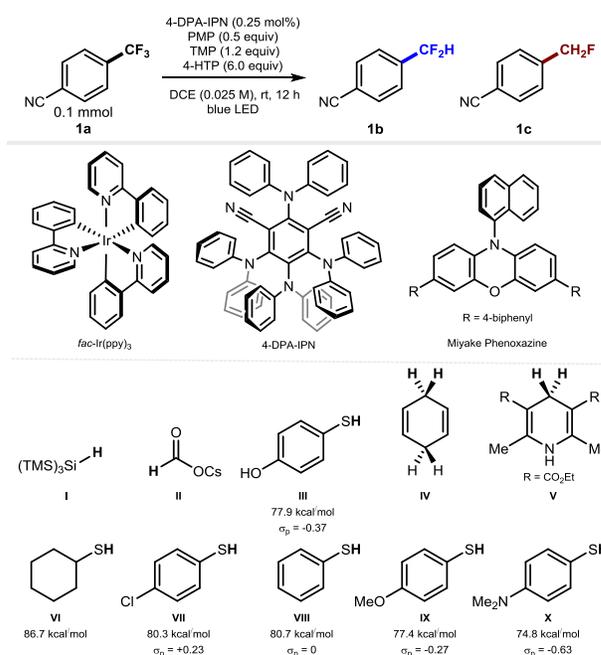


Scheme 2. Electrochemical reductive cleavage of trifluoromethylarenes. Standard reduction potentials (V vs standard calomel electrode (SCE) in DMF) and cleavage rate constants for 4-cyanofluorotoluenes **1a–c**, and trifluoromethylbenzene. ^aE_{1/2} (V vs SCE in DMF) taken from reference 4b.

Preliminary experiments with the model substrate 4-(trifluoromethyl)benzonitrile **1a** showed that no product **1b** was formed applying the metal-based protocols reported by Prakash or Lalic and co-workers (Table 1, entries 1 and 2).⁶ Moreover, the conditions applied for known photoredox defluorination led mainly to the recovery of starting material (Table 1, entries 3–5).^{7a–7c} The more electrophilic nature of the difluorinated benzylic radical derived from electron-deficient trifluoromethylarene **1a** compared to electron-rich substrates encouraged a study examining hydrogen atom donors (HAD) other than cesium formate,^{7b} or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane.^{7c} This investigation indicated that the nature of the HAD was critically important for reactivity (Table 2, entries 9–17); moreover, the use of a base was essential as reductive defluorination did not proceed in its absence (Table 2, entry 20). Gratifyingly, the reaction of **1a** in the presence of 2.5 mol% *fac*-Ir(ppy)₃, 4-hydroxythiophenol (4-HTP) and a combination of 2,2,6,6-tetramethylpiperidine (TMP) and 1,2,2,6,6-pentamethylpiperidine (PMP) in 1,2-dichloroethane (DCE) under visible light activation (blue LED) gave preferentially the difluoromethylated product **1b** in 53% yield with 5:1 selectivity (**1b**:**1c**). The fully reduced 4-methylbenzonitrile product was not detected in the crude reaction mixture (Table 1, entry 6). Organophotocatalyst 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile (4-DPA-IPN) (2.5 mol%) was a suitable metal-free replacement for *fac*-Ir(ppy)₃ affording **1b** in 62% yield with similar selectivity (Table 1, entry 7). Lowering the loading of 4-DPA-IPN to 0.25 mol% did not affect the reaction outcome (65% yield, **1b**:**1c** = 5:1) (Table 1,

entry 8). Other hydrogen atom donors including thiols other than 4-HTP, 1,4-cyclohexadiene, the Hantzsch ester, (Me₃Si)₂SiH, or cesium formate were less or not suitable under otherwise similar reaction conditions (Table 1, entries 9–17). Control experiments demonstrated that the photocatalyst, hydrogen atom donor, base, and blue light are essential components for this transformation to proceed (Table 1, entries 20–23).

Table 1. Range of experiments for the hydrodefluorination of 4-(trifluoromethyl)benzonitrile **1a**.

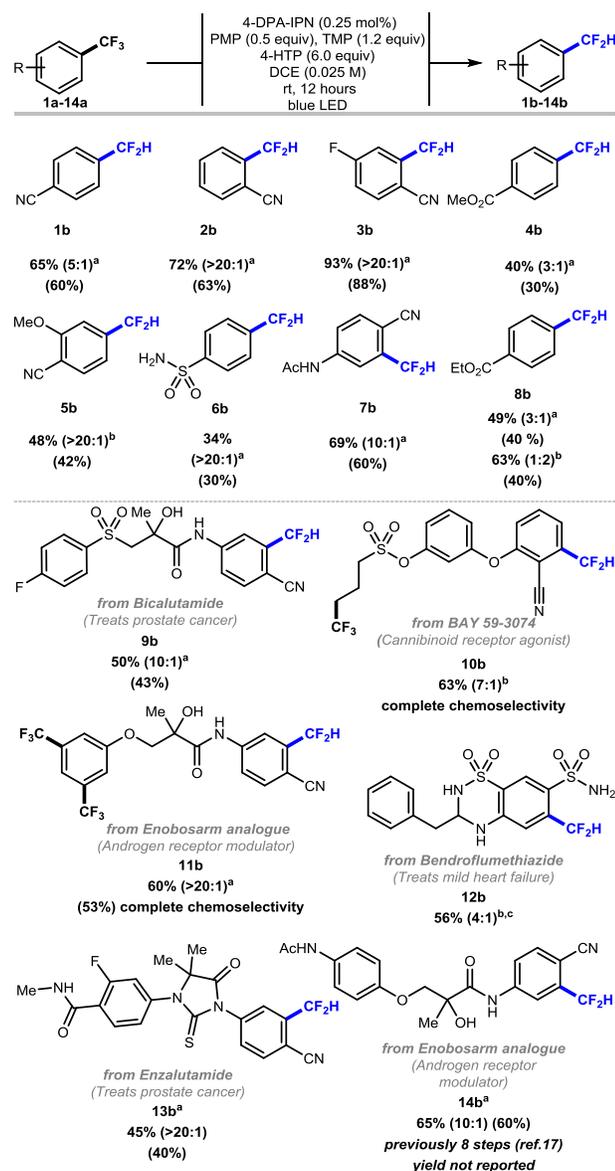


Entry	Alterations to conditions	Yield ^a (ratio 1b : 1c)
1	Mg ⁰ (30 equiv), H ₂ O/AcOH/DMSO	0%
2	Pd(OAc) ₂ (3 mol%), CuF ₂ (20 mol%), 2-pyridone (5 mol%), KOSiMe ₃ (7.0 equiv), DMF, 45 °C, then tBuOH (2.0 equiv), 60 °C	0%
3 ^b	Miyake Phenoxazine (2 mol%), II (3 equiv), blue LED, DMSO, 50 °C, 24 h	4% (2 : 1)
4 ^c	<i>fac</i> -Ir(ppy) ₃ (1.0 mol%), TMP (2.0 equiv), HBPIn (3.0 equiv), blue LED, DCE, rt, 24h.	0%
5 ^d	PTH (10 mol %), VI (10 mol %), II (3 equiv), blue LED, 5% H ₂ O/DMSO, rt, 24 h.	0%
6	<i>fac</i> -Ir(ppy) ₃ (2.5 mol%)	53% (5 : 1)
7	4-DPA-IPN (2.5 mol%)	62% (5 : 1)
8	4-DPA-IPN (0.25 mol%)	65% (5:1)
9	I (6 equiv) instead of III	Trace
10	II (6 equiv) instead of III	Trace
11	IV (6 equiv) instead of III	0%
12	V (6 equiv) instead of III	15% (5 : 1)
13	VI (6 equiv) instead of III	4% (8 : 1)
14	VII (6 equiv) instead of III	4% (8 : 1)
15	VIII (6 equiv) instead of III	5% (8 : 1)
16	IX (6 equiv) instead of III	22% (7 : 1)
17	X (6 equiv) instead of III	22% (7 : 1)
18	no PMP	51% (5 : 1)
19	no TMP	31% (> 20 : 1)
20	no TMP and no PMP	0%
21	no light	0%
22	no 4-HTP	0%
23	no photocatalyst	0%

^aCombined yields of **1b** and **1c** determined by ¹⁹F NMR using 4-fluoroanisole as internal standard; the ratio of **1b**:**1c** is given in parentheses.

ses. ^bReaction carried out on **14a**. ^cConditions of ref. 7c in the absence of alkene. ^dConditions of ref. 7a in the absence of alkene. PTH = 10-phenyl-10H-phenothiazine. BDE values from ref. 11.

With the optimal reaction conditions in hand, we explored the generality of this HDF reaction towards various electron-deficient trifluoromethylarenes (Scheme 3). 2-(Trifluoromethyl)benzonitrile gave **2b** in 63% yield, and a selectivity of > 20:1 favoring CF₂H over CH₂F. Additional functionalities on the aromatic ring including fluorine, methoxy, or acetamide substituents were tolerated (**3b**, **5b** and **7b**, 42–88%) with high selectivity for CF₂H (> 10:1). Methyl and ethyl 4-(trifluoromethyl)benzoate **4a** and **8a** with a carboxylic ester instead of a cyano group were transformed into the corresponding difluoromethylated analogues **4b** and **8b** in moderate yields (30% and 40%) and 3:1 selectivity. When the catalyst loading was increased to 2.5 mol%, the yield was improved (**8b**, 63%) but the product resulting from double reductive defluorination was formed preferentially (**8b**:**8c** = 1:2).

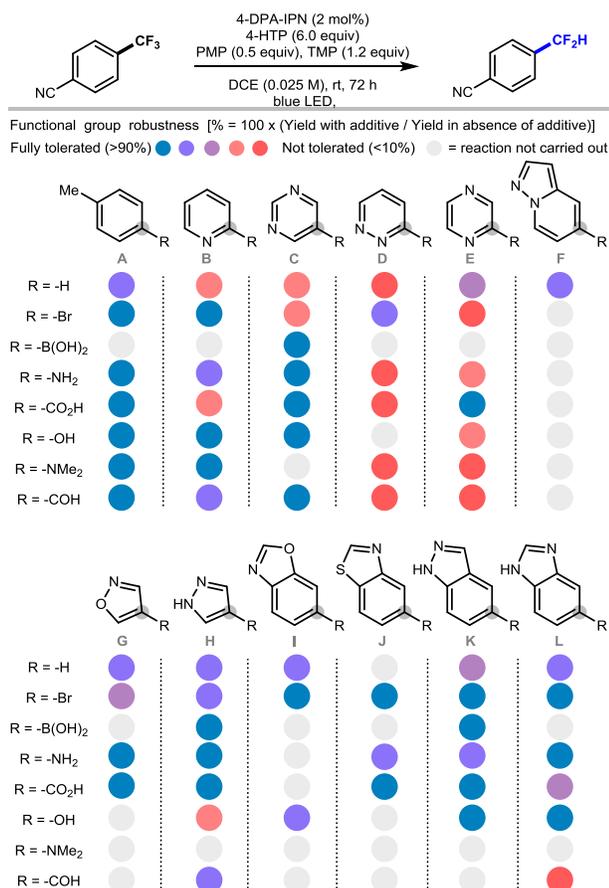


Scheme 3. Scope of photocatalytic HDF of electron-deficient trifluoromethylarenes. ^aGeneral reaction conditions: 0.1 mmol of **1a-14a**, 0.25 mol% 4-DPA-IPN, 0.5 equiv PMP, 1.2 equiv TMP, 6.0 equiv 4-HTP in DCE (0.025 M), irradiated with 455 nm LED light at rt for 12 hours. Yields and CF₂H:CH₂F ratio determined by quantitative ¹⁹F NMR spec-

troscopy using 4-fluoroanisole as internal standard. Yields of isolated products (RCF₂H only) are given in parentheses. ^b2.5 mol% 4-DPA-IPN. ^cReaction solvent is DCE/DMSO (19:1, v/v, c = 0.025 M).

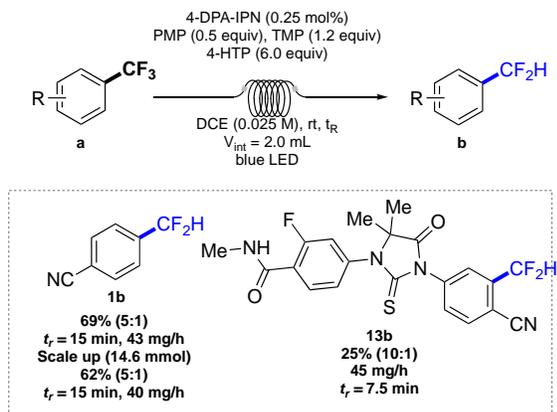
Complex molecules of biological relevance were examined next. Bicalutamide, a drug used to treat prostate cancer, underwent reductive defluorination affording **9b** isolated in 43% yield and 10:1 CF₂H/CH₂F selectivity.¹² As expected, the doubly trifluoromethylated cannabinoid receptor agonist BAY 59-3074 **10a** reacted exclusively at the arene. An analogue of Enobosarm featuring three trifluoromethylaryl groups served the purpose to investigate a more complex case of “arene versus arene” chemoselectivity.¹³ Hydrodefluorination occurred with excellent CF₂H/CH₂F selectivity (> 20:1) at a single site, leaving the 3,5-bistrifluoromethylarene motif untouched (**11b**, 53%); this result corroborates a control experiment that demonstrated that 3,5-bistrifluoromethylbenzene was unreactive under our reaction conditions. Bendroflumethiazide **12a**, a drug used for mild heart failure and hypertension *via* vasodilation,¹⁴ was also subjected to C–F bond reduction. Our protocol, slightly modified in order to solubilize the starting material (solvent mixture of DCE/DMSO (19/1), gave CF₂H-bendroflumethiazide **12b** in 56% yield although in this case with decreased selectivity (CF₂H:CH₂F ratio = 4:1). This result is significant because sulfonamides and/or secondary amines can coordinate metals such as copper for example, rendering late stage cross-coupling strategies towards aryl–CF₂H bond construction more challenging.¹⁵ The usefulness of this HDF protocol was further illustrated with the synthesis of **14b**, a molecule which has demonstrated strong androgen receptor binding affinity *in vivo*.¹⁶ This biologically relevant compound has previously been prepared applying an eight-step linear sequence of reactions.¹⁷ With our protocol in hand, **14b** was obtained in two steps; the trifluoromethylated precursor **14a** was prepared in a single step from commercially available starting materials,¹⁸ and HDF gave **14b** that was isolated in 60% yield, uncontaminated by the monofluorinated side-product. Alternative photoredox HDF protocols were not effective.¹⁹

Given the relevance of this novel HDF methodology for drug discovery, we conducted a robustness screening experiment to gain further information on its tolerance to various pharmacophores and functionalities (Scheme 4).²⁰ Common functional groups compatibility was investigated with para-substituted toluenes **A**, and showed excellent tolerance to bromine, amine, alcohol, carboxylic acid, and aldehyde functionalities. Next, a range of 2-pyridines **B**, 5-pyrimidines **C**, 3-pyridazines **D** and 2-pyrazines **E** were subjected to screening. While 2-pyridines and 5-pyrimidines were broadly tolerated, 3-pyridazines and 2-pyrazines more often prevented hydrodefluorination. Five-membered heterocycles isoxazoles **G** and pyrazoles **H** with various substitution patterns were well accepted. In addition, fused heteroarenes such as pyrazolopyridines **F**, benzooxazoles **I**, benzothiazoles **J**, indazoles **K** and benzoimidazoles **L** did not hamper the HDF of **1a**, a benefit considering the frequency of these motifs in modern pharmaceutical drugs and agrochemicals.²¹ Many of the heterocycles investigated in this study could potentially deactivate transition-metal catalysts by coordination,^{22,23} and the HDF offers an alternative to these methods.



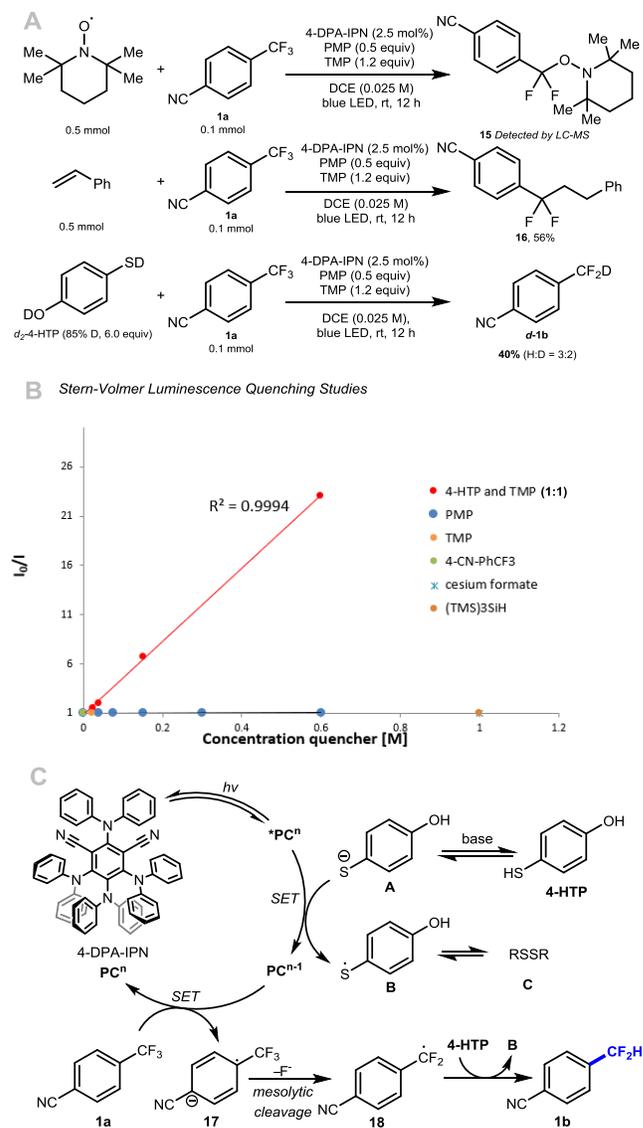
Scheme 4. Additive-Based Reaction Screening. All reactions were performed on 2.5 μmol scale in a 96-well plate suited for photoredox chemistry. Samples of crude mixtures were analyzed by GC-FID/MS.¹⁸

Continuous-flow chemistry is known for more uniform irradiation, and was considered to scale-up the HDF of trifluoromethylarene **1a** (Scheme 5).²⁴ The first reactions were performed in a microflow system made of a perfluoroalkoxyalkane (PFA) capillary (internal volume, 2.0 mL) on a scale similar to batch for comparative purpose (0.2 mmol); **1b** was obtained in 69% yield and selectivity similar to batch (CF₂H:CH₂F, 5:1), within 15 minutes residence time (*t_R*) at a flow rate of 0.133 μL/min. Furthermore, **13b** was isolated in 25% yield in 10:1 selectivity after 7.5 minutes *t_R* at a flow rate of 0.266 μL/min. Starting with 2.5 g of **1a** (14.6 mmol), 1.4 g of **1b** (5:1) was produced in 15 minutes *t_R* at a flow rate of 0.133 μL/min.



Scheme 5. Photoredox hydrodefluorination under continuous-flow conditions; the internal volume of the capillary (*V_{int}*) was 2.0 mL, *t_R* = residence time. Yields of isolated products.

Various experiments were performed to gain preliminary insight on the mechanism of this transformation (Scheme 6).



Scheme 6. A. Mechanistic experiments. General conditions: 2.5 mol% of 4-DPA-IPN, 0.5 equiv PMP, 1.2 equiv TMP, 6.0 equiv 4-HTP in DCE (0.025 M), irradiated with blue LED (455 nm) at rt for 12 hours; Yields determined by quantitative ¹⁹F NMR using 4-fluoroanisole as internal standard. B. Stern-Volmer luminescence quenching studies. C. Proposed reaction mechanism.

A radical scavenger experiment performed with TEMPO led to the formation of the TEMPO-adduct **15** (Scheme 6A). Moreover, when the reaction of **1a** was carried out in the presence of styrene and 4-HTP, **16** was obtained in 56% yield (Scheme 6A). Taken together, these data are consistent with the formation of a benzylic radical species formed by mesolytic C–F bond cleavage of a primary anion radical. Deuterium was incorporated in the product (40% yield, H/D ratio of 3:2) when *d*₂-4-HTP was used instead of 4-HTP, indicating that 4-HTP is a plausible HAD in this reaction (Scheme 6A). Stern-Volmer luminescence quenching experiments provided additional information (Scheme 6B). We found that the combination of 4-HTP and TMP (1:1) quenches *PCⁿ; this is in contrast to TMP, PMP, cesium formate or (TMS)₃SiH. The inability of trifluoromethylarene **1a** to quench the excited state of the photocatalyst *PCⁿ advocates against an oxidative quenching cycle whereby the anion radical **17** would result from SET involv-

ing $^*PC^n/PC^{n+1}$ (-1.28 V).²⁵ These preliminary findings led us to propose the reductive quenching cycle shown in Scheme 6C as a plausible mechanistic pathway. Irradiation with light affords the excited state catalyst PC*. Under basic conditions, deprotonation of 4-HTP leads to a thiolate **A** capable of reductive quenching of PC*, a process yielding the corresponding thiyl radical **B**,²⁶ and the reduced photocatalyst ($PC^n/PC^{n-1} = -1.52$ V).²⁵ In this scenario, the substrate acts as the oxidant to return the photocatalyst to its native oxidation state with concomitant release of the anion radical species that undergoes mesolytic cleavage of fluoride.²⁷ This latter process leads to the C-centered difluorobenzyl radical **18** which is trapped by the hydrogen bond donor 4-HTP affording the difluoromethylarene **1b**.

In conclusion, this study establishes that the reductive defluorination of electron poor trifluoromethylarenes is accomplished under basic conditions with 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile as the organophotocatalyst, 4-hydroxythiophenol as the hydrogen bond donor, and blue light. This operationally simple protocol tolerates a wide range of functional groups and heteroarenes frequently seen in medicinal chemistry programs, and allows the direct conversion of complex trifluoromethylated drugs into their difluoromethyl analogues. Preliminary mechanistic studies allude to a catalytic cycle whereby the photocatalyst is reduced by the HBD and returned in its native oxidation state by the electron-deficient trifluoromethylarene that acts as oxidant.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

T.K. and C.W.A. are employees of Pfizer Inc.

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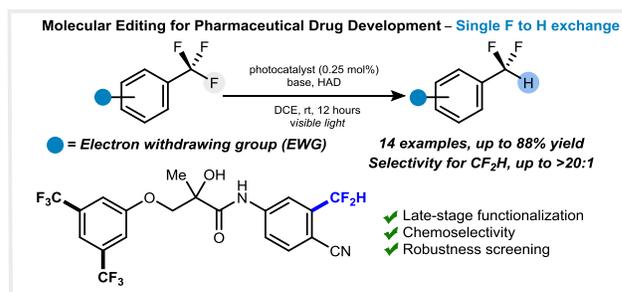
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