Synthetic Methodology

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C_{sp^3}–F Bond Formation: A Free-Radical Approach**

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C–H activation · fluorine · radical reactions · reaction mechanisms · synthetic methodology

The importance of fluorine-containing compounds in pharmaceutical and agrochemical industries has significantly grown in recent years because the unique properties of fluorine. The use of ^{18}F-labeled compounds in molecular imaging using positron emission tomography (PET) has also stimulated efforts to find new and selective methods to introduce fluorine onto a carbon framework. While many approaches have been devised to incorporate atomic fluorine using electrophilic and nucleophilic fluorine sources,[1] the formation of a C–F bond by reaction of a C-centered radical with a fluorine source has been restricted to molecular F_2, hypofluorites, and XeF_2.[2] Although XeF_2 has a very efficient fluorine-transfer rate constant ($k_{abs} = 1.1 \times 10^6\,M^{-1}s^{-1}$ for a primary radical),[2b] it is an expensive noble gas, and F_2 and hypofluorites are hazardous and exhibit uncontrollable reactivities.[2a]

Alternative safer reagents, including *N*-fluorobenzenesulfonimide (NFSI), Selectfluor, and *N*-fluoropyridinium salts are now commonly used as electrophilic sources of atomic fluorine. Recent computational determination[3] of C–F homolytic bond dissociation energies of 60–62 and 63 kcal mol^{-1} for Selectfluor and NFSI, respectively, suggests that these reagents may be suitable as radical fluorine transfer agents.[4] In a very short timespan, elegant solutions to incorporate fluorine onto a carbon framework using a free-radical strategy have been reported. Three complementary approaches have been developed (Figure 1): 1) the hydrofluorination of unactivated olefins,[5] 2) the fluorodecarboxylation of carboxylic acids and anhydrides,[3,6] and 3) aliphatic C–H fluorination.[7] Boger and co-workers have investigated hydrofluorination of unactivated alkenes.[5] In this method, iron(III) salts and $NaBH_4$ function as a radical initiator, and in the presence of Selectfluor, a wide range of olefins were converted into fluorinated compounds with exclusive Markovnikov regioselectivity. The reaction uses inexpensive

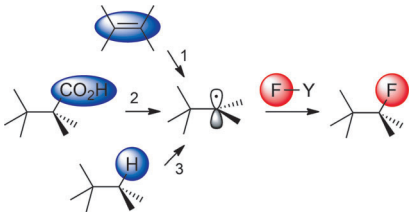
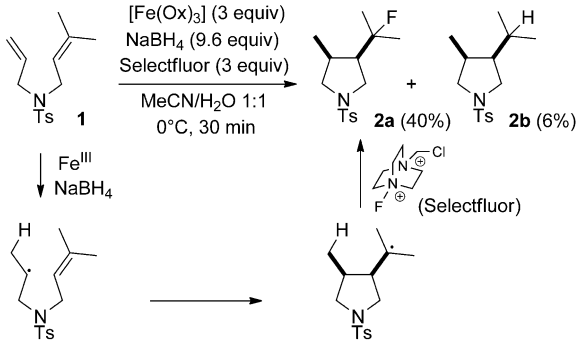


Figure 1. Free-radical fluorination of a C-centered radical.

reagents and shows excellent functional group compatibility. The use of $NaBD_4$ and $NaBT_4$ allows radiolabelling and the process is sufficiently fast to foresee the introduction of ^{18}F for PET studies. Control experiments indicate that this transformation involves radical intermediates rather than carbocations. For example, addition of HF to cyclic alkenes is not diastereospecific and styrenes are not fluorinated but lead to benzylic alcohols and dimers, thus suggesting the formation of a benzylic radical. And, the fluorination of the diene **1** with Selectfluor leads to **2a** and **2b**, whereas the same reaction under electrophilic conditions does not provide the cyclized product (Scheme 1).



Scheme 1. Free-radical hydrofluorination of alkenes. Ts = 4-toluenesulfonyl.

Li and co-workers[6a] have also employed Selectfluor to fluorinate a C-centered radical generated by a Hunsdiecker-type oxidative decarboxylation of a carboxylic acid. The reaction was carried out in an acetone/water medium using $AgNO_3$ as a catalytic oxidant. Selectfluor was used both as a fluorine source and as a reoxidant of the silver catalyst. The fluorinated products are formed in good yields (**3**→**4**; Scheme 2) and the mild reaction conditions are compatible with many functional groups. Relative reactivities of carbox-

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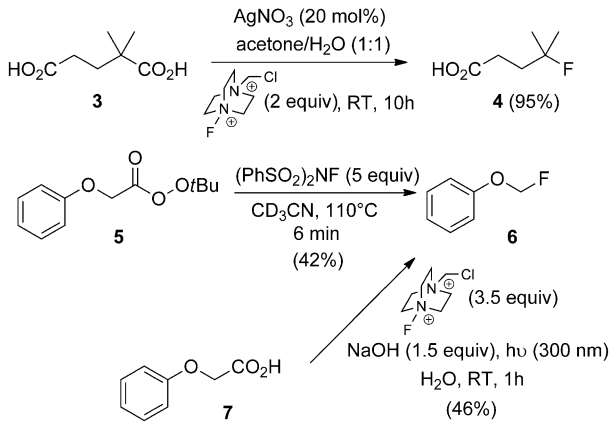
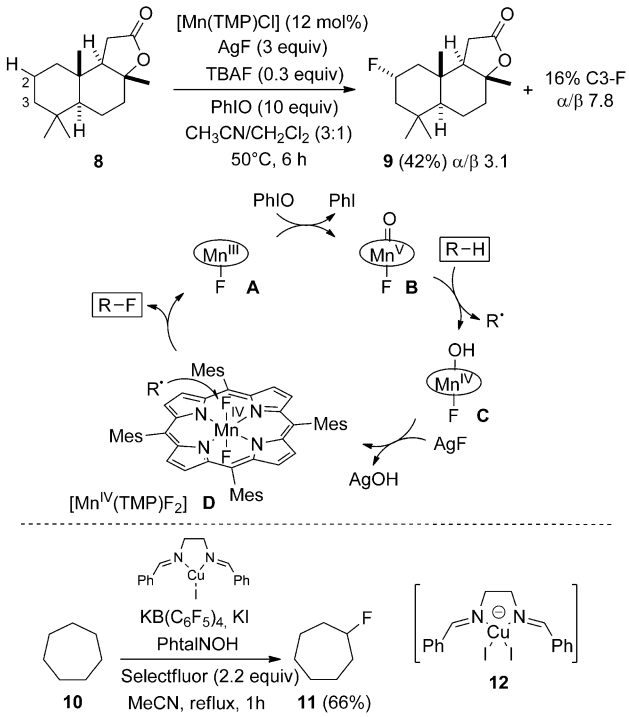


Scheme 2. Free-radical decarboxylative fluorination.



Scheme 3. Selective fluorination of unactivated C_{sp3}–H bonds. Mes = 2,4,6-trimethylphenyl, TBAF = tetra-*n*-butylammonium fluoride.

ylic acids following the trend: tertiary > secondary > primary ≫ aromatic, along with radical-clock experiments support a radical pathway. A tentative mechanism invoking the intermediacy of F-Ag^{II} and F-Ag^{III} complexes has been proposed.[8] Single-electron transfer (SET) between a carboxylate anion and F-Ag^{III} generates the C-centered radical and F-Ag^{II}. Abstraction of fluorine atom from F-Ag^{II} by the alkyl radical leads to the fluorinated compound, along with the regenerated silver(I) catalyst. Additional experiments suggest that direct abstraction of a fluorine atom from Selectfluor by the alkyl radical is not effective. Sammis and co-workers[3] have also developed a decarboxylative fluorination of peroxyesters using NFSI as the fluorinating agent under thermal conditions. The fluorinated products are formed in modest to good yields (**5**→**6**; Scheme 2). The short reaction time is compatible with ^{18}F radiolabeling. The authors suggest two possible mechanisms for their reaction: 1) a concerted fluorine atom transfer from NFSI to the carbon radical; 2) a SET from the alkyl radical to NFSI, followed by the trapping of the resulting carbocation by fluorine. A complementary photochemical protocol has also been reported (**7**→**6**; Scheme 2).[6b] The photochemical protocol is limited to substrates containing an arene or an aryloxy substituent α to the acid function. This observation is consistent with the formation of benzylic and α-aryloxy radicals through an arene excitation/oxidative decarboxylation sequence.

Site-selective fluorination of unactivated C_{sp3}–H bond has enormous potential. This strategy has been elegantly demonstrated using two different organometallic systems.[7] Groves and co-workers have developed a manganese/phorphyrin-mediated fluorination of aliphatic compounds, and it exhibits broad substrate scope and proceeds in satisfactory yields.[7a] Reactions are performed in the presence of [Mn(TMP)Cl] as a catalyst, PhIO as the oxidizing agent, and AgF/TBAF as the fluorine sources. The remarkable selectivity of this method is illustrated by the fluorination of sclareolide (**8**), possessing 26 potentially reactive C_{sp3}–H bonds (Scheme 3). A catalytic cycle which starts with fluorination of the Mn^{III} catalyst (with AgF/TBAF) leading to the F-Mn^{III} complex **A** has been proposed. The intermediate **A** is then oxidized to the highly reactive Mn^{V}-oxo species **B**, which then forms the C-centered radical by H atom abstraction in a rate-determining step (kinetic isotope effect of 6.1). The ensuing radical then abstracts a fluorine atom from [Mn^{IV}(TMP)F_2] (**D**). The intermediate **D** has been prepared independently and structurally characterized. Reaction of cyclooctane with stoichiometric amount of **D** produced cyclooctyl fluoride in 43% yield, thus indicating that this key-intermediate is likely the fluorinating agent.

Lectka and co-workers[7b] reported the monofluorination of various aliphatic substrates (e.g. **10**→**11**) in good yields, using a simple Cu^{I}/Schiff base complex in the presence of Selectfluor. Benzylic and allylic precursors were also selectively fluorinated at room temperature. Improved yields were obtained using a rather complex reaction mixture, including N-hydroxylphthalimide as a cocatalyst, the phase-transfer catalyst $KB(C_6F_5)_4$ to solubilize Selectfluor, and KI to promote the formation of the active cuprate species **12**. A radical pathway has been suggested based on control experiments in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), a radical scavenger.

Fluorine delivery and efficient formation of the C_{sp3}–F bond through radical pathways complement the traditional nucleophilic and electrophilic modes of fluorination. While some of these approaches await more in depth mechanistic investigations, broad substrate scope, functional group tolerance, and practicality represent attractive features of these methodologies. Alternative sources of fluorine, not described herein, include fluorinated solvents[9] and offer additional perspectives to such approaches. This should stimulate further efforts to extend the scope of these methodologies and their

potential use in therapeutic applications, including molecular imaging.

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