Organophotoredox Hydrodefluorination of Trifluoromethylarenes with Translational Applicability to Drug Discovery

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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 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 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 the pharmaceutical and agrochemical sector because of the thermodynamic and kinetic stability of C–F σ-bonds, a property offering protection against enzymatic metabolism. Today, pharmacophores often bear a trifluoromethyl or difluoromethyl motif in an aromatic system, thereby increasing the demand for methods to install or interchange these groups in a late-stage fashion. In this context, 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). Pioneering studies have reported strategies employing boron, silylium or phosphine adducts, and (transition) metals, but uncontrolled defluorination could not be avoided for many of these processes. Jui and co-workers demonstrated that hydrodefluorination is accomplished with cesium formate and the Miyake phenoxazine photocatalyst under blue light activation (Scheme 1B). This 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 to access difluoromethylarenes has not been accomplished. This is unexpected because most 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. Mechanistic studies reported in 1997 by Savéant and Thibault provided useful information on the electrochemical reductive cleavage of C–F bonds for 4-cyanofluorotoluene 1a−c and trifluoromethylbenzene. The process involves fluoride expulsion from a radical anion, followed by reduction of the resulting neutral radical, and protonation. As expected, the standard reduction potential for the formation of the

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radical anion decreases from $1a$ to $1c$, although these are closely spaced (narrow redox window), while the instability of the radical anion toward fluoride mesolytic cleavage increases. Facile exhaustive defluorination is observed experimentally, the challenge at hand for these 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

$$\text{ArCF}_3 + e^- \rightarrow \text{ArCF}_2^- \quad \text{K_{rate}} = 3.8 \times 10^{-6} \text{s}^{-1}$$

$1a$

$E_{1/2} = 1.79 \text{~V}$

$K_{rate} = 3.8 \times 10^{-6} \text{~s}^{-1}$

$1b$

$E_{1/2} = 1.99 \text{~V}$

$K_{rate} = 4.0 \times 10^{-6} \text{~s}^{-1}$

$1c$

$E_{1/2} = 2.02 \text{~V}$

$K_{rate} = 7.0 \times 10^{-6} \text{~s}^{-1}$

$3\text{f}$

$E_{1/2} = 2.50 \text{~V}$

$K_{rate} = 2.8 \times 10^{-6} \text{~s}^{-1}$

$\text{F}_{1/2} (\text{V vs SCE in DMF}).^6$

Preliminary experiments with 4-(trifluoromethyl)-benzonitrile $1a$ showed that no product $1b$ was formed applying the protocols of Prakash or Lalic (Table 1, entries 1 and 2). Moreover, the conditions applied for known photoredox defluorination using trifluoromethylarenes led mainly to recovery of starting material (Table 1, entries 3–5). The more electrophilic nature of the difluorinated benzylic radical derived from electron-deficient $1a$ compared to electron-rich substrates encouraged a study examining hydrogen atom donors (HAD) other than cesium formate. Gratifyingly, the reaction of $1a$ in the presence of 2.5 mol % $\text{fac-Ir(ppy)}_3$, 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 $1b$ in 53% with 5:1 selectivity (Table 1, entry 6). The fully reduced 4-methylbenzonitrile product was not detected (Table 1, entry 6). Organo-photocatalyst 2,4,5,6-tetakis(diphenylamino)isophthalonitrile (4-DPA-IPN, 2.5 mol %) was a suitable metal-free replacement for $\text{fac-Ir(ppy)}_3$, affording $1b$ in 62% yield with similar selectivity (Table 1, entry 7). Lowering catalyst loading did not affect the reaction outcome (65% yield, $1b:1c = 5:1$) (Table 1, entry 8). Hydrogen atom donors including thiols other than 4-HTP, 1,4-cyclohexadiene, the Hantzsch ester, $(\text{Me}_3\text{Si})_3\text{SiH}$, or CsOAc were less or not suitable under otherwise similar reaction conditions (Table 1, entries 9−17). The photocatalyst, HAD, base, and blue light are essential components for this transformation to proceed (Table 1, entries 18–23).

With the optimal reaction conditions in hand, we explored the generality of this HDF reaction (Scheme 3). 2-(Trifluoromethyl)benzonitrile gave $2b$ in 63% yield and >20:1 selectivity favoring CF2H. Additional functionalities on the aromatic ring including fluorine, methoxy, or acetamide 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 carbonyl ester instead of a cyano group were transformed into 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.

Table 1. Experiments for the Hydrodefluorination of 4-(Trifluoromethyl)benzonitrile $1a$

| Entry | Alterations to conditions | Yield$^d$ (ratio $1b:1c$) |
|-------|-------------------------|--------------------------|
| 1     | $\text{Mg}^0$ (30 equiv), H$_2$O/ArOH/DMSO | 0% (trace) |
| 2     | Pd(OAc)$_2$ (3 mol%), CuF$_2$ (20 mol%), 2-pyridine (5 mol%), KO$_2$Si$_2$H$_2$ (7.0 equiv), DCE, 45 °C, then dioxane (2.0 equiv), 60 °C | 0% |
| 3     | Miyake Phenoxazine (2.5 mol%), II (3 equiv), blue LED, DMSO, 50 °C, 24 h | 4% (2:1) |
| 4     | fac-Ir(ppy)$_3$ (1.0 mol%), TMP (2.0 equiv), HBPin (3.0 equiv), blue LED, DCE, rt, 24 h | 0% |
| 5     | PTH (10 mol%), VI (10 mol%), II (3 equiv), blue LED, 5% H$_2$O/DMSO, rt, 24 h | 0% |
| 6     | fac-Ir(ppy)$_3$ (2.5 mol%) | 53% (5:1) |
| 7     | 4-DPA-IPN (2.5 mol%) | 62% (5:1) |
| 8     | No alteration | 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% |

$^a$Combined yields of $1b$ and $1c$ determined by $^{19}$F NMR using 4-fluorooanisole as internal standard; the ratio of $1b:1c$ is given in parentheses. $^b$Reaction carried out on $1a$. $^c$Conditions of ref 7b with no alkene. $^d$Conditions of ref 7b with no alkene. PTH = 10-phenyl-10H-phenothiazine. BDE values for arylthiols from ref 9.
Yields and CF$_2$H/CH$_2$F ratio determined by quantitative $^{19}$F NMR spectroscopy using 4-fluoromisole as internal standard. Yields of isolated products (RCF$_2$H only) are given in parentheses. $^{2,5}$mol % 4-DPA-IPN. $^*$ Solvent is DCE/DMSO (19:1, v/v, $c = 0.025$ M).

(8b:8c = 1:2). Unprotected sulfonamide 6b was within reach with excellent selectivity.

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 CF$_2$H/CH$_2$F selectivity. 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. Hydrodefluorination occurred with excellent CF$_2$H/CH$_2$F selectivity (>20:1) at a single site, leaving the 3,5-bis-trifluoromethylecaine motif untouched (11b, 53%); this result corroborates a control experiment that demonstrated that 3,5-bis-trifluoromethylecaine was unreactive under our reaction conditions. Bendroflumethiazide 12a, a drug used for mild heart failure and hypertension via vasodilation, was also subjected to C–F bond reduction. Our protocol, slightly modified in order to solubilize the starting material (solvent mixture of DCE/DMSO), gave CF$_2$H-bendroflumethiazide 12b in 56% yield although with decreased selectivity (CF$_2$H/CH$_2$F ratio = 4:1). This result is significant because sulfonamides and/or amines can coordinate some metals, rendering late-stage cross-coupling strategies toward aryl–CF$_2$H bond construction more challenging. Enzalutamide, a hormonal therapy drug used to treat prostate cancer, also underwent HDF. This reaction yielded with excellent selectivity the difluoromethylated analogue 13b isolated in 40% yield. The usefulness of this HDF protocol was further illustrated with the synthesis of 14b, a molecule with strong androgen receptor binding affinity in vivo. This biologically relevant compound was previously prepared in eight steps. With our protocol, 14b was obtained in two steps; the precursor 14a was prepared in one step from commercially available materials and HDF gave 14b isolated in 60% yield. Alternative photoredox HDF protocols were not effective.

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). Common functional groups compatibility was investigated with para-substituted toluenes, revealing tolerance to bromine, amine, alcohol, carboxylic acid, and aldehyde functionalities. Next, a range of 2-pyridines, 5-pyrimidines, 3-pyridazines, and 2-pyrazines were subjected to screening. While 2-pyridines and 5-pyrimidines were broadly tolerated, 3-pyridazines and 2-pyrazines more often prevented hydrodefluorination. Isoxazoles G and pyrazoles H with various substitution patterns were well accepted. In addition, fused heteroarenes such as pyrazolopyridines F, benzoazoxoles I, benzothiazoles J, indazoles K, and benzimidazoles L did not hamper the HDF of 1a, a benefit considering the frequency of these motifs in modern pharmaceutical drugs. Many of the heterocycles investigated in this study could deactivate transition-metal catalysts by coordination, and the HDF offers an alternative to these methods.

Continuous-flow chemistry was considered to scale-up the HDF of 1a (Scheme 5). The first reactions were performed in a microflow system made of a perfluorooalkoxalkane capillary (internal diameter = 0.5 mm; internal volume = 2.0 mL) on a scale similar to batch (0.2 mmol); 1b was obtained in 69% yield with 5:1 selectivity (CF$_2$H/CH$_2$F), within a 15 min residence time ($t_0$) at a flow rate of 0.133 $\mu$L/min. Additionally, 13b (0.2 mmol) was isolated in 25% yield with 10:1 selectivity after a 7.5 $\mu$L/min 15 min residence time ($t_0$) at a flow rate of 0.266 $\mu$L/min. Starting with 2.5 g of 1a (14.6 mmol), 1.4 g of 1b (5:1) was produced in a 15 min $t_0$ at a flow rate of 0.133 $\mu$L/min. Various experiments were performed to gain preliminary insight on the mechanism of this transformation (Scheme 6). A radical scavenger experiment performed with TEMPO led to the formation of adduct 15 (Scheme 6A). When the reaction of 1a was carried out in the presence of styrene and 4-HTP, 16 was obtained in 56% yield (Scheme 6A). These data are consistent with the formation of a benzylic radical species formed by mesosylic C–F bond cleavage of a radical anion. Deuterium was incorporated in the product (40% yield, H/D
(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 *PC,* and the reduced photocatalyst (PC−/PC−1 = −1.52 V). 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, and the reduced photocatalyst (PC−/PC−1 = −1.52 V). In this scenario, the substrate acts as the oxidant to return the photocatalyst to its native oxidation state with release of the radical anion species that undergoes mesolytic cleavage of fluoride. The latter process leads to the C-centered difluorobenzylic radical 18 which is trapped by 4-HTP affording 1b.

In conclusion, the reductive defluorination of electron-poor trifluoromethylarenes is accomplished under basic conditions...
with 2,4,5,6-tetraakis(diphenylamino)isophthalonitrile as the organophotocatalyst,26 4-hydroxythiophenol as the HAD, 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 difluoromethylated drugs into their difluoromethyl analogues. Mechanistic studies allude to a catalytic cycle whereby the photocatalyst is reduced by the HAD and returned in its native oxidation state by the difluoromethylenearane that acts as oxidant.

■ ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c03881.

Additional optimization, mechanistic data, cyclic voltammetry, experimental procedures and analytical data (H, 19F, 13C NMR, high resolution mass spectrometry) for all new compounds (PDF).

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Notes

The authors declare the following competing financial interest(s): T.K. and C.W.A. are employees of Pfizer Inc.; C.F.M. and A.A.T. are employees of Janssen; C.G. is an employee of UCB Biopharma Sprl.

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