Decarboxylative Fluorination | Hot Paper

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Targeted Fluorination with the Fluoride Ion by Manganese-Catalyzed Decarboxylation**

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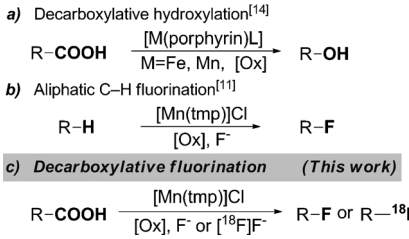
Abstract: *We describe the first catalytic decarboxylative fluorination reaction based on the nucleophilic fluoride ion. The reported method allows the facile replacement of various aliphatic carboxylic acid groups with fluorine. Moreover, the potential of this method for PET imaging has been demonstrated by the successful ^{18}F labeling of a variety of carboxylic acids with radiochemical conversions up to 50 %, representing a targeted decarboxylative ^{18}F labeling method with no-carrier-added [^{18}F]fluoride. Mechanistic probes suggest that the reaction proceeds through the interaction of the manganese catalyst with iodine(III) carboxylates formed in situ from iodosylbenzene and the carboxylic acid substrates.*

Organofluorine compounds are of significant importance for the agrochemical and pharmaceutical industries as well as for PET imaging applications.[1] Despite the broad impact of organofluorine compounds and the intrinsic strength of the C–F bond, the incorporation of fluorine into organic molecules remains challenging.[2] Conventional fluorination methods typically involve harsh reaction conditions, displaying poor functional-group tolerance and low selectivity.[2] These limitations have inspired the development of a number of new methods, especially catalytic approaches, for constructing C–F bonds.

During the past ten years, remarkable advances have been made in the field of catalytic fluorination.[2,3] The majority of these newly developed methods are based on electrophilic fluorination reagents (F^+), such as Selectfluor and other *N*-fluoroammonium analogues, *N*-fluoropyridinium salts (NFPs), and *N*-fluorosulfonamides.[3b] For catalytic fluorinations with fluoride-based reagents (F^-),[3a] only a handful of reactions have been developed, which allow the synthesis of aryl fluorides,[4] alkenyl fluorides,[5] allylic fluorides,[6] fluorohydrins,[7] ^{18}F-labeled trifluoromethyl arenes,[8] and benzylic fluorides.[9]

A general catalytic method for constructing aliphatic C–F bonds with simple nucleophilic fluoride remains a challenging task.[10] In 2012, our laboratory reported an efficient aliphatic C–H fluorination reaction that employed manganese tetramesitylporphyrin [Mn(tmp)]Cl as the catalyst and silver fluoride/tetrabutylammonium fluoride trihydrate (TBAF·3 H_2O) as the fluoride source.[11] The reaction was shown to proceed via a novel *trans*-difluoromanganese(IV) porphyrin complex that served as the fluorine transfer agent. Insights gained from the facile capture of substrate carbon radicals by $F–Mn^{IV}–F$ species led to the development of benzylic C–H fluorination reactions using manganese salen catalysts.[12] Very recently, we reported the first ^{18}F labeling reaction of aliphatic C–H bonds with no-carrier-added [^{18}F]fluoride and Mn(salen) catalysts.[13]

We have sought a complementary Mn–F fluorination protocol that would employ a ubiquitous and easily managed target functional group. A possible approach was suggested by reports of Mn-catalyzed oxidative decarboxylations from the 1990s.[14] This decarboxylative hydroxylation reaction is fast and has a wide functional-group tolerance. Functionalities like olefinic C=C bonds and reactive C–H bonds, which are reactive under common metalloporphyrin-catalyzed oxidative conditions, were well tolerated. Driven by these appealing features, we aimed to develop a catalytic fluorodecarboxylation reaction based on nucleophilic fluoride (F^-) (Scheme 1).



Scheme 1. The concept of manganese-catalyzed decarboxylative fluorination.

The concept of decarboxylative fluorination was first demonstrated by Grakauskas with fluorine gas in 1969 and later by Patrick et al. with XeF_2.[15] Applications of these reactions were severely limited however, due to the highly reactive, electrophilic fluorination reagents. Several catalytic

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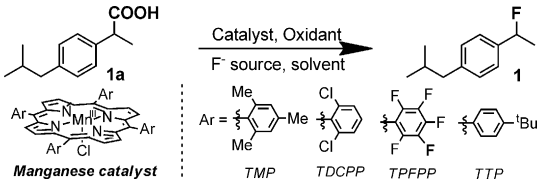
decarboxylative fluorination methods have been developed recently based on modern electrophilic fluorination reagents such as Selectfluor[16] that have enabled transformations of various types of carboxylic acids to the corresponding fluorides under mild conditions.

A decarboxylative fluorination using the fluoride ion has not been described until this report. The major advantages of using fluoride for PET imaging applications are the significantly higher specific activities that can be achieved with [^{18}F]fluoride compared to [^{18}F]F$^+$ reagents, as well as the ease of preparing and handling [^{18}F]fluoride salts.[1b,4b] Moreover, decarboxylative fluorination may enable easier purifications given the marked difference (polarity/charge) in the precursor carboxylic acid and the fluorinated product.

With ibuprofen (**1a**) as an initial model substrate, exploratory reaction conditions afforded fluorination product **1** in a promising 13% yield (Table 1, entry 1). The modest yield is likely due to the formation of insoluble silver carboxylates that were observed during the reaction. We thus turned to a less basic fluoride source, triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$),[17] with which the yield increased to 53% (Table 1, entry 2). After extensive screening a 65% yield was obtained with [Mn(tmp)]Cl as the catalyst, iodosylbenzene (PhIO) as the oxidant, DCE as solvent and 0.5 equiv benzoic acid as the additive (Table 1, entry 9). No fluorination products were detected in control experiments with the catalyst or oxidant omitted.

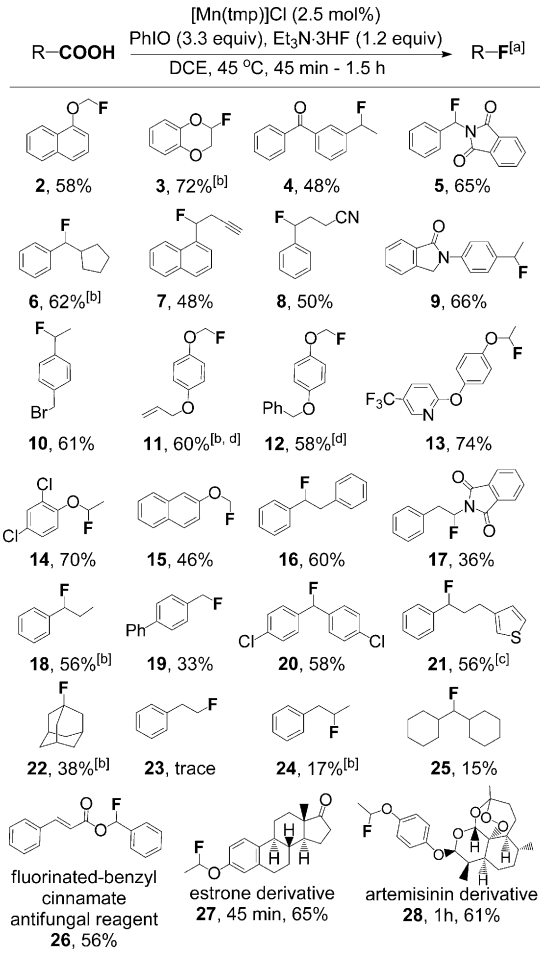
Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst[b]	Oxidant	F$^-$ (equiv)	Solvent[c]	Yield [%]
1	[Mn(tmp)]Cl	PhIO	AgF/ TBAF·3 H_2O	ACN/ DCM	13
2	[Mn(tmp)]Cl	PhIO	$Et_3N{\cdot}3$ HF (1.2)	ACN/ DCM	53
3	[Mn(tmp)]Cl	PhIO	$Et_3N{\cdot}3$ HF (1.2)	DCE	61
4	[Mn(ttp)]Cl	PhIO	$Et_3N{\cdot}3$ HF (1.2)	DCE	43
5	[Mn(tdcpp)]Cl	PhIO	$Et_3N{\cdot}3$ HF (1.2)	DCE	16
6	[Mn(tpfpp)]Cl	PhIO	$Et_3N{\cdot}3$ HF (1.2)	DCE	trace
7	[Mn(tmp)]Cl	PhI(OPiv)$_2$	$Et_3N{\cdot}3$ HF (1.2)	DCE	45
8	[Mn(tmp)]Cl	PhI(OAc)$_2$	$Et_3N{\cdot}3$ HF (1.2)	DCE	50
9	***[Mn(tmp)]Cl***	***PhIO***	***$Et_3N{\cdot}3$ HF (1.2)***	***DCE***	***65[d]***

[a] Reaction conditions: Nitrogen atmosphere, **1a** (103 mg, 0.5 mmol), catalyst (10 mg, 2.5 mol%), oxidant (370 mg, 3.3 equiv), and solvent (1 mL). Yields were determined by ^{19}F NMR spectroscopy with 20 μL fluorobenzene as standard. [b] tmp: tetramesitylporphyrin; ttp: 5,10,15,20-tetrakis(*p*-tolyl)porphyrin; tdcpp: 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin; tpfpp: 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin. [c] ACN: acetonitrile; DCM: dichloromethane; DCE: 1,2-dichloroethane. [d] 0.5 equiv benzoic acid as additive.

Having identified the optimal conditions, we then examined the substrate scope of this reaction. As shown in Scheme 2, a variety of functional groups, including heterocycle, amide, imide, ester, ketone, ether, nitrile, halogen, and even alkene and alkyne, are well tolerated. Higher yields were generally observed for substrates bearing electron-donating substituents. Molecules containing strongly electron-rich aromatic rings, which are challenging substrates for Selectfluor-based decarboxylative fluorination methods because of the competing aryl fluorination,[16d] were readily fluorinated without any ring fluorination (**11**–**13**). The tolerance to

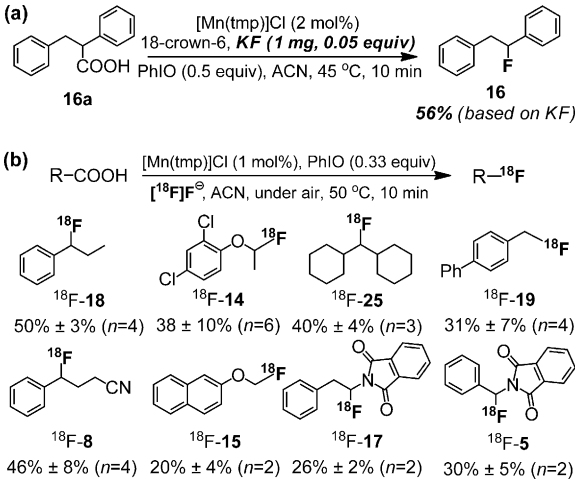


Scheme 2. Substrate scope and functional-group tolerance. [a] Standard conditions: substrate (0.5 mmol), [Mn(tmp)]Cl (2.5 mol%), $Et_3N{\cdot}3$ HF (1.2 equiv), benzoic acid additive (0.5 equiv), DCE (1 mL). PhIO (3.3 equiv) was added in small portions within 45 min to 1.5 h at 45 °C under N_2 protection. The reported yields are those of isolated products unless otherwise noted. [b] Yields were determined by ^{19}F NMR spectroscopy. [c] Iodosylmesitylene was used as the oxidant. [d] 2 equiv of oxidant were used.

reactive functional groups like halogens (**10**) and alkynes (**7**) further broadens the application of the present method, as various structural motifs can be accessed through these functionalities by well-established methods such as cross coupling or "click" reactions. Surprisingly, no epoxidation or C–H activation products were observed with substrates containing olefinic C=C bonds (e.g., **11** and **26**), despite the well-known [Mn(tmp)]Cl/PhIO catalytic system that efficiently performs these reactions.[18] While the present method efficiently fluorinated benzylic and aryloxy carboxylic acids, tertiary, secondary, and primary acids were less reactive (**22**–**25**). The same trend was observed for the related Mn-catalyzed decarboxylative hydroxylation reaction.[19] The results suggest a free-radical pathway, as the reactivity pattern is consistent with variations of the C–COOH bond dissociation energies.[20]

The mildness of the fluorination conditions prompted us to test its application to fluorinating molecules with structures of biological importance (Scheme 2). Fluorinated benzyl cinnamate and a fluorinated estrone derivative could be obtained in 56% and 65% yield, respectively, from the corresponding acids. Moreover, this procedure could be applied to fragile, complex structures like artemisinin, for which the decarboxylative fluorination proceeded smoothly to afford **28** in 61% yield in 1 h. These results clearly demonstrate the significant potential of the reported method for late-stage fluorination of bioactive molecules.

Compared to current decarboxylative fluorination methods that are based on F^+ reagents, the major advantage of this fluoride-based decarboxylative fluorination reaction is its applicability to ^{18}F labeling with [^{18}F]fluoride. To demonstrate this potential, we first tested the reaction with limiting amounts of K^{19}F, since a functional reaction for ^{18}F labeling should be able to incorporate sub-stoichiometric amounts of fluoride into substrate molecules.[1b,4d,21] Thus, treating acid **16a** with [Mn(tmp)]Cl, PhIO, and only 0.05 equiv of K^{19}F in ACN for 10 min afforded the fluorinated product **16** in 56% yield based on the amount of fluoride (Scheme 3a). Inspired by this promising result, we further evaluated the efficacy of this method for radiofluorination with no-carrier-added [^{18}F]fluoride (Scheme 3b). We found that carboxylic acids underwent efficient decarboxylative ^{18}F-fluorination with RCCs ranging from 20% to 50% under similar reaction conditions to those used with K^{19}F. Less reactive acids under ^{19}F conditions, such as secondary carboxylic acid **25a**, could be readily ^{18}F-labeled (40% RCC for ^{18}F-**25**), which is presumably due to the very low concentration of [^{18}F]fluoride and the large excess of other reactants. In our previous work, we demonstrated that the tedious azeotropic K^{18}F drying step could be eliminated by directly eluting [^{18}F]fluoride from the ion exchange cartridge with a solution of the [Mn(salen)]OTs catalyst. With a similar protocol, ^{18}F-**19** was obtained with a non-decay-corrected radiochemical yield (RCY) of 10%. The specific activity was determined to be 1.78 Ci μmol^{-1} (at end of bombardment; EOB). This transformation represents the first general decarboxylative ^{18}F labeling method with no-carrier-added [^{18}F]fluoride. Efforts are ongoing to expand the substrate scope of this novel ^{18}F labeling method and adapt it to PET imaging applications.



Scheme 3. a) Decarboxylative fluorination with KF as fluoride source. b) Adapting the manganese-catalyzed decarboxylative fluorination to ^{18}F labeling. Radiochemical conversions (RCCs) are averaged over *n* experiments.

A proposed reaction mechanism is shown in Figure 1. There are two likely pathways for the activation of the carboxylic acid. The first involves the preformation of an iodine(III) carboxylate ester that oxidizes the manganese(III)

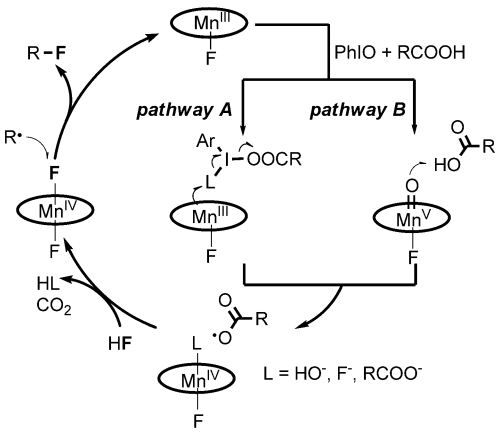
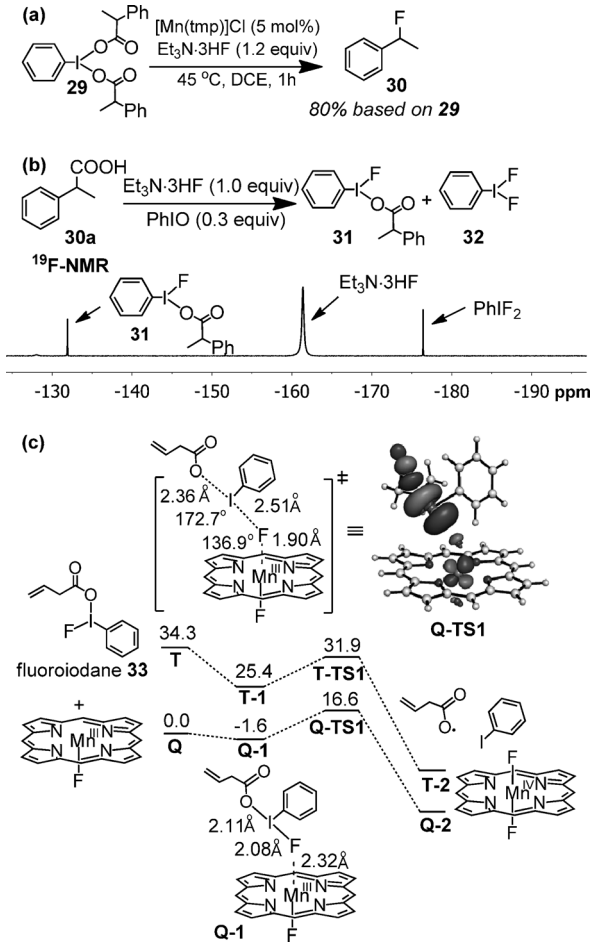


Figure 1. Mechanistic probes of the fluorine-transfer step.

porphyrin to a fluoromanganese(IV) intermediate with concurrent decarboxylation (pathway A). The second pathway proceeds through a direct hydrogen abstraction from the hydroxy group of the carboxylic acid by an oxomanganese(V) porphyrin intermediate (pathway B). Although further work is needed to differentiate the two pathways, current evidence suggests pathway A, since both PhI(OPiv)$_2$ and PhI(OAc)$_2$ were efficient oxidants for decarboxylative fluorination in the absence of water (Table 1, entries 7 and 8).

To explore whether iodine(III) carboxylates could react with manganese(III) porphyrins to afford the fluorination products, iodobenzene dicarboxylate **29** was synthesized and subjected to a DCE solution of [Mn(tmp)]Cl and Et$_3$N·3HF (Scheme 4a). Heating the reaction mixture at 45 °C for 1 h

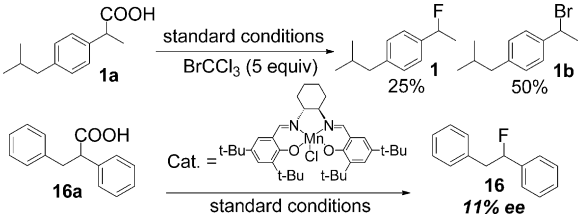


Scheme 4. a) Fluorination of iodine(III) dicarboxylate **29**. b) ^{19}F NMR spectrum of a solution of [Mn(tmp)]Cl, $Et_3N{\cdot}3HF$, and acid **30a**. c) Potential energy surfaces (kcal mol^{-1}) for the formation of carboxyl radicals through the interaction of an iodine(III) carboxylate complex and a manganese(III) porphyrin. T and Q refer to triplet and quintet states, respectively.

afforded (1-fluoroethyl)benzene (**30**) in 80% yield, demonstrating that the iodine(III) carboxylate complex is highly reactive toward the manganese(III) porphyrin. The formation of an iodine(III) carboxylate was further indicated by NMR spectroscopy (Scheme 4b). Adding 0.3 equiv of PhIO to a CD_2Cl_2 solution of acid **30a** and $Et_3N{\cdot}3HF$ (1.0 equiv) led to immediate dissolution of solid PhIO. The ^{19}F NMR spectrum of this clear solution revealed the resonances of $Et_3N{\cdot}3HF$ (−160 ppm) and $PhIF_2$ (−177 ppm),[9] as well as a new resonance at −132 ppm, which was identified as belonging to fluoroiodane **31** from the titration experiment between **29** and $Et_3N{\cdot}3HF$ (Figure S1 in the Supporting Information). Adding 2 mol% [Mn(tmp)]Cl catalyst to this clear solution afforded fluoroethylbenzene in 40% yield, which, again, demonstrates that an iodine(III) carboxylate complex can react productively with the manganese porphyrin catalyst.

The formation of carboxyl radicals through the interaction between the iodine(III) carboxylate and the manganese porphyrin is also supported by DFT calculations (Scheme 4c). The lowest-energy reaction profile was on the quintet energy surface, as expected for a manganese(III) porphyrin. Fluoroiodane **33** first forms an adduct with the manganese(III) porphyrin, which is thermodynamically favored by 1.6 kcal mol^{-1}. This adduct then undergoes a facile dissociation at the iodine center with a barrier of 18.2 kcal mol^{-1}. In the transition state, the frontier orbital interaction involves the d_{yz} orbital of [Mn(PorH)]F and the σ* orbital of the O–I–F bond with bonding interactions between fluorine and manganese. Significant elongations of both the I–O bond (from 2.11 Å in Q-1 to 2.36 Å in Q-TS1) and the I–F bond (from 2.08 Å to 2.51 Å) are observed with a concurrent contraction of the Mn–F bond (from 2.32 Å to 1.90 Å). These results are consistent with a dissociation of the carboxyl radical from iodine and a synchronous F-atom transfer to Mn^{III} to afford $F–Mn^{IV}–F$.

For the fluorine-transfer step, the radical nature of the reaction was demonstrated by adding 5 equiv CCl_3Br as an alkyl radical trap (Scheme 5, top). The major product was the alkyl bromide **1b**. Since the rate constant for bromine transfer



Scheme 5. Mechanistic studies of the fluorine-transfer step.

from $BrCCl_3$ to alkyl radicals is known to be about 10^8 M^{-1}s^{-1},[22] the 1:2 fluorination/bromination (**1**/**1b**) ratio corresponds to a nanosecond radical lifetime, which is comparable to the rate of the manganese porphyrin catalyzed C–H fluorination reaction. When a chiral manganese salen complex was used as the catalyst, fluorination of acid **16a** afforded **16** in 11% *ee* (Scheme 5, bottom). This low but mechanistically informative *ee* value provides strong additional support for a manganese-bound fluoride in the intermediate of the fluorine-transfer step.

In summary, we have described a catalytic decarboxylative fluorination based on nucleophilic fluoride. This Mn-catalyzed transformation is characterized by its high rate, wide functional-group tolerance and high specificity. The potential of this method for PET imaging applications has been demonstrated by successful ^{18}F labeling of a variety of target carboxylic acids, which represents the first decarboxylative ^{18}F labeling method based on no-carrier-added [^{18}F]fluoride. Ongoing work will focus on expanding the substrate scope of this novel ^{18}F labeling method and adapting it to PET imaging applications.

Experimental Section

An oven-dried 5 mL Schlenk flask was placed under an atmosphere of N_2. [Mn(tmp)]Cl (10 mg, 2.5 mol%), acid substrate (0.5 mmol), $Et_3N{\cdot}3HF$ (100 μL, 1.2 equiv), benzoic acid (30 mg, 0.5 equiv), and DCE (1.0 mL) were added to the vial and heated to 45 °C. Under a stream of N_2, PhIO (370 mg, 1.6 mmol, 3.3 equiv) was added to the

reaction mixture in small portions over a period of 45 min–1.5 h. The reaction was monitored by GC/MS with naphthalene (0.195 mmol) as an internal standard. After the reaction was complete, the products were isolated by silica gel column chromatography.

Keywords: decarboxylation · fluoride · fluorination · labeling with ^{18}F · manganese porphyrins

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