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Electro-oxidative Deoxyfluorination of Arenes with NEt_3·3HF

En-Chih Liu, Sabrina M. Reich, Mayank Tanwar, Matthew Neurock,* Long Luo,* and Melanie S. Sanford*

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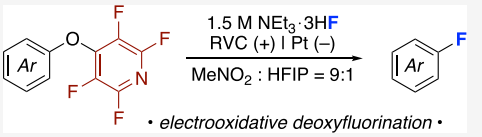
ABSTRACT: This report describes the design, development, and optimization of an electrochemical deoxyfluorination of arenes using a tetrafluoropyridine-derived leaving group. NEt_3·3HF serves as the fluoride source, and the reactions are conducted using either constant potential or constant current electrolysis in an undivided electrochemical cell. Mechanistic studies support a net oxidative pathway, in which initial single-electron oxidation generates a radical cation intermediate that is trapped by fluoride. The resulting radical undergoes a second oxidation reaction, followed by the loss of the leaving group to yield the fluoroarene product.

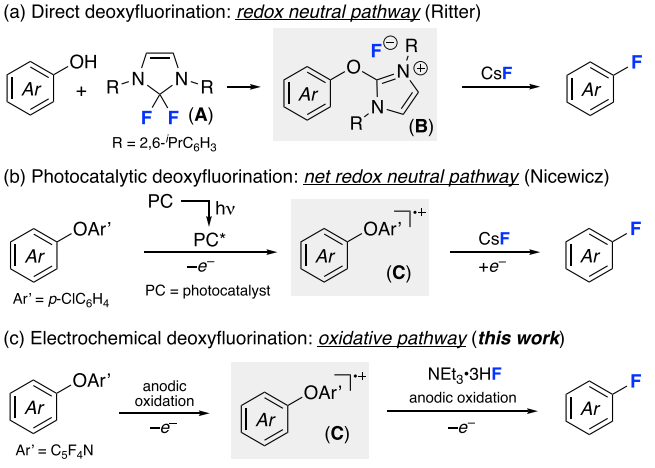


INTRODUCTION

Aryl fluorides (ArF) are common functional groups in pharmaceuticals, agrochemicals, and PET imaging agents.[1] As such, there is a high demand for synthetic methods that form C(sp^2)−F bonds.[2] One attractive but underdeveloped approach involves the deoxyfluorination of phenol derivatives. Phenols are particularly desirable starting materials because they are abundant, inexpensive, and often derived from biomass.[3]

The first reported examples of phenol deoxyfluorination involved converting the −OH into a leaving group (−OR) and then subjecting the resulting intermediate to direct substitution with fluoride.[4−6] For instance, in 2011, Ritter showed that the treatment of phenols with PhenoFluor (**A** in Scheme 1a) generates uronium intermediates (**B**)[7] that react with CsF to afford ArF. Subsequent work by our group leveraged sulfonyl fluoride[6a] or triflate[6b] leaving groups to achieve similar transformations. These reactions typically work best with (hetero)arene substrates bearing electron-withdrawing substituents, and they require rigorously dry fluoride sources. The anhydrous, aprotic conditions are necessary to limit the formation of FHF^-, which is not sufficiently nucleophilic to participate in direct substitution.

Scheme 1. (a,b) Known Redox Neutral Pathways for Deoxyfluorination and (c) This Work: Electro-oxidative Deoxyfluorination



In 2020, Nicewicz reported an alternative cation-radical accelerated (CRA) substitution pathway for arene deoxyfluorination, involving the reaction of diaryl ether substrates (Ar' = 4-chlorophenyl) with CsF in the presence of an acridinium photocatalyst (Scheme 1b).[8] Upon irradiation with visible light, the excited catalyst (PC*) oxidizes the arene substrate, resulting in an arene radical cation, **C**.[9] This intermediate is proposed to undergo substitution with fluoride and subsequent reduction by the reduced photocatalyst ($PC^{\cdot}$) to yield ArF. This method works best with electron rich substrates whose redox potentials are matched to that of the photocatalyst. A key advantage of this approach is that rigorously anhydrous conditions are not necessary due to the high electrophilicity of intermediate **C**.

Electrochemical oxidation is a well-known, complementary approach for generating arene radical cation intermediate **C** (Scheme 1c).[10] Literature reports have shown that such intermediates can be trapped with NEt_3·3HF under electro-oxidative conditions to achieve C(sp^2)−H fluorination (Scheme 2a).[11−14] We hypothesized that, with appropriate design of substrate and leaving group, related intermediates

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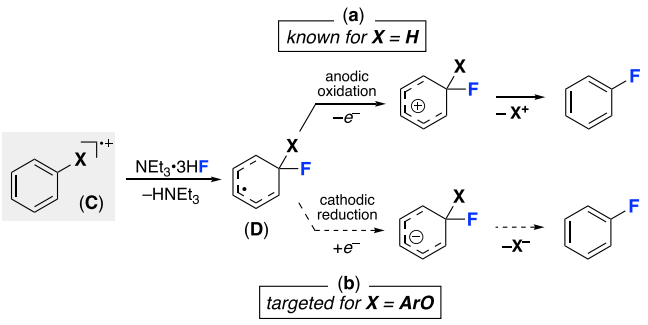
Scheme 2. (a) Oxidative Pathway for Electrochemical C−H Fluorination and (b) Initially Proposed Redox Neutral Pathway for Electrochemical Deoxyfluorination



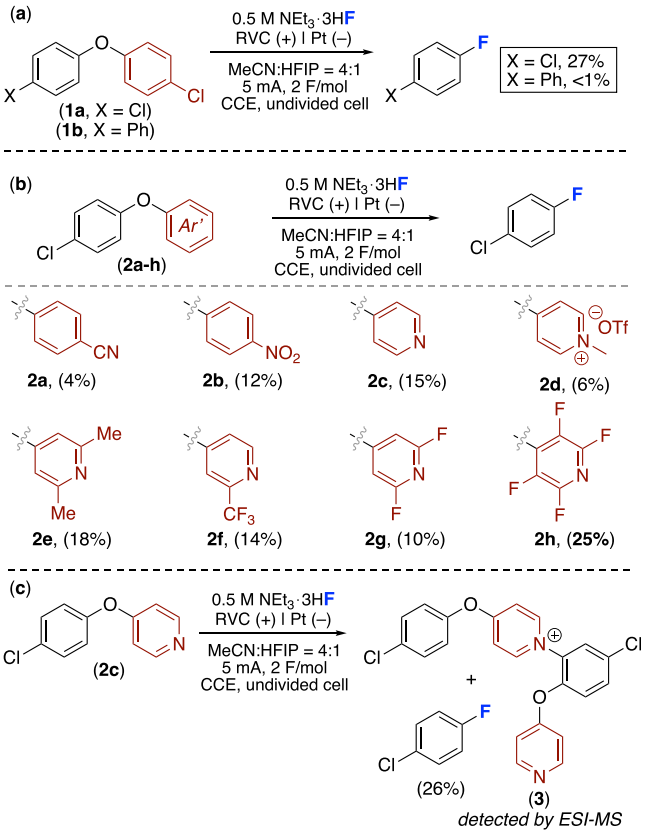
could be leveraged for a net deoxyfluorination (Scheme 2b, X = OAr'). Herein, we report the design, development, and optimization of an electrochemical deoxyfluorination of arenes using a readily accessible tetrafluoropyridine-based leaving group (Scheme 1c). Mechanistic studies of this transformation provide evidence for an unexpected net oxidative pathway.

RESULTS AND DISCUSSION

We initially reasoned that electrochemical deoxyfluorination could be achieved via the redox-neutral pathway outlined in Scheme 2b. By analogy to known ArH fluorination reactions (Scheme 2a), anodic oxidation to form radical cation **C** could be followed by trapping with NEt_3·3HF to generate **D**. Cathodic reduction of **D** and loss of the leaving group would then generate the fluorinated product in a sequence mimicking Nicewicz's photochemical CRA process.[8] We first evaluated the proposed electrochemical deoxyfluorination with substrates **1a** and **1b** (with Ar' = *p*-ClC_6H_4). These were selected as a starting point because both afforded good yields (79% and 60%, respectively) under the optimal photochemical CRA conditions.[8] The reactions were conducted in an undivided electrochemical cell (to enable both the oxidation and reduction steps required for the mechanism in Scheme 2b) using 0.5 M NEt_3·3HF as the supporting electrolyte with a mixture of MeCN and HFIP[15] as the solvent. Electrolysis was performed using a constant current of 5 mA, passing 2 F/mol of the substrate, with reticulated vitreous carbon (RVC) as the anode and Pt as the cathode. Under these conditions, **1a** reacted to form 1-chloro-4-fluorobenzene in 27% yield, while **1b** afforded <1% of 4-fluoro-1,1′-biphenyl (Scheme 3a). The large difference in outcome for these substrates provides preliminary evidence for different mechanisms between the electrochemical and photochemical processes.

We next hypothesized that the electrochemical deoxyfluorination could be optimized by tuning the OAr' leaving group. Importantly, Ar' must be electron deficient to ensure that the radical cation remains localized on the ring undergoing fluorination.[8] With this in mind, we synthesized and tested a series of Ar' derivatives bearing electron-withdrawing substituents and/or electron-deficient heterocycles (**2a−h** in Scheme 3b). Derivatives containing *p*-CN (**2a**) and *p*-NO_2 groups (**2b**) (which were also effective in the photochemical CRA reactions) afforded lower yields than **1a** (4% and 12%, respectively). Pyridine-based leaving groups were next explored, starting with Ar' = 4-pyridyl (**1c**). This substrate afforded 1-chloro-4-fluorobenzene in 15% yield. Here, electrospray ionization mass spectrometry showed a mass consistent

Scheme 3. Initial Studies of Electrochemical Deoxyfluorination with (a) Substrates 1a and 1b, (b) Substrates 2a−h,and (c) Competing C−H Pyridination of 2c



with the formation of **3** as a side product (Scheme 3c). **3** derives from oxidative C−H pyridination of the substrate,[16] and we hypothesized that this side reaction could be limited by decreasing the nucleophilicity of the pyridine nitrogen through *N*-alkylation (**2d**), installation of sterically large groups at the 2- and/or 6-positions (**2e, f**), or installation of electron-withdrawing CF_3 or F substituents (**2f−h**). As shown in Scheme 3b, these changes led to mixed results, with the use of Ar' = 2,3,5,6-tetrafluoropyridine (TFP) affording the highest overall yield (25%) of 1-chloro-4-fluorobenzene. Notably, this Ar' group is straightforward to install via an S_NAr reaction of the phenol with commercially available pentafluoropyridine.[17]

The reaction with 2,3,5,6-tetrafluoropyridine substrate **2h** was further optimized by varying the concentration of NEt_3·3HF, the solvent, and the electrolysis conditions (see Tables S1 and S2 for complete details).[18] The yield of 1-chloro-4-fluorobenzene was improved by increasing the concentration of NEt_3·3HF to 1.5 M and changing the solvent to a 9:1 mixture of $MeNO_2$/HFIP. Using constant current electrolysis (CCE, 5 mA, 4 F/mol), the fluoroarene was formed in 53% yield, with diene **4** as the major side product (Scheme 4).[19] Constant potential electrolysis (CPE) at 1.7 V using a Au wire quasi-reference electrode afforded a slightly higher yield of 1-chloro-4-fluorobenzene (56%) and a lower yield of **3** (11%).[20,21]

As noted above, the reactivity trends in Scheme 3 are quite different from those reported for the redox-neutral photochemical CRA reactions. In addition, when our optimal substrate **2h** was subjected to the photochemical CRA

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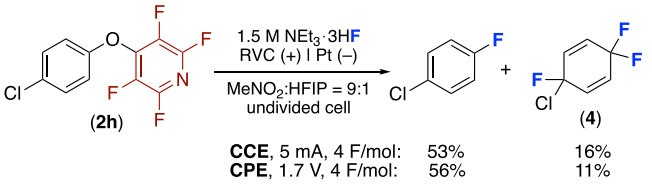
Scheme 4. Optimal Conditions for Deoxyfluorination of 2h under CCE and CPE



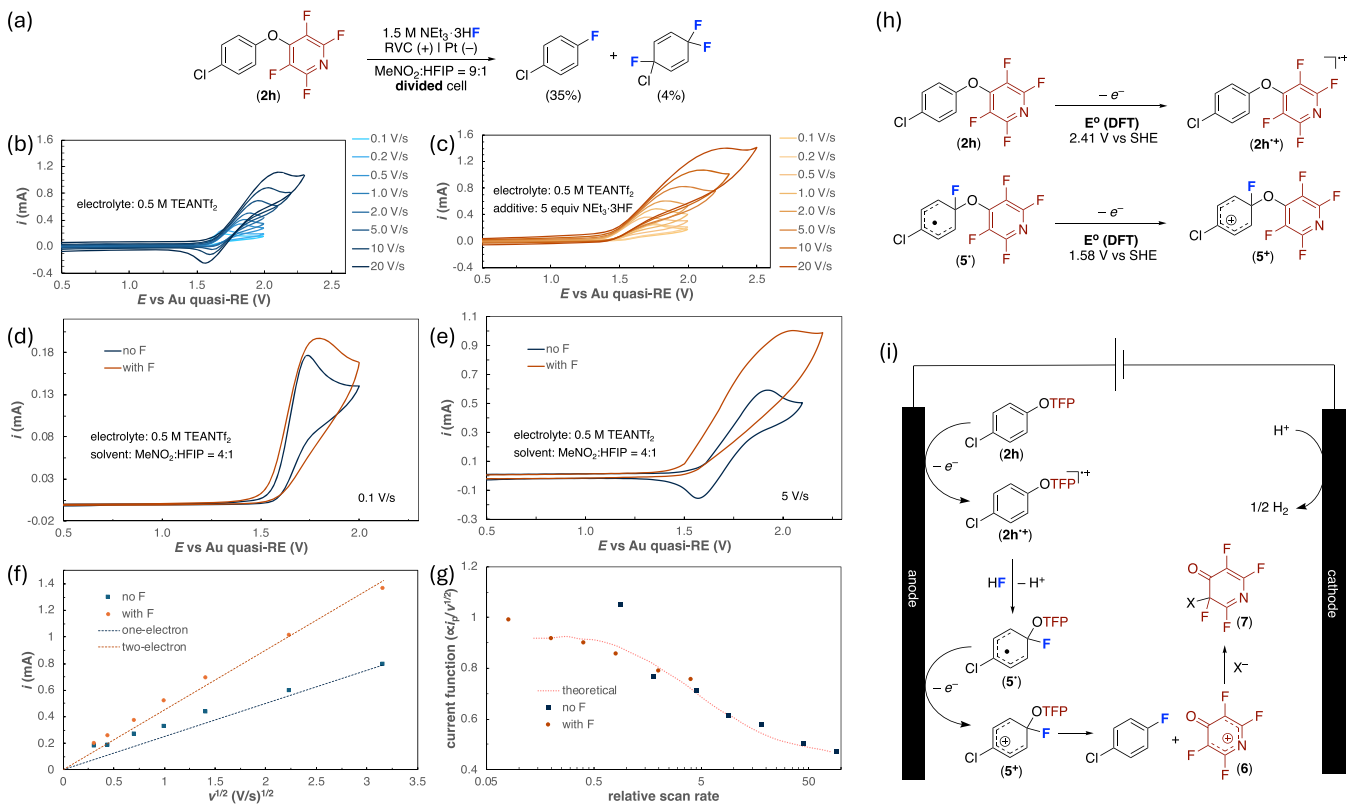
conditions, no 1-chloro-4-fluorobenzene was detected. Furthermore, the side products formed under the electrochemical conditions (**3** and **4** in Scheme 4) derive from net oxidative transformations. Collectively, these data led us to hypothesize that electrochemical deoxyfluorination might proceed by a net oxidative pathway. To preliminarily test this proposal, we conducted the reaction in a divided cell under otherwise identical conditions to those in Scheme 3b. A 35% yield of 1-chloro-4-fluorobenzene was obtained along with 8% of **4** (Scheme 5a). Importantly, in a divided cell, the oxidation reaction is isolated from the cathode; as such, this result shows that the reduction of intermediate **D** is not required to form the fluorinated product.

We next conducted cyclic voltammetry (CV) studies on substrate **2h** in the presence and absence of fluoride nucleophiles at various scan rates. In the absence of fluoride and at a low scan rate (0.1 V/s), oxidation occurs at ∼1.6 V versus a Au quasi-reference electrode, and the subsequent reduction is irreversible. However, at scan rates >2 V/s, a reduction peak at 1.6 V begins to emerge (Scheme 5b). This voltammetric behavior is characteristic of an EC mechanism, in which a reversible electron transfer is followed by a chemical reaction.[22] At slow scan rates, $\mathbf{2h}^{\cdot+}$ is completely consumed in the chemical reaction. As such, **2h** is not electrochemically regenerated during the potential reversal, and no reduction peak is observed. However, with increasing scan rate, electrochemical reduction becomes fast relative to chemical reactions of $\mathbf{2h}^{\cdot+}$, leading to the appearance of the reduction peak in the CV.

As shown in Scheme 5c, the CV behavior of **2h** changes dramatically upon the addition of 5 equiv of NEt_3·3HF. Here, no reduction peak is observed, even at scan rates as high as 20 V/s. This is consistent with a rapid chemical reaction between fluoride and $\mathbf{2h}^{\cdot+}$. Comparison of the anodic peak currents between the CVs of **2h** with and without fluoride (Scheme 5d,e) shows a significant difference as a function of scan rate. At 0.1 V/s, the anodic peak currents are similar, while at 5 V/s, the anodic peak in the presence of fluoride is nearly double that in the absence of fluoride. This finding suggests that the presence of fluoride affects not only the reversibility of the electrochemical oxidation of **2h**, but also the degree of its oxidation.

To gain quantitative information about the degree of **2h** oxidation, we conducted a Randles-Sevcik[22,23] analysis of the anodic peak current as a function of scan rate. The Randles-Sevcik plot for the "with fluoride" data points in Scheme 5f shows a nearly perfect proportionality between peak current (i) and the square root of scan rate ($v^{1/2}$), indicating that **2h** is oxidized by a fixed number of electrons at all scan rates. In comparison, the plot for the "without fluoride" data shows the i

Scheme 5. Mechanistic Studies[a]



[a](a) Electrochemical deoxyfluorination in a divided cell, (b–g) voltammetric studies, (h) computed oxidation potentials, and (i) proposed mechanism.

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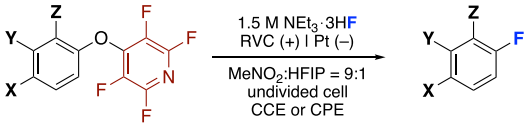
to $v^{1/2}$ ratio increases by a factor of 2 between 20 V/s to 0.1 V/s. Collectively, these results are consistent with an ECE mechanism (Scheme 5h) involving (1) initial one-electron oxidation of **2h** to $\mathbf{2h}^{\cdot+}$; (2) chemical reaction between $\mathbf{2h}^{\cdot+}$ and $NEt_3{\cdot}3HF$ to form a new intermediate $\mathbf{5}^{\cdot}$; and (3) fast one-electron oxidation of $\mathbf{5}^{\cdot}$ to $\mathbf{5}^{+}$. This mechanism is closely analogous to that reported for oxidative ArH fluorination (Scheme 2a). In the presence of fluoride, the chemical reaction between $\mathbf{2h}^{\cdot+}$ and $NEt_3{\cdot}3HF$ to form $\mathbf{5}^{\cdot}$ is rapid (faster than the time scale of the scan rates tested in our CV experiments), leading to a constant two-electron oxidation of **2h** to $\mathbf{5}^{+}$. In contrast, in the absence of fluoride, chemical reactions of $\mathbf{2h}^{\cdot+}$ are slow due to the absence of a strong nucleophile in solution. Thus, without fluoride present, two-electron oxidation is only observed at slow scan rates, which gives sufficient time for trapping by weak nucleophiles such as HFIP or Tf_2N^-.

We next compared these experimental data with the theoretical relationship between the current function ($\propto i_p/v^{1/2}$) and the relative scan rate ($\propto v$) for an ECE mechanism reaction.[24] As shown in Scheme 5g, these show excellent agreement, further supporting the proposed mechanism. In parallel, we computed the oxidation potentials of **2h** and $\mathbf{5}^{\cdot}$ to test the feasibility of the ECE mechanism from a thermodynamic perspective. Density functional theory (DFT) calculations indicate that the single-electron oxidation of **2h** to $\mathbf{2h}^{\cdot+}$ takes place at 2.41 V versus the standard hydrogen electrode (SHE) in nitromethane. After fluoride trapping to form $\mathbf{5}^{\cdot}$, the second single electron oxidation is calculated to occur at a much lower potential of 1.60 V versus SHE. The higher first oxidation potential of **2h** relative to $\mathbf{5}^{\cdot}$ can be attributed to its higher lowest unoccupied molecular orbital (LUMO)-highest occupied molecular orbital (HOMO) gap of 0.28 eV compared to 0.16 eV for $\mathbf{5}^{\cdot}$. Overall, the less positive potential for the second oxidation is consistent with our CV results, indicating two-electron oxidation in the presence of fluoride. After the two-electron oxidation, $\mathbf{5}^{+}$ is expected to undergo rearomatization to form 1-chloro-4-fluorobenzene and release the OTFP leaving group as a carbocation (**6**), which is likely trapped with a nucleophile to form **7**. We hypothesize that pi-donation from the fluorine substituents provides some stabilization to the cationic leaving group in this system.[25,26]

Based on the above results, we propose the overall mechanism depicted in Scheme 5i. The single electron oxidation of **2h** at the anode generates the radical cation $\mathbf{2h}^{\cdot+}$. This intermediate is rapidly captured by fluoride, forming radical $\mathbf{5}^{\cdot}$. Subsequent oxidation of $\mathbf{5}^{\cdot}$ occurs at the anode, producing cation $\mathbf{5}^{+}$. Upon rearomatization, the aryl fluoride product is generated along with **6**. Notably, experimental attempts to isolate products derived from **6** were unsuccessful, likely due to its high reactivity and the mixture of nucleophiles that could trap this electrophilic species.[26] On the cathode side, the oxidation is balanced by proton reduction, as evidenced by the evolution of hydrogen gas during electrolysis.

Finally, we evaluated the scope of this reaction with a series of substrates bearing OTFP leaving groups (Table 1). Overall, substrates bearing a halogen substituent (Cl or Br) at the *o*- or *p*-position relative to the leaving group gave the best results. For instance, considering a series of different *p*-substituents, good yield was obtained for *p*-Cl, while other substituents (*p*-MeO, *p*-^{t}Bu, *p*-Ph, *p*-H) resulted in dramatically lower yields. In the latter cases, complete conversion of the starting material was observed, but overoxidation of the product appears to be competitive. Substrates bearing *o*-Cl or *o*-Br substituents

Table 1. Substrate Scope of Electrochemical Deoxyfluorination[a,b]



entry	X	Y	Z	yield (%)
1	Cl	H	H	51
2	Ph	H	H	7
3	MeO	H	H	<1
4	^{t}Bu	H	H	25
5	H	H	H	19
6	H	H	Cl	53
7	H	H	Br	45
8	Cl	F	H	28
9	Cl	CO_2Me	H	46 (32)[c]
10	Cl	OCF_3	H	42[d]
11	Cl	CF_3	H	53[d]
12	Cl	H	Br	45
13	Cl	H	Cl	53[d]
14	Br	H	Cl	53
15	Cl	H	CO_2Me	54 (40)[c]
16	Cl	H	C(O)Me	58
17	Cl	H	C(O)Ph	59 (47)[c]
18	Cl	H	CHO	35
19	Cl	H	CN	22

[a]Reaction conducted with substrate (0.1 mmol) and $NEt_3{\cdot}3HF$ (7.5 mmol) in $MeNO_2$/HFIP (5 mL). The applied potential was determined by performing constant current electrolysis (5 mA). [b]Yields were determined by ^{19}F NMR. [c]Isolated yields. [d]Reaction solvent: $MeNO_2$/HFIP = 4:1.

afforded yields similar to those of the *p*-analogues (entries 6–7). With a halogen on the *p*- position, various functional groups could be incorporated at the *m*- or *o*-positions (e.g., CF_3, CO_2Me, C(O)Me, CHO, OCF_3, CN; entries 8–19). The reaction in entry 17 afforded 47% isolated yield of the aryl fluoride product **P17** at the optimization scale (0.1 mmol). Scaling to 1 mmol (with a 5-fold increase in concentration) afforded comparable 39% isolated yield of this product. In both cases, the remaining starting material and fluorinated product were challenging to separate. As such, the OTFP group of the starting material was deprotected to the phenol with KF/18-crown-6[17] in order to facilitate isolation.

CONCLUSIONS

In conclusion, this work demonstrates the first example of an electro-oxidative deoxyfluorination of phenol derivatives. The installation of the 2,3,5,6-tetrafluoropyridine leaving group is straightforward, and the resulting substrates react with $NEt_3{\cdot}3HF$ under electrochemical conditions to form aryl fluoride products. Voltammetry studies implicate a net oxidative mechanism in which the fluoride nucleophile traps an initially generated arene radical cation followed by a rapid second oxidation. Moving forward, we aim to leverage this pathway to achieve deoxyfunctionalization of arenes with a wider variety of nucleophiles and arene substrates.

EXPERIMENTAL SECTION

General Methods. The manipulation of solid reagents was conducted on the benchtop unless otherwise stated. Reactions were conducted under ambient atmosphere unless otherwise stated. Cyclic

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voltammetry (CV) was performed with a CHI 650E potentiostat, using a three-electrode electrochemical cell, consisting of a glassy carbon disk working electrode (0.071 cm^2, BASi), a silver wire pseudo reference electrode, and a platinum wire counter electrode. The glassy carbon disc electrode was polished between experiments first using diamond polishing solutions on separate nylon pads (15, 3, and 1 μm) and then using alumina polishing solution on microcloth pads. Polishing solutions and pads were all obtained from BASi. All cyclic voltammograms were obtained at ambient temperature. Electrolysis experiments were carried out with a Biologic VSP multichannel potentiostat/galvanostat using a ElectraSyn electrochemical cell (diameter × height = 22 mm × 64 mm for a 10 mL vial and diameter × height = 27 mm × 75 mm for a 20 mL vial). Computational details are provided in the Supporting Information.

Representative Procedure for Deoxyfluorination: Synthesis of (5-Chloro-2-fluorophenyl)(phenyl)methanone. A 20 mL ElectraSyn vial was equipped with a stir bar and charged with the aryl ether starting material (381.7 mg, 1.00 mmol), nitromethane (9 mL), and HFIP (1 mL). Triethylamine trihydrofluoride (NEt_3·3HF, 2.4 mL, 15 mmol) was added while stirring the solution. The vial was equipped with RVC as anode, platinum foil as cathode (0.8 × 3.0 cm^2), and gold wire (10 cm, 0.5 mm diameter) as quasi-reference electrode. The electrolysis was conducted at a constant potential of 1.7 V until 4 F/mol was passed. After the electrolysis was complete, the solution was diluted with water (~15 mL), transferred to a separatory funnel, and extracted with ethyl acetate. The resulting aqueous solution was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with saturated $NaHCO_3$ aqueous solution followed by brine, dried over $MgSO_4$, and concentrated under reduced pressure.

Note: The crude reaction mixture contained a mixture of product and unreacted starting material, which were inseparable by column chromatography. Therefore, the deprotection of OTFP, generating the corresponding phenol, was performed to achieve an efficient separation as follows. In a 20 mL vial, the crude reaction mixture was reconstituted in acetonitrile (5 mL), and KF (117 mg, 2 mmol), 18-crown-6 (792 mg, 3 mmol), and methyl thioglycolate (0.9 mL) were added. The vial was sealed with a Teflon-lined cap under air, and the reaction was heated at 50 °C for 3 h. The reaction was allowed to cool to room temperature and then transferred to a separatory funnel. Water (40 mL) and diethyl ether (60 mL) were added. The organic extracts were collected and washed with a 0.1 M aqueous solution of KOH (3 × 40 mL) followed by brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate in hexanes, 0−5%) afforded the title product as a colorless oil (92.2 mg, 39% yield). R_f: 0.5 (hexanes:EtOAc = 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, J = 7.9 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.55−7.44 (m, 4H), 7.12 (t, J = 8.9 Hz, 1H). ^{13}C{1H} NMR (126 MHz, $CDCl_3$): δ 191.9, 158.5 (d, J = 252.4 Hz), 136.8, 133.8, 132.8 (d, J = 8.4 Hz), 130.3 (d, J = 3.3 Hz), 129.8 (d, J = 1.1 Hz), 129.7 (d, J = 3.5 Hz), 128.6, 128.4 (d, J = 17.0 Hz), 117.8 (d, J = 23.7 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ −113.9 to −114.0 (m, 1F). HRMS-EI: [M]+ Calcd for $C_{13}H_8ClFO^+$: 234.0248; Found: 234.0248.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c02540.

Experimental details; synthesis and characterization of substrates and products; general procedures for deoxyfluorination and for cyclic voltammetry studies; computational studies; and preparative-scale electrolysis (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Matthew Neurock − *Department of Chemical Engineering and Materials Science and Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, United States;* orcid.org/0000-0003-1458-7837; Email: mneurock@umn.edu

Long Luo − *Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, United States;* orcid.org/0000-0001-5771-6892; Email: long.luo@utah.edu

Melanie S. Sanford − *Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States;* orcid.org/0000-0001-9342-9436; Email: mssanfor@umich.edu

Authors

En-Chih Liu − *Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States;* orcid.org/0000-0002-5985-2705

Sabrina M. Reich − *Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States;* orcid.org/0009-0002-6946-9408

Mayank Tanwar − *Department of Chemical Engineering and Materials Science and Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, United States;* orcid.org/0000-0003-2205-6016

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.4c02540

Notes

The authors declare no competing financial interest.

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