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Electrochemical C–F bond activation of trifluoromethylarenes using silylium ions†

Subhojit Mondal, Boris Stevanovic, Eric Butler, Jason W. Wang and Michael W. Meanwell *

We report a mild, electrochemical trihydrodefluorination (e-THDF) for breaking highly stable C–F bonds in trifluoromethyl arenes to form the corresponding methyl arene products. Uniquely, this "green" approach relies on the *in situ* generation of Lewis acidic silyl cations that mediate fluoride abstraction. Overall, e-THDF has significantly improved functional group tolerance over current methods and should inspire the continued development of defluorinative processes.

The C–F bond is considered among the most inert bonds in organic chemistry (BDE = 490 kJ mol^{-1}). Its high stability has rendered fluorinated organic molecules immensely useful in many commercial industries such as pharmaceuticals,[1] agrochemicals,[2] textiles,[3] electronics,[4] and others.[5] For instance, fluorine incorporation is used in drug discovery to improve a compound's stability against metabolic oxidation in the body.[1] Due to their prevalence in modern society and relative inertness to both biological and chemical degradation, these organofluorine substances accumulate and persist in water resources and sediment leading to detrimental effects on human health and the environment.[6–8] As such, chemical defluorinative processes that facilitate the degradation of fluorochemicals are highly sought for water remediation efforts and treatment of organofluorine-containing waste.[9,10] Trifluoromethyl arenes are a class of persistent organic pollutants (POPs) that are common structural motifs found in many pharmaceuticals, agrochemicals, and materials.[11–13] In fact, more than 170 pharmaceuticals and agrochemicals contain a trifluoromethyl arene.[2,14] Fluorinated pharmaceuticals enter water systems through wastewater outflow and have been found to persist in surface water (*i.e.*, levels in the range of 1–100 ng g^{-1}), while fluorinated agrochemicals are introduced into the environment through direct application and agricultural run-off.[13] The stability, degradation, and toxicity of trifluoromethyl arenes in the environment remains an intense area of research.[11–13] For these reasons, we sought to develop a new method for exhaustive defluorination of trifluoromethyl arenes as a fundamental study into new modes of catalysis for deconstructing organofluorine pollutants.

Current trihydrodefluorination methods have largely utilized strong Lewis acid catalysts (*i.e.*, $NbCl_5$,[15] $TiCl_4$,[16,17] and $Et_3Si[B(C_6F_5)_4]$[18]) in combination with a hydride source (*i.e.*, $LiAlH_4$ and Et_3SiH) to promote trihydrodeflourination of trifluoromethylarenes (see **1** to **2**, Fig. 1). Such harsh conditions inherently possess poor functional group tolerance, are required to be carried out under strict anhydrous conditions, and to date have only found applications in the reduction of simple trifluoromethylarenes with minimal functional group diversity.[15–18] Electrochemical THDF represents an attractive "green" alternative and remains mostly undeveloped in organic chemistry.[19–21] Since Lund's initial discovery in 1959 demonstrating the electrochemical THDF of hydroflumethiazide (**3**) using a dropping mercury electrode in aqueous methanol, scarce electrochemical THDF reactions have been reported.[19] In a rare recent example, Xia and coworkers applied their method for the electrochemical reduction of aryl halides and nitriles, and *N*-acetyl/tosyl deprotection towards the exhaustive reduction of a very small subset of trifluoromethylarenes.[21] Here, the authors noted formation of mono- and di-fluoromethyl side-products as a complicating factor (Fig. 1, **4**). Given the poor

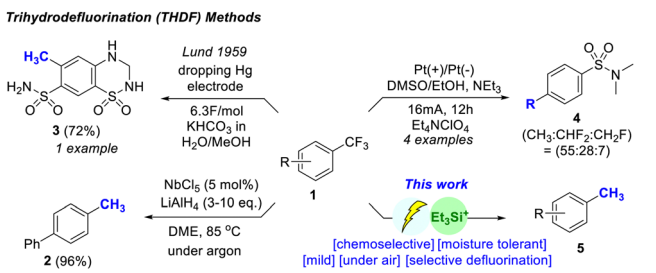

Fig. 1 Lewis acid/hydride and electrochemical trihydrodefluorination (THDF) methods.

Department of Chemistry, University of Alberta, Edmonton, Canada.
E-mail: meanwell@ualberta.ca

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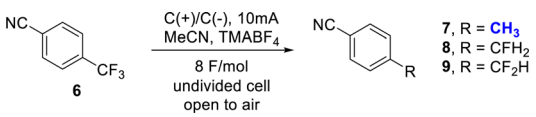
functional group tolerance and documented selectivity challenges of current THDF methods,[15–21] we sought to address these shortcomings in an effort to establish a robust process for exhaustive defluorination. Towards this goal, we report a mild and chemoselective electrochemical THDF that relies on the *in situ* electrochemical generation of silyl cations to mediate defluorination of aryl trifluoromethyl groups (**1**) to the corresponding aryl methyl products (**5**).

Since the vast majority of the reported THDF reactions have utilized concentrated reaction mixtures of Lewis Acids with hydride sources to effect this transformation, we chose to begin our investigations with 4-trifluoromethyl benzonitrile, a substrate that is inherently incompatible with these traditional methods. Despite exhaustive defluorination being thermodynamically favorable over the formation of the intermediate mono- and difluoromethyl derivatives (**8** and **9** respectively),[22] our early attempts struggled to achieve trihydrodeflurorination of **6** selectively. Additionally, these reactions proceeded in poor yields (<20%). As summarized in Table 1, utilizing graphite as both the cathode and the anode in an undivided cell with MeCN as the solvent afforded a 61 : 24 : 15 mixture of methyl and mono- and di-fluoromethyl products in 10% yield. While employing different electrode materials improved trihydrodefluorination selectivity (entry 1), the yields remained poor (see entries 2–5). Following extensive optimization (see ESI†), we found that the addition of one equivalent of triethylsilane modestly enhanced the selectivity and yield of the reaction (entry 6). Remarkably, an additional two equivalents led to a dramatic increase in yield with complete hydrodefluorination to the aryl methyl product (**7**, entry 7). While we continued to screen several other conditions including various silane additives, electrolytes, and solvents, the aforementioned conditions proved to be most optimal. Intriguingly, changing the electrolyte to either $LiClO_4$ or LiSFI (entries 8 and 9) dramatically decreased reaction productivity suggesting that $TMABF_4$ may also be participating in the reaction mechanism. In the absence of electrolysis, no reaction occurred thus confirming the cooperative roles electrolysis and triethylsilane play in mediating the trihydrodefluorination process (entry 11). Importantly, this reaction is not air- or moisture-sensitive which obviates the need for the strict anhydrous conditions typically employed in traditional Lewis acid mediated THDF reactions.[15–18]

Table 1 Optimization of reaction conditions for the trihydrodeflurorination of **6**



Entry[a]	Variation from above	7/8/9[b]	Yield[c] (%)
1	None	61/24/15	10
2	Pt cathode	100/0/0	19
3	Steel cathode and Mg anode	95/5/0	18
4	Ni cathode	100/0/0	29
5	Pt cathode and Pt anode	93/7/0	25
6	Addition of Et_3SiH (1 equiv.)	100/0/0	32
7	Addition of Et_3SiH (3 equiv.)	100/0/0	76
8	Same as entry 7 and $LiClO_4$ as electrolyte	100/0/0	8
9	Same as entry 7 and LiSFI as electrolyte	30/15/55	3
10	Addition of $(TMS)_3SiH$ (3 equiv.)	ND	0
11	Same as entry 7 and no electricity	ND	0

[a] Conditions: **6** (1 equiv.), $TMABF_4$ (1 equiv.), and MeCN (0.075 M). [b] Ratio of products determined from ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. [c] ^1H NMR yield of **7**.

With our optimized conditions in hand, we proceeded to evaluate a diverse subset of trifluoromethylarenes. Critically, the electrochemical THDF (e-THDF) only affords the desired arylmethyl products as no mono- or di-flluoromethyl products were observed. In general, e-THDF works well on electron-deficient arenes and is tolerant to a range of functional groups that are incompatible with Lewis acid/hydride approaches. Nitriles (**7**, **11**, **17–19**), esters (**14**, **15**), carboxylic acid (**12**), amide **16**, and sulfonamide **13** all underwent e-THDF selectively while showing no signs of undesired nitrile/carbonyl reduction. Varying the position of the electron-withdrawing substituent with respect to the trifluoromethyl group had little effect on the reaction yield. Substrates with electrochemical sensitive functional groups such as olefin **15** and aryl fluorides (**17–19**) also worked well. While $C(sp^2)$–F often preferentially undergo HDF over $C(sp^3)$–F bonds, no defluorination of the aryl fluoride was observed in **17–19**.[23] We also demonstrate THDF occurs selectively at the aryl trifluoromethyl in the presence of an alkyl trifluoromethyl group (see **14**), which further highlights the orthogonal nature of our e-THDF reaction. We sought to explore our reactions' utility for the THDF of drug-like molecules. Towards this goal, we carried out the e-THDF on Celecoxib (Celebrex®). Celecoxib cleanly underwent e-THDF to afford its methyl analogue **20a** in 34% (52% brsm, Fig. 2A). Intriguingly, when using MeCN-d_3 as the solvent in our e-THDF reaction, we gained direct access to a high-value aryl-CD_3 analogue of Celecoxib (**20b**) which serves to highlight a potential alternative utility of our process for late-stage deuterium labeling in drug design.[24] To demonstrate the scalability of our process, we performed the e-THDF on one gram of **6** without any further optimization. We were successfully able to isolate the desired product **7** in 68% yield (see Fig. 2B).

We proceeded to investigate the mechanism of e-THDF in order to ascertain the critical role triethylsilane plays in the success of this reaction. We considered triethylsilane functioning as a hydride source or hydrogen atom donor (HAD)[25] in our reaction. However, when replacing triethylsilane with triethyl(silane-d), we did not observe any deuterium incorporation into the product (**7**, Fig. 3). Previous reports have demonstrated that silanes ($E_{p/2} \sim 2.2$ V *vs.* Ag electrode) can readily undergo anodic oxidation to generate silyl cations (**23**)[26] which themselves are well-known to mediate fluoride abstraction processes.[18,27–30] Silyl cations, in combination with hydride sources, have previously been utilized under strictly inert conditions for the defluorination of trifluoromethyl arenes. To assess this possibility, we carried out electrolysis of triethylsilane for 1.5 F mol^{-1} in the absence of starting material under our standard conditions (Fig. 3) to generate small amounts of silyl cations (**23**) in solution. When electrolysis was complete, **6** was added to the reaction mixture

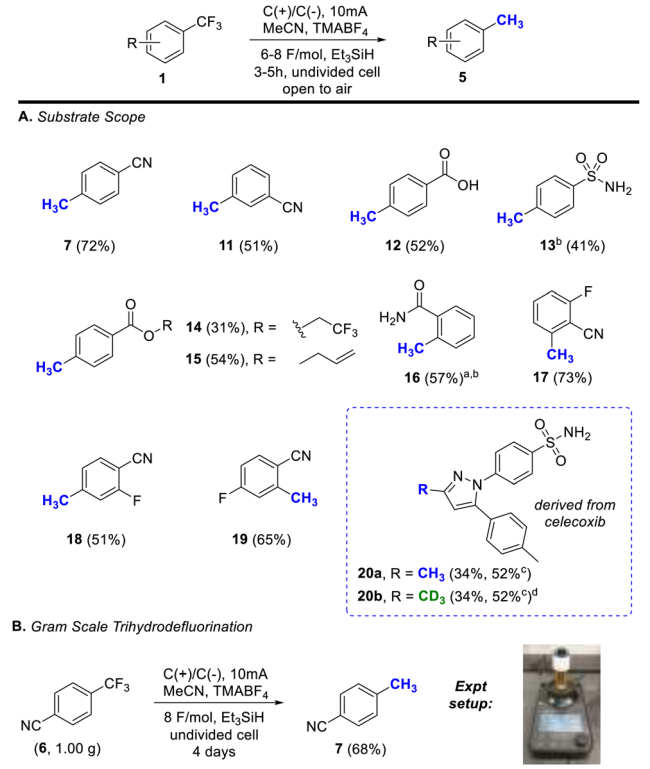


Fig. 2 (A) Conditions: 1 (1 equiv.), $TMABF_4$ (1 equiv.), Et_3SiH (3 equiv.) and MeCN (0.075 M); [a] ^1H NMR yield; [b] ~10% of fluorinated side-products formed. [c] Yield based on recovered starting material; [d] 79% CD_3 incorporation. (B) Gram scale e-THDF.

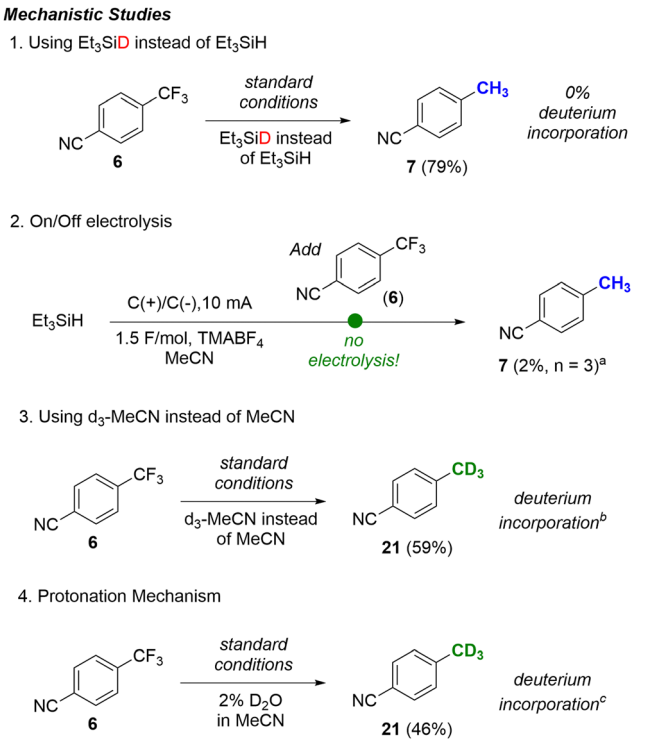


Fig. 3 Mechanistic studies. [a] n = replicates; [b] 50% CD_3 incorporation; [c] 29% CD_3 incorporation.

and allowed to stir for 14 h. This experiment effectively recreates the traditional Lewis acid/hydride trihydrodefluorination conditions albeit at much lower concentrations and without requiring an inert atmosphere.[15–18] Notably, 2% (n = 3) of product **7** was still obtained suggesting silyl cation mediated fluoride abstraction maybe operative. Similar to Lewis acid/hydride approaches, the remaining unreacted triethylsilane likely serves as a hydride source here to trap the carbocation formed from fluoride abstraction of the trifluoromethyl arene (**24**) in this case. The low yield obtained in this experiment also shows the importance of electrolysis for reaction turnover. We considered a non-innocent role of the tetrafluoroborate electrolyte participating in the fluoride abstraction process. It has previously been shown that silyl cations can abstract fluoride from tetrafluoroborate anions to afford boron trifluoride, another strong fluorophilic Lewis acid capable of catalyzing defluorination of C(sp^3)–F bonds.[31–34] However, when running the e-THDF reaction in the presence of either $TBAClO_4$ or $TMAPF_6$ moderate yields (see ESI† for details) were still obtained for the aryl methyl product. We did not observe any product when using boron trifluoride acetonitrile adduct in place of triethylsilane (see ESI†), further ruling out the involvement of boron trifluoride in fluoride abstraction. From our deuteriation of Celecoxib, it was evident that the solvent served as the hydrogen source in our reaction which we further verified as a general observation in the trideuterodefluorination of **6**. Recent work by Lennox suggests that electrochemical defluorination proceeds *via* proton transfer from solvent to trap an intermediate benzylic carbanion (**25**) that is formed from successive and rapid cathodic reduction.[35] We suspected a similar mechanism may be operative in our own reaction given that no olefin radical addition products were detected in the e-THDF of **15**. Since MeCN can either function as a HAD source or a proton source, we performed our reaction in the presence of 2% (vol) D_2O in MeCN to further probe whether our reaction proceeded *via* proton transfer or hydrogen atom transfer. Here, we observed deuterium incorporation which strongly indicates a proton trapping mechanism since D_2O cannot function as a HAD source (Fig. 3). While *in situ* generated BF_3 from the electrolyte is not involved in the fluoride abstraction step, it is likely that it serves to decrease the pK_a of MeCN to make proton transfer more facile. Overall, our e-THDF reaction represents the first example of electrochemical silyl cation mediated defluorination (Fig. 4).

In summary, an electrochemical trihydrodefluorination reaction has been developed for transforming trifluoromethyl arenes into their corresponding methyl arene products. Our e-THDF reaction is the first general method for THDF of trifluoromethyl arenes and overcomes the poor functional group tolerance inherent to previous approaches. This operationally simple process was shown to be scalable and tolerant to a range of functional groups. Most uniquely, our mechanistic investigations revealed that this process relies on the *in situ* generation of silyl cations, which are typically used under strict inert conditions, to mediate defluorination. Furthermore, this

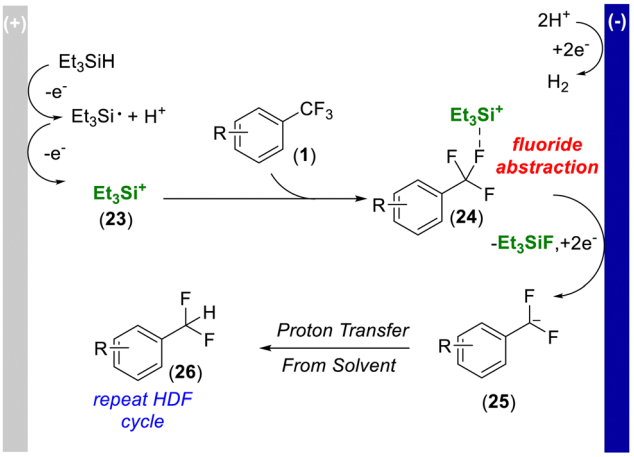


Fig. 4 Proposed trihydrodefluorination mechanism.

is a unique example of silyl ion catalysis for C–F bond activation. These insights should guide us forward in developing new defluorination processes for environmental science.

S. M., B. S., E. B., J. W. W., and M. W. M. performed experiments. S. M. and M. W. M. performed mechanistic studies. S. M., J. W. W. and M. W. M. collected all data. M. W. M. designed experiments and conceived the project. M. W. M. wrote the manuscript. S. M. and J. W. W. edited the manuscript.

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Conflicts of interest

There are no conflicts to declare.

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