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Nucleophilic (Radio)Fluorination of Redox-Active Esters via Radical-Polar Crossover Enabled by Photoredox Catalysis

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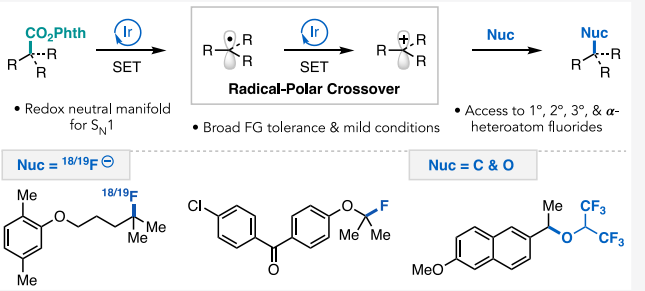
ABSTRACT: We report a redox-neutral method for nucleophilic fluorination of *N*-hydroxyphthalimide esters using an Ir photocatalyst under visible light irradiation. The method provides access to a broad range of aliphatic fluorides, including primary, secondary, and tertiary benzylic fluorides as well as unactivated tertiary fluorides, that are typically inaccessible by nucleophilic fluorination due to competing elimination. In addition, we show that the decarboxylative fluorination conditions are readily adapted to radiofluorination with [^{18}F]KF. We propose that the reactions proceed by two electron transfers between the Ir catalyst and redox-active ester substrate to afford a carbocation intermediate that undergoes subsequent trapping by fluoride. Examples of trapping with O- and C-centered nucleophiles and deoxyfluorination via *N*-hydroxyphthalimidoyl oxalates are also presented, suggesting that this approach may offer a general blueprint for affecting redox-neutral S_N1 substitutions under mild conditions.



INTRODUCTION

Aliphatic organofluorine compounds are important structural motifs in pharmaceuticals, agrochemicals, and materials, conferring valuable biological and physical properties.[1] This motif is also prominently featured in positron emission tomography (PET) radiotracers.[1a] Consequently, the identification of mild methods for late-stage introduction of fluorine has been a longstanding goal, with distinct strategies arising using nucleophilic and electrophilic fluorine sources.[2] For reasons of cost, functional group compatibility, and translation to radiofluorination, researchers have sought mild methods for the preparation of fluoroalkyl groups using nucleophilic fluoride.[1,2] In most of these methods, Csp^3–F bond formation follows a bimolecular nucleophilic substitution pathway (S_N2 mechanism) and is thus limited to the preparation of activated or unhindered aliphatic fluorides (Scheme 1A).[3] Indeed, the typical restrictions on substrate scope for bimolecular nucleophilic substitution reactions are even more acute for fluoride due to its low nucleophilicity and high Brønsted basicity, leading to competitive elimination.[4,5]

Stepwise nucleophilic fluorination reactions that proceed through a carbocation intermediate (S_N1 mechanism) provide a complementary strategy to bimolecular alkyl fluoride synthesis, enabling access to unactivated and hindered aliphatic fluorides. However, the generation of carbocation intermediates typically requires harsh Brønsted[6] or Lewis acidic conditions[7] that show poor functional group tolerance and lead to elimination and rearrangement pathways (Scheme 1B).

To overcome these limitations, researchers have recently explored new strategies for carbocation generation under nonacidic conditions. The Knowles group introduced a methodology to access carbocation intermediates via mesolytic cleavage following the oxidation of TEMPO-derived alkoxyamine substrates;[8] although a wide range of nucleophiles are compatible with this approach, the method was not shown to work with fluoride and the substrates can be challenging to access (Scheme 1C). Just recently, the Baran lab reported an electrochemical approach to carbocation generation from readily available carboxylic acids (Scheme 1D).[9] The method affords access to a broad range of hindered ethers from alcohol nucleophiles and four examples of alkylfluorides from KF. Although this report has significantly advanced the state of the art, the requirement for oxidizing conditions places limits on the substrate scope and the method was not shown to be amenable to radiofluorination. This report was closely followed by the disclosure of a photocatalytic decarboxylative ether synthesis by Ohmiya, Nagao, and co-workers.[10] Yet further discovery and development of complementary methods for carbocation generation are necessary to enable broad access to

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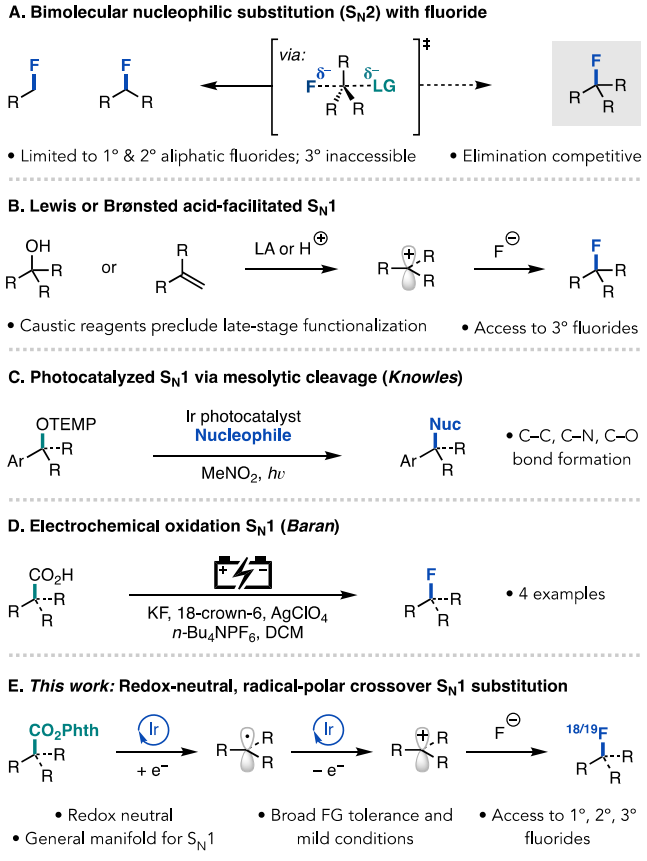
Scheme 1. Nucleophilic Fluorination



hindered and unactivated aliphatic fluorides, including for late-stage fluorination and radiofluorination, as well as expanding the repertoire for additional synthetic applications.

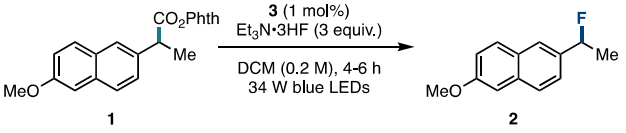
In this context, we sought to develop a redox-neutral method for carbocation generation via radical-polar crossover[10,11] from *N*-hydroxyphthalimide esters (Scheme 1 E). We selected redox active esters as a substrate class since numerous research groups have recently reported their use as precursors to alkyl radicals via single-electron reduction and decarboxylation with release of a non-nucleophilic leaving group.[12] We hypothesized that upon single-electron reduction of the substrate by the excited state of a suitable photoredox catalyst, the resulting radical could be oxidized to the corresponding carbocation by the oxidized photocatalyst and subsequently trapped with fluoride.[13] Given the similar trends in stability between radical and carbocation species,[14] we anticipated that highly substituted aliphatic substrates should be particularly amenable to both radical and carbocation generation in a radical-polar crossover, thereby expanding the scope of aliphatic fluorides available via nucleophilic fluorination. This approach would also provide a useful complement to radical methodologies for decarboxylative fluorination that require oxidizing electrophilic fluorine sources[15] or the combination of a nucleophilic fluoride source with a stoichiometric oxidant, as described by the Groves lab.[16]

Here we report a redox-neutral decarboxylative nucleophilic fluorination that delivers primary, secondary, and tertiary benzylic fluorides and unactivated tertiary fluorides with broad functional group tolerance. We also describe mechanistic experiments that provide evidence for both radical and carbocation intermediates; in so doing, we present applications to the construction of sterically congested ethers and C–C bonds, establishing the generality of the strategy as a blueprint for affecting redox-neutral S_N1 substitutions. Finally, we show that the method is amenable to ^{18}F-radiofluorination.

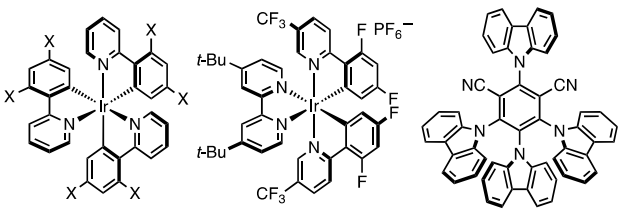
RESULTS AND DISCUSSION

Optimization. We initiated our studies with the *N*-hydroxyphthalimide ester **1** derived from naproxen, as naproxen's electron-rich arene would likely be incompatible with decarboxylative fluorination conditions that utilize electrophilic fluorine sources or stoichiometric oxidants.[15b] Subjecting **1** to irradiation with 34 W blue LEDs in the presence of 1 mol % Ir(dF-ppy)$_3$ **3** and 3 equiv of Et$_3$N·3HF delivered benzylic fluoride **2** in almost quantitative yield (Table 1, entry 1). Fluorination does not proceed in the absence of light or photocatalyst, resulting in recovery of starting material (Table 1, entries 2 and 3). More reducing or oxidizing iridium photocatalysts were competent in the reaction, as was the organic photocatalyst 4CzIPN, all displaying high yet diminished reactivity compared to photocatalyst **3** (Table 1, entries 4–6). While DCM was found to be the optimal solvent for the reaction, fluorination proceeded with moderate to good yield in tetrahydrofuran and

Table 1. Optimization of Reaction Conditions[a,b]



entry	deviation from standard conditions	yield 2 (%)[c]
1	No deviation	99
2	No photocatalyst	0
3	No light	0
4	Ir(ppy)$_3$ **4** instead of **3**	96
5	[Ir(dF-CF$_3$-ppy)$_2$(dtbpy)]PF$_6$ **5** instead of **3**	94
6	4CzIPN **6** instead of **3**	91
7	THF instead of DCM	22
8	MeCN instead of DCM	68
9	3 equiv. KF instead of Et$_3$N·3HF	0
10	3 equiv. KF/10 equiv. HFIP instead of Et$_3$N·3HF	4
11	4 mmol scale[d]	90 (75)[e]
12	0.0625 mol% Ir(dF-ppy)$_3$	85



[a]0.2 mmol scale. [b]All potentials given are versus a saturated calomel electrode (SCE) and taken from ref 19. [c]Yields determined by ^{19}F-NMR using 1-fluoronaphthalene as an external standard. [d]General conditions except 0.4 M, 1.5 equiv of Et$_3$N·3HF. [e]Isolated yield.

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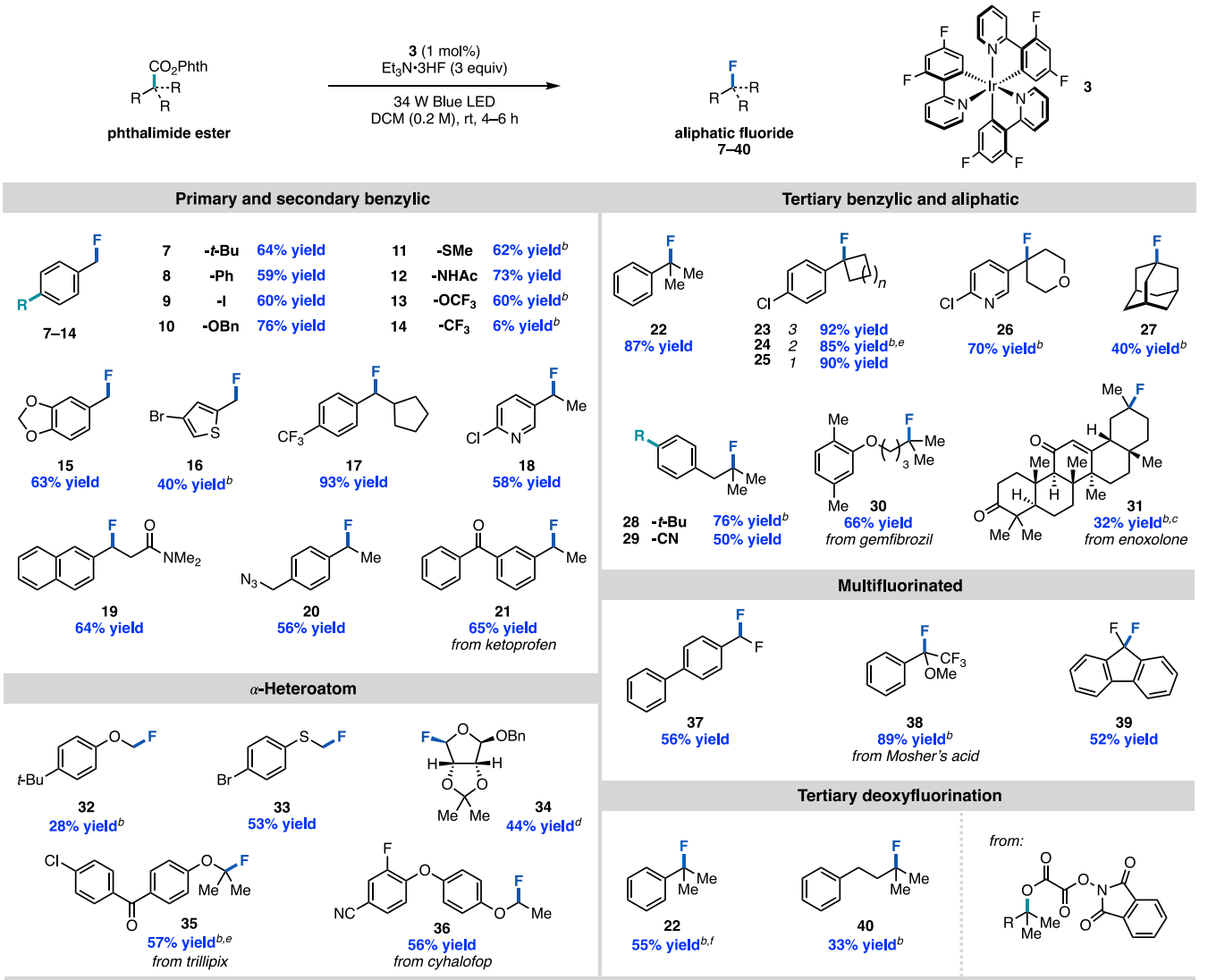
Table 2. Substrate Scope for Photocatalytic Decarboxylative Fluorination[a]



[a]Isolated yields of an average of two runs on 0.5−1.0 mmol scale. [b]Yield determined by ^{19}F-NMR using 1-fluoronaphthalene as an external standard. [c]1.3:1 d.r. [d]>20:1 d.r. [e]Product unstable. [f]Yield corrected for starting material contamination with residual alcohol.

acetonitrile, solvents that are commonly used in radiofluorination (Table 1, entries 7 and 8). Only trace product was observed using KF/HFIP (1,1,1,3,3,3-hexafluoroisopropanol)[17] instead of $Et_3N{\cdot}3HF$, and no product was observed using KF in the absence of HFIP (Table 1, entries 9 and 10). Although impractical from a preparative standpoint, this result provides support for possible translation to radiofluorination since [^{18}F]KF is the most common reagent for ^{18}F-radiochemistry (*vida infra*).[18] Finally, we found that the reaction could be readily scaled to 4 mmol (Table 1, entry 11) and photocatalyst loading could be reduced to 0.0625 mol % with minimal impact on the reaction efficiency (Table 1, entry 12). This speaks to the practicality of the method, and the ability to use such low photocatalyst loading holds important mechanistic implications (*vide infra*).

Scope Elucidation. With optimized conditions in hand, we evaluated the scope of the transformation. We found that a variety of primary benzylic fluorides could be obtained in good to excellent yields (Table 2, **7**−**13**, **15**, and **16**). Several substrates bearing electron-rich functionality otherwise susceptible to oxidation under previously reported decarboxylative fluorination conditions were tolerated,[15b] delivering dioxole **15**, benzyl-protected phenol **10**, and thioether **11**. Fluorinated products bearing medicinally relevant amides and trifluoromethoxy groups were generated in good yields (**12** and **13**). Whereas these electron-rich and electron-neutral primary benzylic phthalimide esters were competent substrates, electron-deficient substrates afforded benzylic fluorides in low yield at high conversion (**14**), presumably because single-electron reduction and decarboxylation to the carbon-centered radical is facile but oxidation of the radical to the cation is disfavored due to the electron-withdrawing substituent.[13] As expected on the basis of this hypothesis, we found that replacing the primary benzylic substrate with a secondary substrate bearing the same substitution pattern restored reactivity, with fluorinated product **17** obtained in 93% yield.

A common limitation in nucleophilic fluorination methods that deliver secondary benzylic fluorides is elimination to styrene byproducts.[3d,f] For all of the secondary substrates

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examined in Table 2, less than 5% elimination was observed, a testament to the mildness of the conditions. Indeed, even product **19** was obtained in high yield with minimal elimination despite the presence of a β-carbonyl functional group. By comparison, access to β-fluoro carbonyl derivatives by deoxyfluorination has presented a major challenge to date due to competing elimination.[3d,f] Several handles for subsequent transition metal-mediated coupling were tolerated, including aryl iodides **9**, bromides **16** and **33**, and chlorides **18** and **23**−**26**. This tolerance for easily reduced functionality can even be extended to azide-containing product **20**, which was generated in 56% yield and offers a reactive handle for subsequent "click" chemistry that is widely used in bioconjugation.[21] Additionally, basic heterocycles and heteroaromatic groups otherwise susceptible to oxidation or Minisci chemistry underwent decarboxylative fluorination in good yields (**18** and **26**).

In contrast to typical methods for nucleophilic fluorination, we found that access to benzylic and unactivated tertiary fluorides is possible. For example, acyclic **22** as well as tertiary benzylic fluorides embedded within carbocyclic and heterocyclic ring systems are generated in 70−92% yield, as in the cases of **23**−**26**. Likewise, both cyclic and acyclic unactivated tertiary fluorides could be obtained (**27**−**31**). Whereas neighboring group participation may be operative in the generation of the homobenzylic tertiary fluorides **28** and **29**, it does not appear to be necessary given the success of the cyano-substituted homobenzylic fluoride **29** and fluorides **27** and **31** that do not possess a proximal nucleophilic residue. Notably, we were able to extend this protocol to the fluorination of gemfibrozil **30** in 66% yield.

Fluoroether and fluorothioether functionality has been shown to confer unique and valuable properties to biologically active small molecules.[22] We found that the redox-neutral decarboxylative nucleophilic fluorination also delivers α-oxy- and α-thioether motifs in moderate to good yield (**32** and **33**). As a demonstration of the viability of the method for late-stage derivatization, fluorinated ribose **34**, trillipix-derivative **35**, and the herbicide cyhalofop-derived **36** were all readily accommodated. Likewise, application of the optimal conditions to the preparation of difluoromethyl and perfluorinated groups was successful,[23] as in the cases of **37** and **38**, and permitted the synthesis of difluorofluorene **39**, a motif featured in the hepatitis C drug ledipasvir.

Fluorine incorporation is commonly used as a bioisostere for several functionalities including C−OH and C−H bonds.[1b] In this regard, the conversion of abundant alcohols into the corresponding alkyl fluorides via deoxyfluorination represents an attractive synthetic disconnection. However, deoxyfluorinations of tertiary alcohols to access tertiary fluorides are typically unsuccessful.[24] MacMillan and co-workers have recently reported a deoxyfluorination of oxalate half-esters to access tertiary fluorides.[25] However, the method uses an electrophilic fluorine source. Since *tert*-alkyl *N*-hydroxyphthalimidoyl oxalates are similar in redox potential to *N*-hydroxyphthalimide esters, we hypothesized that these may be amenable to the catalytic nucleophilic fluorination strategy outlined herein.[26] Indeed, we were pleased to find that tertiary fluorides **22** and **40** could be obtained in 55% and 33% yield from *tert*-alkyl *N*-hydroxyphthalimidoyl oxalate esters under otherwise identical conditions. Since these substrates are readily available from alcohols, the method represents a complementary approach to nucleophilic deoxyfluorination which is typically limited to primary and secondary alcohols.[3a−f]

Mechanistic Investigations. We propose that excited **3** ($E_{1/2}$* = −1.28 vs SCE[19a]) undergoes single-electron transfer (SET) with the *N*-hydroxyphthalimide ester **A** (∼−1.3 V vs SCE[20]) (Figure 1). Fragmentation of the resulting phthalimide

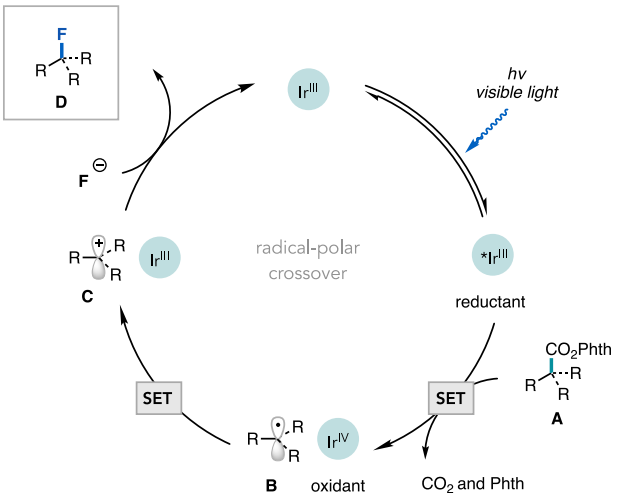

Figure 1. Mechanistic proposal.

ester radical anion and subsequent extrusion of carbon dioxide generate carbon-centered radical **B**. Radical intermediate **B** ($E_{1/2}^{ox}$ = < 0.73 V vs SCE for 1° benzylic, $E_{1/2}^{ox}$ = 0.09 V vs SCE for tertiary aliphatic[13b]) is then oxidized by photocatalyst 3^+ ($Ir^{IV}/Ir^{III}E_{1/2}$ = 0.94 V vs SCE[19a]), turning over the photocatalyst and furnishing carbocation **C**. Finally, this carbocation is trapped by the fluoride source to furnish the desired alkyl fluoride **D**.

A number of experimental observations provide support for the proposed mechanism. Stern−Volmer quenching analysis of the individual components of the reaction mixture indicates that the phthalimide ester quenches the excited state photocatalyst with an observed K_{SV} of 4.7×10^9 M^{-1} s^{-1}, which is similar to the quenching rate of the reaction mixture.[27] The quantum yield of this fluorination reaction is 0.37, indicating that chain mechanisms are unlikely or inefficient.[27,28] This result, combined with the observation that the fluorinations proceed with high reaction efficiency at extremely low photocatalyst loadings (0.0625 mol % of **3** in Table 1, entry 12), suggests that the reaction is unimolecular in photocatalyst.

Subjecting tertiary phthalimide ester **41** to the fluorination conditions in the presence of several known radical traps provides evidence for the intermediacy of a radical. For example, addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to the reaction resulted in complete inhibition of fluorination, with concomitant detection of TEMPO adduct **42** (Figure 2). In the presence of methyl acrylate, radical addition product **43** was observed, along with a diminished yield of tertiary fluoride **30** (66% isolated vs 45% by ^{19}F NMR in the presence of methyl acrylate). However, fluoride is not incorporated into **43**, presumably because radical oxidation adjacent to the ester carbonyl is unfavorable. On the other hand, conducting the fluorination reaction in the presence of 1.5 equiv of styrene afforded a new fluorinated product **44** in addition to the direct fluorination product **30**. **44** is most likely

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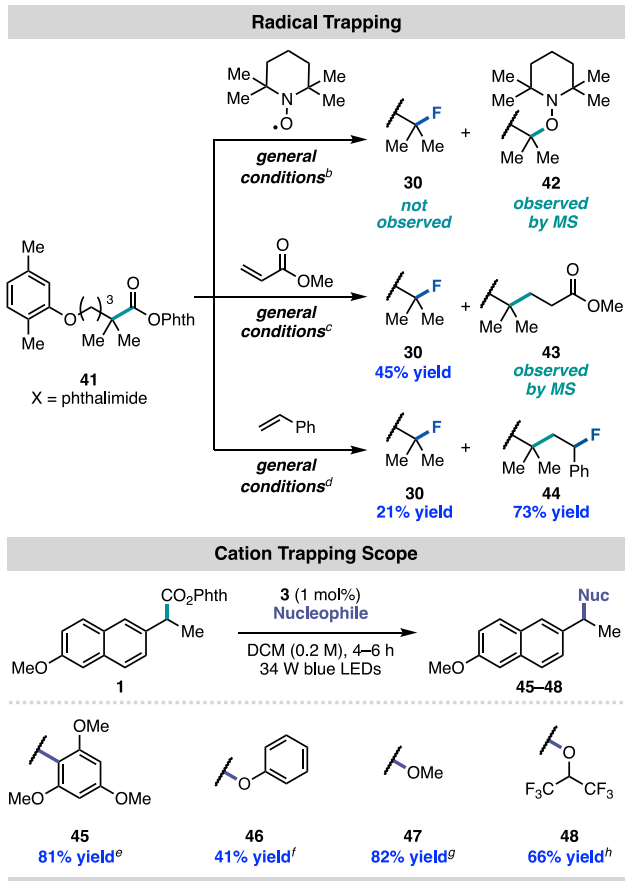


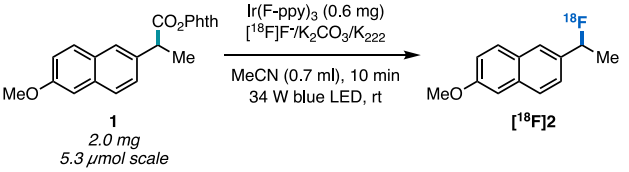
Figure 2. Radical and cation trapping. [a]General conditions: 1 mol % Ir(dF-ppy)$_3$, 0.2 mmol of **41**, 3 equiv of Et$_3$N·3HF. [b]1.5 equiv of TEMPO. [c]1.5 equiv of methyl acrylate. [d]1.5 equiv of styrene. [e]3 equiv of 1,3,5-trimethoxybenzene and 0.3 equiv of Et$_3$N·3HF. [f]5 equiv of phenol and 0.3 equiv of Et$_3$N·3HF. [g]6 equiv of methanol and 0.3 equiv of Et$_3$N·3HF. [h]5 equiv of HFIP and run for 24 h; ^{19}F NMR yield vs external 1-fluoronaphthalene.

generated via addition of radical **B** to the styrene followed by oxidation of the resulting benzylic radical and trapping with fluoride. Evaluation of a series of electronically differentiated styrene substrates, and the outcome of the reaction with methyl acrylate, provides evidence against an alternative pathway wherein radical oxidation to cation **C** precedes olefin addition.[27]

As a test for the intermediacy of a carbocation, we investigated whether other polar nucleophiles could be used in the decarboxylative substitution reaction. Notably, we found that C- and O-centered nucleophiles were competent with only minor changes to the reaction parameters (Table 3, **45**–**48**).[29] For example, 1,3,5-trimethoxybenzene underwent addition to generate benzhydryl **45** in 81% yield. This reaction represents a Friedel–Crafts substitution without a Lewis acid using abundant carboxylic acid precursors in place of alkyl halide substrates. Likewise, several alcohol nucleophiles delivered ether products **46**–**48** in good yield. The broad tolerance for a range of nucleophiles, including sterically hindered and poorly nucleophilic species, implicates the intermediacy of a carbocation and demonstrates the generality of the strategy to effect a range of challenging substitution reactions under remarkably mild conditions.

Radiochemistry. Aliphatic ^{18}F-radiolabeled PET tracers are almost exclusively prepared by nucleophilic substitution of

Table 3. Development of Radiochemical Protocol[a]



Entry	Deviation from Standard Conditions	RCC (%)[b]
1	none	64$_{n=2}$
2	no photocatalyst	0$_{n=1}$
3	no light	0$_{n=2}$
4	**3** instead of Ir(F-ppy)$_3$	6$_{n=2}$
5	Ir(CF$_3$-ppy)$_3$ instead of Ir(F-ppy)$_3$	43$_{n=2}$
6	Ir(dF-*t*-Bu-ppy)$_3$ instead of Ir(F-ppy)$_3$	24$_{n=2}$
7	Ir(F-*t*-Bu-ppy)$_3$ instead of Ir(F-ppy)$_3$	49$_{n=2}$
8	2 min instead of 10 min	62$_{n=1}$
9	100 μL HFIP added	33$_{n=2}$

[a]Typical reaction conditions: 5.3 mol of **1**, 16 mol % photocatalyst, 0.7 mL of MeCN, and [^{18}F]F$^-$/K$_2$CO$_3$/K$_{222}$ (~0.370 Gbq of activity per reaction). [b]RCC was determined by radio-TLC with number of replicates noted.

alkyl sulfonates with [^{18}F]KF in the presence of a phase transfer reagent Kryptofix 2.2.2 (K$_{222}$).[18] As such, access to high specific activity radiolabeled targets bearing unactivated secondary or tertiary fluorides remains a critical challenge. Moreover, the harsh conditions necessary for substitution of even primary or activated secondary substrates (>100 °C and high basicity) are often not suitable for late-stage radiofluorination and often lead to inseparable olefin byproducts.[18] We anticipated that successful translation of the photocatalytic decarboxylative nucleophilic fluorination method would therefore enable access to previously challenging or impossible to prepare radiotracers.

To translate our method, we elected to pursue the decarboxylative radiofluorination in acetonitrile to avoid any potential clinical issues with dichloromethane. Testing the radiofluorinations in CH$_3$CN using [^{18}F]KF/K$_{222}$ as the fluoride source, we found that the previously optimized photocatalyst **3** was no longer the most effective, with Ir(F-ppy)$_3$ instead affording the highest radiochemical incorporation (Table 3, entries 1 and 4–7).[27] No radiofluorination was observed in the absence of light or photocatalyst as determined by radio-TLC or radio-HPLC (Table 3, entries 2 and 3). While we had previously found that HFIP was necessary for achieving fluorination using [^{19}F]KF under the nonradiochemical conditions (Table 1, entries 10 and 11), the addition of HFIP proved detrimental in the radiochemical system (Table 3, entry 9). Under the optimal conditions, the reaction is particularly fast, furnishing [^{18}F]**2** in 62% radiochemical conversion (RCC) within 2 min of irradiation (Table 3, entry 8). The radiofluorination was also scalable (1850–3700 MBq) albeit with diminished radiochemical conversion, permitting generation of sufficient quantities of [^{18}F]**2** to determine its molar activity (36.6 ± 18.8 GBq/μmol, decay corrected to end of synthesis), which is on par with other no-carrier added nucleophilic fluorination protocols.[17,18,30] Notably, these radiochemical reactions were conducted in a 3D-printed apparatus that permits automated

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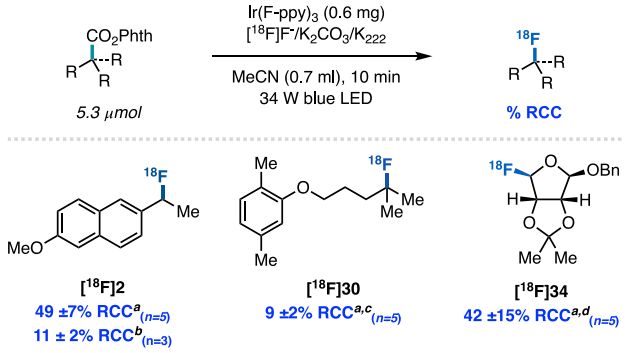
handling of radioactivity with irradiation taking place from the bottom of the vials.[27]

Access to [^{18}F]**2** is significant since its synthesis by S_N2 displacement with [^{18}F]KF would likely be plagued by rapid formation of elimination byproduct. We also briefly explored application of the radiofluorination conditions to the radiosynthesis of other fluorinated motifs that are challenging to access using conventional methods (Table 4). For example, the

Table 4. Scope of Photocatalyzed Radiofluorination



[a]Typical reaction conditions: 5.3 mol of **1**, 0.6 mg of Ir(F-ppy)$_3$, 0.7 mL of MeCN, and [^{18}F]F$^-$/K_2CO_3/K_{222} (~0.370 GBq of activity per reaction). RCC was determined by radio-TLC with number of replicates noted. Product identity was typically confirmed by HPLC coinjection. [b]Reactions were conducted with 1.85−3.70 GBq of activity per reaction. [c]Reactions conducted using photocatalyst **3**. [d]Product identity confirmed via TLC.

radiofluorination protocol is amenable to the installation of a tertiary fluoride: [^{18}F]**30** derived from gemfibrozil was obtained in 9 ± 2% RCC. Furthermore, we found that ribose analogue [^{18}F]**34** could be prepared in 42% RCC. In this case, the sulfonate precursor readily decomposes at room temperature, severely limiting access to radiolabeled ribose analogues by conventional substitution reactions.[31]

CONCLUSION

We have developed a photocatalytic method for nucleophilic fluorination of *N*-hydroxyphthalimide esters that exploits the redox activity of radicals as a route to carbocation formation. The approach generates a variety of useful fluorinated motifs under mild conditions and is compatible with functional groups that challenge other synthetic methods using both nucleophilic and electrophilic fluorine sources, such as access to tertiary aliphatic fluorides and tolerance to electron-rich functionality. Moreover, translation of the method to a radiochemical protocol was possible, enabling radiofluorination of derivatives of bioactive molecules. We present a preliminary demonstration of the generality of this approach to redox-neutral S_N1-like substitutions in extensions to a new substrate class, such as deoxyfluorination of tertiary *N*-hydroxyphthalimidoyl oxalates, and to new nucleophiles, as in the construction of sterically congested ethers and C−C bonds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c03125.

Experimental procedures and characterization and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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