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Fluorine Transfer to Alkyl Radicals

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Supporting Information

ABSTRACT: The development of new synthetic technologies for the selective fluorination of organic compounds has increased with the escalating importance of fluorine-containing pharmaceuticals. Traditional methods potentially applicable to drug synthesis rely on the use of ionic forms of fluorine (F^- or F^+). Radical methods, while potentially attractive as a complementary approach, are hindered by a paucity of safe sources of atomic fluorine ($F^\bullet$). A new approach to alkyl fluorination has been developed that utilizes the reagent *N*-fluorobenzenesulfonimide as a fluorine transfer agent to alkyl radicals. This approach is successful for a broad range of alkyl radicals, including primary, secondary, tertiary, benzylic, and heteroatom-stabilized radicals. Furthermore, calculations reveal that fluorine-containing ionic reagents are likely candidates for further expansion of this approach to polar reaction media. The use of these reagents in alkyl radical fluorination has the potential to enable powerful new transformations that otherwise would take multiple synthetic steps.

The observation that fluorine incorporation into drugs often leads to significantly improved medicinal properties has revolutionized the development of pharmaceuticals.[1−5] Indeed, there were no fluorinated medicaments on the market in 1957, while today more than 20% of medicinal compounds contain fluorine.[6,7] As a consequence, synthetic technologies for the selective fluorination of organic substrates are receiving increasing attention.[2,3] Virtually all contemporary fluorination methods potentially applicable to drug synthesis rely on the use of ionic forms of the halogen, i.e., on sources of F^- or F^+ (Figure 1). Notable among the latter are reagents such as *N*-fluorobenzenesulfonimide (NFSI),[8] Selectfluor® reagent (Air Products and Chemicals, Inc.),[9,10] and *N*-fluoropyridinium salts (NFPY).[11,12]

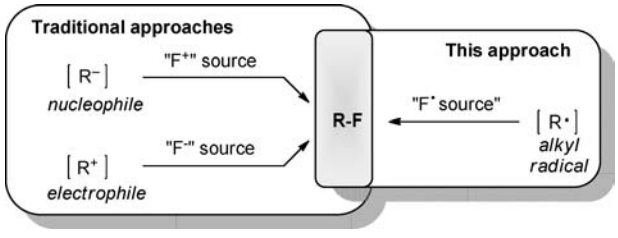

Figure 1. Synthetic approaches for the incorporation of fluorine.

It occurred to us that a technique for the fluorination of *carbon radicals*, especially aliphatic ones, would be a powerful tool that would nicely complement methodologies based on the above reagents. Unfortunately, there are very few sources of atomic fluorine ($F^\bullet$) that might be serviceable in such a transformation. Molecular fluorine is a definite possibility,[13] but its notoriously uncontrollable reactivity and the hazards associated with its use overshadow its application in preparative operations.[3] Similarly, fluoroxytrifluoromethane (trifluoromethyl hypofluorite) is a potential source of atomic fluorine, but it is similar to molecular fluorine in its reactivity, along with the associated hazards.[14] At this time, the sole selective source of fluorine atoms appears to be the expensive noble gas compound, XeF_2,[15] although perfluoroalkanes may behave similarly, at least toward aryl radicals.[16,17]

Literature data[10] on Selectfluor imply that it, as well as its congeners, may be suitable as radical transfer agents. Computational studies[18] supported the foregoing surmise. Calculated N−F homolytic bond dissociation energies (Table 1, D_{NF}) indicate that Selectfluor and NFSI share very similar homolytic bond dissociation properties that are essentially independent of the dielectric properties of the medium.

The greater electronegativity of the formally cationic nitrogen in Selectfluor results in a more positively charged (and thus electrophilic) fluorine atom (q_F) than for NFSI. While NFPY has a comparatively larger D_{NF}, which is likely due to poor delocalization of the unpaired electron in the resultant nitrogen-centered radical, the N−F bond should be sufficiently weak to react with most alkyl radicals. Thus, the use of these reagents in alkyl radical fluorination has the potential to revolutionize organic radical fluorination and enable powerful new transformations that otherwise would take multiple synthetic steps.[19]

Experimental verification of our hypothesis focused on the interaction of NFSI, which is soluble in organic media suitable for conducting radical reactions, with lauroyl peroxide, a well-known source of alkyl radicals.[20,21] Heating a solution of lauroyl peroxide and NFSI in benzene-d_6 afforded 1-fluoroundecane (**2**) in 20% yield (Scheme 1, eq 1). The majority of the remaining mass balance was accounted for in the formation of

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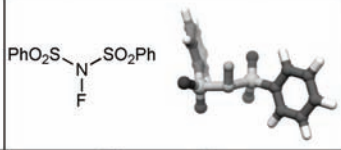
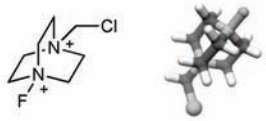
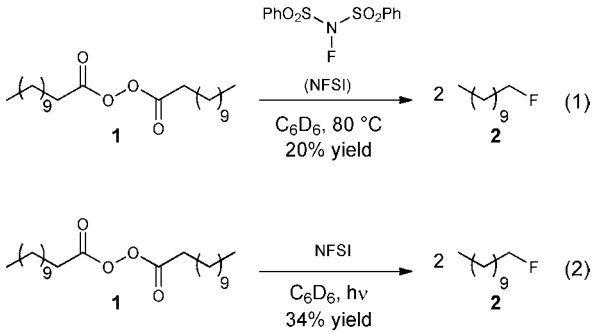
Table 1. Comparison of DFT-Calculated Properties of the N−F bond in NFSI, Selectfluor® Reagent, and NFPY Species

	N-fluorobenzenesulfonimide (NFSI)[a]				*Selectfluor®* [a,b]				*N-fluoropyridinium salts (NFPY)* [a,b]			
												
solvent	r_{NF} (pm)	BO_{NF}	D_{NF} (kcal/mol)	q_F	r_{NF} (pm)	BO_{NF}	D_{NF} (kcal/mol)	q_F	r_{NF} (pm)	BO_{NF}	D_{NF} (kcal/mol)	q_F
hexane	143.8	0.839	63.4	-0.14	141.4	0.986	61.0	0.00	137.5	0.933	76.1	-0.02
THF	143.8	0.837	63.3	-0.14	141.9	0.966	61.7	-0.02	137.8	0.922	75.4	-0.05
MeCN	143.7	0.839	63.1	-0.14	142.1	0.956	60.9	-0.03	137.8	0.915	75.1	-0.06
H_2O	143.7	0.831	63.5	-0.14	142.2	0.956	62.2	-0.03	137.9	0.914	75.3	-0.06

[a]DFT calculations were performed using ORCA wth the VWN/BPP86 functional and the available TZV/P basis set for all atoms. Molecular geometries were optimized using the COSMO solvation model as implemented in ORCA with a variety of different solvents ranging from *n*-hexane to acetonitrile. Additional details are provided in the SI. [b]Computational results for the cationic reagents without counterions are shown in this table. Results from calculations with appropriate counterions differ slightly due to ion pairing effects; these differences do not affect the overall conclusions herein. For each species, the N−F bond distance (r_{NF} in pm), Mayer bond order (BO_{NF}), and bond dissociation energy (D_{NF} in kcal/mol) are computed in four different solvents: hexane, tetrahydrofuran, acetonitrile, and water. In addition, the Loewdin charge on the fluorine atom (q_F) is given.

Scheme 1. Decarboxylative Radical Fluorination of Lauroyl Peroxide[a]



[a]The reported yields are the average GC yields of three trials and are based on the formation of two undecyl radicals for every molecule of lauroyl peroxide.

the expected radical recombination product (*n*-$C_{22}H_{46}$). To further confirm that this process involves radical intermediates, the reaction was carried out under photolytic conditions (Scheme 1, eq 2). Indeed, irradiation of a benzene-d_6 solution of lauroyl peroxide and NFSI with UV light (300 nm) provided a comparable 34% yield of fluorinated product.

These proof-of-concept experiments represent the first examples of fluorine transfer from an organic reagent to an alkyl radical.[22] For the approach to be broadly applicable, it needs to be viable for less reactive secondary, tertiary, and benzylic radicals, and radicals α to heteroatoms. Studies in that sense centered on the thermolysis of the peresters shown in Table 2 (entries 2−8). As a point of comparison with lauroyl peroxide and diacylperoxide **3** (entry 1), perester **5** should homolytically fragment to a primary radical with reactivity comparable to that of a 1-undecyl radical. Indeed, thermolysis of **5** provided fluorine-containing product **4** in 24% yield (entry 2), which is comparable to what was observed with both lauroyl peroxide and diacylperoxide **3**. Thermolysis of the secondary radical precursor **6** provided fluorinated product **7** in 98% yield (entry 3).[23] It is noteworthy that the less reactive secondary radical is fluorinated more efficiently. This increase in yield is consistent with previously reported slower homodimerization rates of bulky aliphatic radicals.[24−26] Not only is the yield of secondary fluoride **7** synthetically useful, but the decarboxylative fluorination of a secondary position could enable an enantioselective variant of the reaction, perhaps by the use of a chiral fluorine transfer agent.[27] Thermolysis of tertiary radical precursor[28] **8** afforded fluorinated product **9** in 98% yield (entry 4). This result is important as tertiary fluorides are difficult to access using nucleophilic fluorine sources. Perester **10**, which homolyzes to a benzylic radical, afforded the desired fluorine-containing product **11** in 45% yield (entry 5). The yield of fluorinated product **11** is slightly lower than was observed with fluorinated products **7** and **9** (entries 3 and 4) due to product degradation under the reaction conditions.

We next examined radical fluorodecarboxylations α to heteroatoms (Table 2, entries 6−8). Fluorination was successfully achieved α to both oxygen (entries 6 and 7) and nitrogen (entry 8). Similar to the fluorination of perester **10**, the slightly lower yields of fluorinated product are due to product degradation under reaction conditions.[29] For some peresters, such as **12**, the yield of fluorinated product could be increased by changing the solvent from benzene to acetonitrile (entries 6 and 7). In a preliminary investigation, Selectfluor was successfully utilized in the radical fluorodecarboxylation of perester **12** to provide fluoride **13** in 52% yield. Under the same conditions, NFPY provided no fluorinated product. Overall, these results demonstrate that even tertiary, benzylic, and heteroatom-stabilized radicals are sufficiently reactive to undergo a fluorine transfer reaction with NFSI.

The fast reaction times needed to perform the radical fluorodecarboxylation make it well-suited for application to PET imaging. As the half-life of ^{18}F is ~2 h,[6] any methodology that incorporates this radioisotope into an organic molecule must be a relatively fast process. Isotopically enriched NFSI can be prepared, and with the exception of primary substrates

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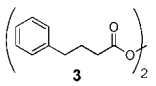
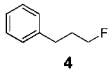
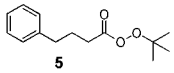
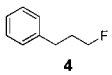
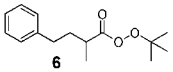
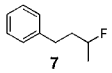
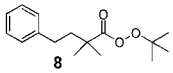
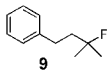
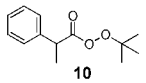
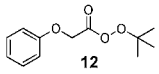
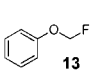
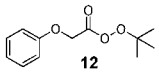
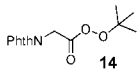
Table 2. Substitution Patterns Compatible with Decarboxylative Radical Fluorination

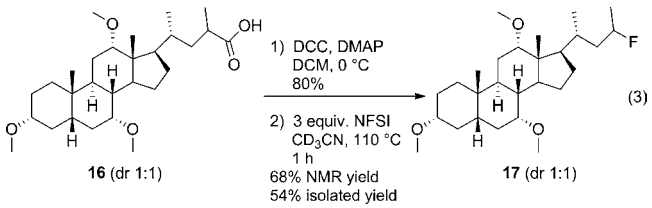
entry	substrate	product	time	yield (%)
1	 3	 4	16 h	24[a,c]
2	 5	 4	12 h	24[a,c]
3	 6	 7	19 min	98[a,c] (54)[b,d,e]
4	 8	 9	15 min	98[a,f]
5	 10	 11	6 min	45[b,f]
6	 12	 13	4 min	44[a,f] (C_6D_6)
7	 12	 13	6 min	57[b,f] (CD_3CN) (42)[d]
8	 14	 15	10 min	57[a,f] (45)[d]

[a]Conditions: 5 equiv of NFSI, 0.21 M benzene-d_6, 110 °C. [b]Conditions: 5 equiv of NFSI, 0.1 M acetonitrile-d_3, 110 °C. See SI for a discussion on solvent effects in these transformations. [c]Yield determined by GC and reported as an average of three runs. [d]Isolated yield after distillation. See SI for details. [e]The NMR yield in acetonitrile-d_3 is 86%. [f]Yield determined by ^{1}H NMR using ethyltrifluoroacetate as an internal standard and reported as an average of three runs.

(Table 2, entries 1 and 2), all of the substrates have sufficiently fast rates to allow for ^{18}F incorporation.

We next explored this new radical fluorodecarboxylation in the context of the larger substrate, cholic acid derivative **16**. Formation of the perester from **16**, followed by treatment with 3 equiv of NFSI in acetonitrile, provided the desired fluorine-containing product **17** in 68% NMR yield and 54% isolated yield (Scheme 2).

Scheme 2. Fluorination of Cholic Acid Derivative 16



The successful utilization of NFSI as a fluorine transfer reagent with alkyl radicals represents a new paradigm for synthetic fluorination. This approach works for a broad range of alkyl radicals, including tertiary, benzylic, and heteroatom-stabilized radicals. Furthermore, Selectfluor and related ionic reagents are likely candidates for further expansion of this approach to polar, or even aqueous, reaction media. Current efforts are focused on expanding the range of potential radical fluorinations from these and other traditional "electrophilic" fluorinating agents. We believe that careful and systematic choice of appropriate fluorinating agents will allow a rapid expansion of both the scope and utility of this reaction.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and ^{1}H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) There are two likely mechanisms that may be occurring in this radical fluorination process. The first is a concerted fluorine atom transfer from NFSI to the alkyl radical. The second is an initial SET from the alkyl radical to NFSI, followed fluoride transfer to the newly generated alkyl cation.
(23) NFSI is converted to dibenzenesulfonamide during the reaction. See SI for details.
(24) For studies on the pair production and cage reactions with diacyl peroxide decomposition, see: Sheldon, R. A.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 4395−4404.
(25) The increased yield of the secondary substrate is also consistent with an SET mechanism (see ref 22).
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(29) Fluorides, such as **13**, are known to be unstable and prone to hydrolysis. See the following study for further details: Ochiai, M.; Yoshimura, A.; Miyamoto, K. *Tetrahedron Lett.* **2009**, *50*, 4792−4795.