Fluorinated Compounds

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Manganese-Catalyzed Oxidative Benzylic C–H Fluorination by Fluoride Ions**

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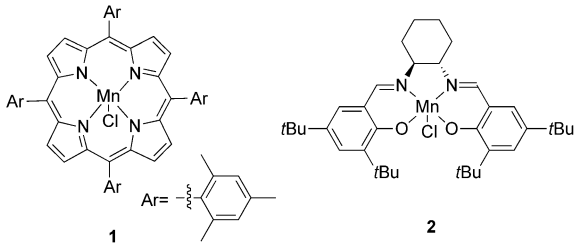
Fluorinated organic compounds are extremely important as pharmaceuticals, fine chemicals, and materials.[1] In addition, radioactive ^{18}F-labeled imaging agents, such as 2-[^{18}F]fluoro-2-deoxyglucose, are widely used for positron emission tomography (PET) in oncology and imaging the brain.[2] The transformation of C–H bonds into C–F bonds within organic molecules can have profound effects on biological activity, phase 1 metabolism, and hydrophobicity.[3] However, despite the increasing importance of fluorine-containing molecules and their applications, the development of synthetic methods to form C–F bonds selectively, under mild conditions is still challenging.[4] Conventional fluorination reactions developed in the twentieth century are generally limited to simple molecules and involve the use of difficult-to-handle reagents, such as elemental fluorine[5] and various metal fluorides.[6] Although chemists have developed a variety of new methods for the fluorination of organic molecules over the past five years, general methodologies for forming C(sp^3)–F bonds are still limited,[7] in contrast to the comparatively well-developed methods for aryl C(sp^2)–F bond formation.[8] In particular, there are relatively few methods available that can selectively convert unactivated C(sp^3)–H bonds to C(sp^3)–F bonds by direct C–H activation, particularly in chemically inaccessible carbocyclic rings.[9]

In the context of C(sp^3)–F-containing molecules, the benzylic fluoride fragment could be an effective substitute for benzylic C–H groups in many bioactive molecules. Traditionally, benzylic fluorides can be prepared by halogen exchange, electrochemical methods, and the dehydroxyfluorination of benzylic alcohols with diethylaminosulfur trifluoride (DAST) and bis(2-methoxy-ethyl)aminosulfur trifluoride (Deoxo-Fluor).[10] However, these methods require prefunctionalization at the benzylic positions and often suffer from elimination by-products. Further, the fluorine source is often incompatible with the preparation of ^{18}F-labeled compounds. Recently, Sanford and co-workers have reported a palladium-catalyzed direct benzylic C–H fluorination on a variety of 8-methylquinoline derivatives by using silver fluoride.[11] However, this approach requires a directing group on the arene ring.

Given the potential importance of benzylic fluorides and the paucity of current preparative methods, a general, transition-metal-catalyzed direct C–H fluorination at benzylic positions with a nucleophilic fluorine source would be highly desirable. Such a method could be of great value for both radiolabeling applications of biomolecules and structure–activity relationship (SAR) studies of drug candidates.

Recently, we reported an efficient process for the conversion of unactivated aliphatic C–H bonds into C–F bonds that employed a manganese porphyrin catalyst (**1**, Scheme 1) with silver fluoride/tetrabutylammonium fluoride trihydrate (TBAF·3H_2O) as the fluorine source.[12] The reaction is believed to proceed through a catalytic cycle



Scheme 1. Manganese C–H fluorination catalysts used.

involving a novel *trans*-difluoro manganese(IV) species, which efficiently transfers a fluorine atom to short-lived alkyl radicals generated by a reactive oxoMn^{V} intermediate.[13] An intriguing and particularly useful aspect of this C–H fluorination was a marked preference for methylene C–H bonds in carbocyclic rings, apparently owing to steric and stereoelectronic effects. When we applied this fluorination protocol to substrates containing benzylic C–H bonds, such as 4-ethylbiphenyl (**3**), we observed the formation of the benzylic fluorinated product **3a** in 44% yield as expected. However, analysis of the reaction mixture revealed that nearly equal amounts of oxygenated compounds (benzylic alcohol and ketone) were also formed (Table 1, entry 1). Since the reactions were conducted under anaerobic conditions, the oxygen in these by-products must derive from the oxidant, iodosylbenzene (PhIO), or water. Our rationale for the formation of the oxygenation products is that the relatively low ionization potential of the incipient benzylic radical leads to a rapid carbon radical rebound to the Mn^{IV}–OH intermediate.[14]

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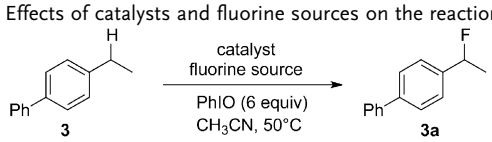
Table 1: Effects of catalysts and fluorine sources on the reactions.



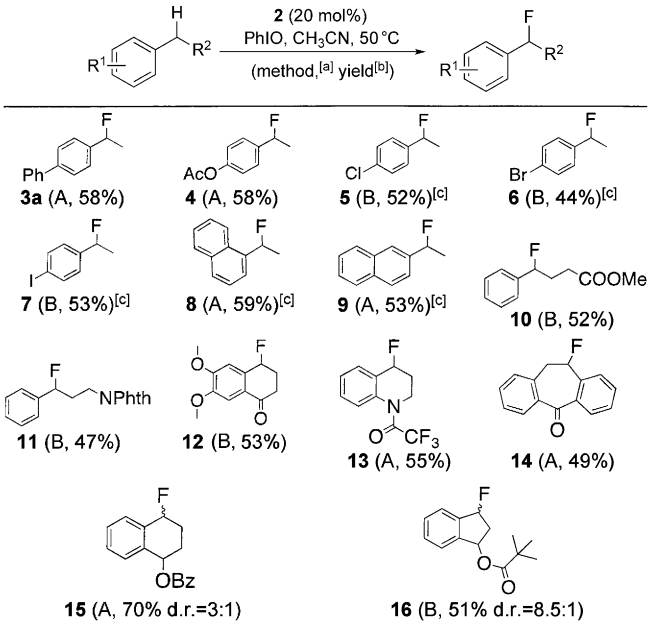
Entry	Catalyst (mol%)	F source (equiv)	Conv. [%][a]	Yield [%][b]	-F/-O[a]
1[c]	**1** (10)	TBAF·3 H_2O (0.2) AgF (3)	94	44	1:1
2[c]	**2** (10)	TBAF·3 H_2O (0.2) AgF (3)	50	40	5:1
3	**2** (10)	TREAT·HF (1.5)	42	37	12:1
4	**2** (20)	TREAT·HF (1.5)	75	59[d]	6:1
5[c]	**2** (20)	TREAT·HF (0.5) AgF (3)	81	60	5:1

[a] The ratio of fluorinated to oxygenated compounds was determined by GC/MS. [b] Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [c] Reactions were carried out under exclusion of light. [d] Yield of isolated product based on starting material.

Accordingly, we sought a catalyst system that might display complementary selectivity to that of the manganese porphyrin catalysts and mediate benzylic C–H fluorinations. Upon screening a number of other ligand systems, we found that a manganese–salen complex (**2**; Scheme 1), originally developed by Jacobsen and co-workers for oxygen transfer,[15] did favor the efficient formation of benzylic fluorides while effectively suppressing the oxygenation products observed with **1**, albeit in a relatively low conversion (Table 1, entry 2). After further screening of reaction conditions, we discovered that triethylamine trihydrofluoride (TREAT·HF)[16] is a superior fluorine source for this reaction compared to the combination of TBAF·3 H_2O and AgF in terms of the selectivity for fluorination over oxygenation (Table 1, entry 3). Upon optimizing the catalyst load, we found that in the presence of 20 mol% **2**, fluorination of **3** afforded the benzylic fluoride **3a** in 59% yield (Table 1, entry 4, Method A). The combination of TREAT·HF and AgF also served as a good fluorine source, although slightly diminished selectivity for fluorination was observed in this case (Table 1, entry 5, Method B). Control reactions in the absence of the Mn(salen) catalyst showed none of the fluorinated product. No aromatic fluorination was observed in any of the cases examined. Approximately 5% of the *gem*-difluoride product was observed in the crude reaction mixture for **3**.

With the optimized reaction conditions in hand, we investigated the scope of this fluorination protocol (Scheme 2). The method has a broad scope and exhibits high functional-group tolerance. Substrates containing amide, ether, ester, carbonyl, halide, imide, and aryl groups were mono-fluorinated efficiently at the benzylic sites. For compounds that contain electron-withdrawing groups, AgF was found to be advantageous (Method B). The fact that a variety of halogens was tolerated is of interest, because this strategy could provide sites for further modification of the fluorinated motif. Moreover, a wide array of ring systems, most of which are important scaffolds in biologically active molecules, such as tetrahydronaphtahlene, indan, tetrahydroquinoline, and dibenzocycloheptene were all successfully fluorinated.

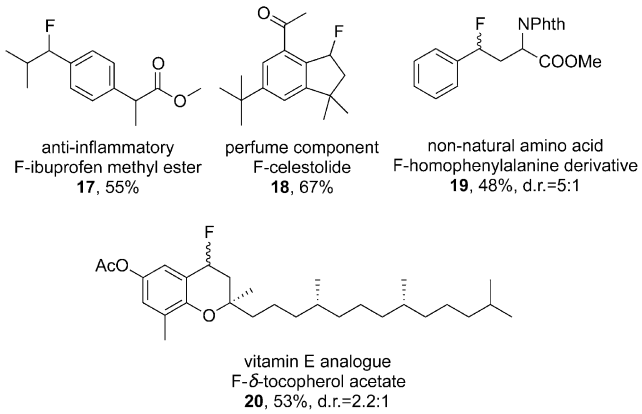
Encouraged by the generality of the reaction, we next turned our attention to the late-stage fluorination of drug-like



Scheme 2. Substrate scope of the benzylic fluorination. [a] Method A: substrate (0.8 mmol), PhIO (6–9 equiv), TREAT·HF (1.2 mmol), CH_3CN (0.5 mL), 50°C, 6–9 h. Method B: substrate (0.8 mmol), PhIO (6–9 equiv), TREAT·HF (0.4 mmol), AgF (2.4 mmol), CH_3CN (0.5 mL), 50°C, 6–9 h. [b] Yields of isolated products are indicated below each product, unless otherwise noted. [c] Yields for volatile compounds were determined by ^{19}F NMR spectroscopy.

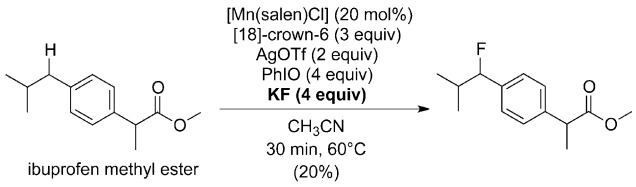
compounds. Several biologically active molecules were subjected to this Mn(salen) fluorination procedure. In all cases, highly selective benzylic fluorinations were observed (Scheme 3). As examples, a nonsteroidal anti-inflammatory drug (ibuprofen methyl ester), a vitamin E analogue (δ-tocopherol acetate), a commercial perfume component (celestolide) and a non-natural amino acid derivative (homophenylalanine), were each selectively fluorinated at a single position with good efficiency. The fluorinated ibuprofen derivative has also been prepared previously by a two-step enzymatic hydroxylation–chemical fluorination protocol.[17]

For potential application of this C–H fluorination to ^{18}F PET imaging it would be desirable to replace TREAT·HF or



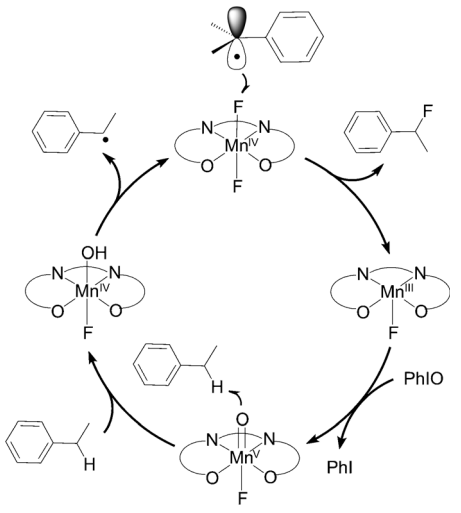
Scheme 3. Results of benzylic fluorinations of bioactive molecules.

AgF with potassium fluoride.[2d,10f,18] Furthermore, short reaction times are required because of the short half-life of ^{18}F (110 min). We have found conditions that meet these two important criteria. Treating ibuprofen methyl ester with **2** (20 mol%) as the catalyst, potassium fluoride as the sole fluorine source, [18]-crown-6 as the phase transfer catalyst, as well as silver triflate, afforded the corresponding benzylic fluoride analogue in 20% yield within 30 min (Scheme 4). Further development along these lines and the application of flow techniques[19] are under way.



Scheme 4. Fluorination of ibuprofen methyl ester using KF.

A likely mechanism for this benzylic fluorination (Scheme 5) is analogous to the Mn–porphyrin case we recently described.[12] The starting $[Mn^{III}(salen)F]$ or $[Mn^{III}(salen)F_2]^-$ catalyst, formed in situ, is oxidized to $[Mn^{V}(O)(salen)F]$, which then abstracts a hydrogen atom from the substrate, forming the benzyl radical and a manganese(IV) species. In the fluorine transfer step, the radical reacts with the $[Mn^{IV}(salen)F_2]$ complex, thereby affording the fluorinated products. This step also regenerates the resting Mn^{III} catalyst. While further work is required to elucidate the mechanistic aspects of this reaction more fully, several preliminary observations warrant comment. The ESI mass spectrum of the starting catalyst/fluoride mixture showed a large peak at *m/z* 637.5 (Figure S1 in the Supporting Information), which is the mass of the $[Mn^{III}(salen)F_2]^-$ catalyst. A significant kinetic isotope effect (5.6 ± 0.6) was observed for a 1:1 mixture of ethylbenzene and $[D_{10}]$ethylbenzene as the substrate. A similar KIE value (4.6 ± 1.0) was observed by Katsuki and co-workers for a Mn(salen)-catalyzed C–H hydroxylation reaction,[20] thus suggesting a common $\{Mn^{V}(O)(salen)\}$ intermediate and a similar transition state for the C–H bond cleavage. Analysis of compounds **8** and **18** by HPLC on a chiral stationary phase (Figures S2 and S3 in the Supporting Information) showed that readily detectable enantioselectivities were achieved (11% and 20% *ee*, respectively). Compound **18** could be obtained in 40% *ee* at −40 °C in approximately 5% yield. The relatively low enantioselectivities observed are probably due to a very early transition state for the fluorine transfer step and a linear Mn–F–C geometry (top-on approach) as indicated by DFT calculations on a related manganese porphyrin system.[12] C–H hydroxylations mediated by chiral Mn(salen) complexes also show modest *ee* values.[20] By contrast, the high enantioselectivities observed for olefin epoxidation by manganese salen catalysts have been attributed to a side-on approach of the substrate π bond to the manganyl group (Mn=O) of the catalyst, thus increasing the steric contacts during the oxygen atom transfer from Mn^{V}=O.[21] Despite the modest enantiomeric ratios for C–H fluorination, the observation that the asymmetric Mn catalyst can afford the observed degree of stereoinduction provides strong support for a manganese-bound fluorine source in the fluorine transfer step.



Scheme 5. Proposed catalytic cycle for benzylic C–H fluorination.

In conclusion, we have presented here a general Mn-catalyzed method for the formation of benzylic fluorides directly from C–H bonds. In contrast to previous efforts in this area, the reaction does not require a directing group and uses simple and easily handled nucleophilic fluoride reagents. The success of this direct C–H fluorination reaction suggests a general strategy for late-stage drug diversification and building block construction. Ongoing efforts in our laboratory seek to probe the mechanism of the current reaction and to evaluate the potential of this transformation for PET imaging applications.

Experimental Section

Representative procedure for the synthesis of fluorinated products: An oven-dried, 5 mL Schlenk flask equipped with a stir bar was placed under an atmosphere of N_2. Mn(salen)Cl (100 mg, 20 mol%), substrate (0.8 mmol), and TREAT·HF (0.2 mL, 1.2 mmol, 1.5 equiv) were then added, followed by degassed CH_3CN (0.5 mL). The reaction mixture was then heated to 50 °C. Iodosylbenzene was added slowly to the reaction mixture in solid form under a stream of N_2 over a period of 6–9 h. Significant decreases in yield were obtained if the iodosylbenzene was added rapidly. After the reaction was complete, the solution was allowed to cool to 25 °C and diluted with hexanes (2 mL). Products were separated from the reaction residue by column chromatography.

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