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Iron(II)-Catalyzed Benzylic Fluorination

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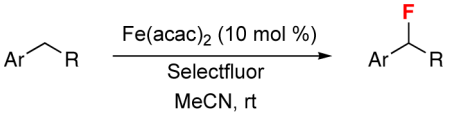
ABSTRACT



Direct C−F functionalization of benzylic sp^3 C−H bonds is a synthetic challenge that has yet to be propitiously overcome. A mild, one-pot synthesis of monofluorinated benzylic substrates is reported with commercially available iron(II) acetylacetonate and Selectfluor in good to excellent yields and selectivity. A convenient route to β-fluorinated products of 3-aryl ketones is also highlighted, providing a synthetic equivalent to the difficult to accomplish conjugate addition of fluoride to α,β-unsaturated ketones.

Practical, direct conversions of benzylic sp^3 C−H bonds into C−F bonds offer a potentially valuable addition to the category of C−H functionalization.[1] Despite developments in site-specific oxygenation,[2] amination,[3] and other halogenation methods,[4] innate benzylic fluorination remains an underdeveloped synthetic transformation,[5] one that relies heavily on the use of electrochemical methods[6] or harsh, unselective reagents.[7] Considering the growing importance of fluorinated compounds in drug discovery, a mild benzylic fluorination method may prove itself a useful instrument for the medicinal chemist (e.g., potentially by allowing inhibition of cytochrome P450 oxidation and increasing the lifetime of a drug in vivo, among other applications).[8] Thus, our laboratory has recently taken an interest in the development of a straightforward, metal-catalyzed benzylic fluorination method.

Both we (copper(I) bisimine, Selectfluor[9]) and the Groves group (manganese porphyrin, fluoride ion, iodosobenzene[10]) have reported unique catalytic systems for the selective fluorination of aliphatic C−H bonds. In our original copper system, we found that, although applicable to a select few benzylic substrates, fluorination proved somewhat difficult, notwithstanding the enhanced reactivity of benzylic C−H bonds. Inspired by the oxidation capabilities of certain biological catalysts, cost-effectiveness, commercial availability, and/or ease of preparation, we turned our attention to prospective iron

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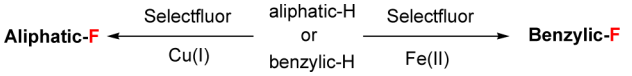
catalysts (Scheme 1). Herein, we report our studies on a catalyzed fluorination of benzylic substrates using an inexpensive iron(II) salt, iron(II) acetylacetonate ($Fe(acac)_2$), and commercially available Selectfluor, under mild conditions.

Scheme 1. Effect of Catalyst on Substrate Scope

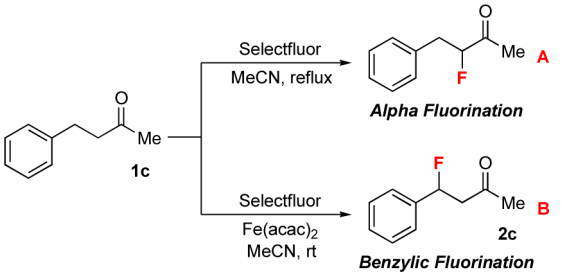


This unique system produces an array of benzylic fluorinated products in good to excellent yields and selectivity. Moreover, we demonstrate the possibility for a strategically placed carbonyl group to result in site-specific fluorination in the β-position, a potentially desirable synthetic transformation. Further study of this and similar systems may also provide a more clear understanding of halogenase enzymes[11] and potential use of ketones as directing groups in C−H bond activation.[12]

Noting previous success in the literature in C−H functionalization by nonheme iron catalysts,[13] we reasoned that iron(II) salts could be effective for this transformation. We began our initial survey of iron salts as potential catalysts with 3-phenylpropyl acetate **1a** as a model substrate. Among the iron salts screened, only $Fe(acac)_2$ yielded the desired 3-fluoro-3-phenylpropyl acetate **2a**. The use of other iron salts, e.g., halides, sulfates, and nitrates, failed to yield any fluorinated products under our specified conditions. Perhaps this can be explained by the fact that hard, polydentate O-donor ligands, such as anionic acetylacetonate, allow easy access to higher oxidation states, facilitating oxidative functionalization. Accordingly, several late-transition-metal complexes containing one or more acetylacetonate (acac) ligands have appeared in recent years capable of C−H bond activation.[14]

Subsequently, we evaluated the scope of our system by screening a series of benzylic substrates. To our satisfaction, several substrates underwent sufficient benzylic fluorination in good yields and in excellent selectivity (Table 1). Some general observations were as follows: (1) Electron-poor or more neutral alkyl benzenes proved most promising, whereas electron-rich aromatic systems lead to varying quantities of polyfluorinated products, often ring fluorination adducts.[15] (2) A particularly interesting case, cymene, **1b**, afforded fluorinated **2b** *exclusively*, in direct contrast to our previously reported copper system in which fluorination of the tertiary carbon is preferred. The formation of **2b** may be suggestive of a change in mechanism whereby steric constraints influence selectivity more so than trends in radical stability. (3) Carbonyl-containing compounds demonstrated a notable shift in selectivity to benzylic fluorination over an expected background reaction (Scheme 2).

Scheme 2. Iron(II)-Promoted Reversal in Selectivity



Traditionally, Selectfluor is known to react with carbonyl-containing compounds to yield α-fluorinated products.[16] For example, benzylacetone **1c** reacts readily with Selectfluor at elevated temperatures in acetonitrile to yield α-fluorinated ketone (Scheme 2, path A). Interestingly enough, under our catalytic conditions, benzylacetone reacts at room temperature to give solely benzylic fluorinated compound **2c** (Scheme 2, path B). What is more, **2c** would be the retrosynthetic product of a 1,4-conjugate addition of a fluoride anion to the analogous α,β-unsaturated ketone (Figure 1), an attractive transformation in modern synthetic chemistry. In a similar instance, ibuprofen methyl ester **1d** affords predominantly benzylic fluorinated **2d** under our conditions, potentially a pharmaceutically

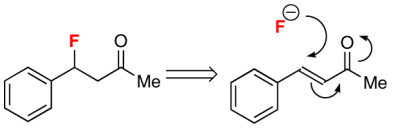


Figure 1. Retrosynthetic 1,4-conjugate addition of fluoride.

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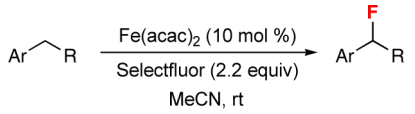
Table 1. Survey of Benzylic Substrates



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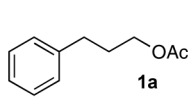
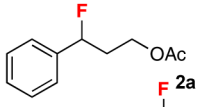
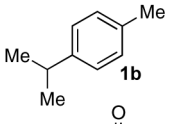
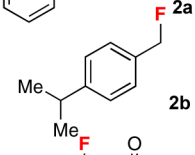
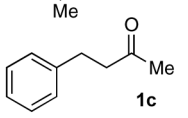
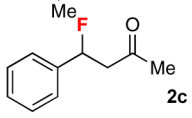
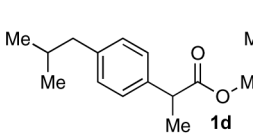
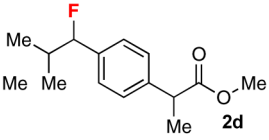
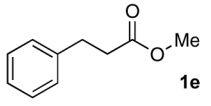
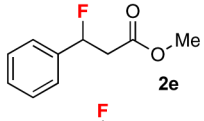
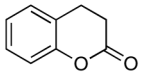
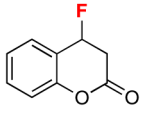
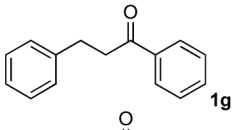
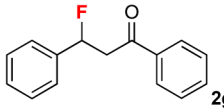
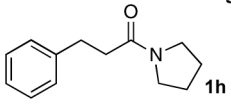
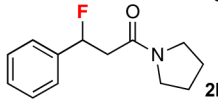
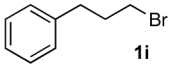
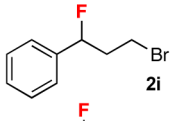
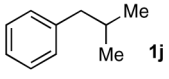
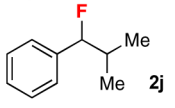
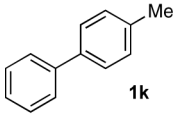
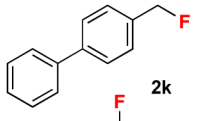
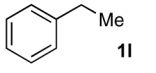
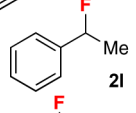
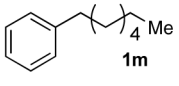
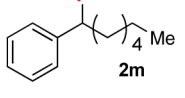
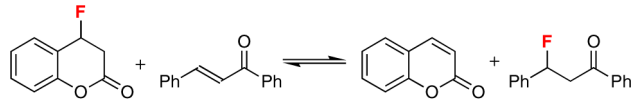
1	 1a	 2a	71
2	 1b	 2b	66
3	 1c	 2c	76
4	 1d	 2d	64[b]
5	 1e	 2e	52
6	 1f	 2f	35[a]
7	 1g	 2g	61
8	 1h	 2h	41[b]
9	 1i	 2i	58[a]
10	 1j	 2j	57[a]
11	 1k	 2k	59
12	 1l	 2l	65[a]
13	 1m	 2m	68[a]

[a] Yields determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard. [b] Isolated as the major benzylic product with minor fluorinated isomers. All reactions were performed at room temperature over 24 h unless otherwise stated.

Scheme 3. Isodesmic Reaction for Dehydrofluorination to Coumarin at B3LYP/6-311++G**



ΔE = -5.3 kcal/mol

interesting transformation, rather than the α-fluorinated ketone.

Clearly, iron is crucial in reaction selectivity favoring the benzylic position over chemistry at the more acidic α-carbon. Moreso, the system is highly tolerable as aryl ketones, esters, aliphatic ketones, amides, and other halogenated substrates fluorinate with near equal propensity. It is important to note that the majority of our substrates do not undergo dehydrohalogenation upon workup, a common problem in benzylic halogenation. Surprisingly, *β*-fluoro ketones proved particularly stable, contrary to our previous finding that 2-fluorodihydrocoumarin **2f** readily dehydrofluorinates.

In this instance, analysis of an isodesmic reaction between a compound which readily dehydrofluorinates, fluorodihydrocoumarin **2f**, and one which does not, fluorodihydrochalcone **2g**, offers some insight (Scheme 3). At the B3LYP/6-311++G** level of theory, ΔE of the isodesmic reaction is −5.3 kcal/mol,[17] suggesting a more exothermic process, whereby fluorine is lost in favor of desaturation and resultant gain in the aromatic character of coumarin.

Nitrogen-containing compounds (such as amines) were likewise problematic. In most cases, *N*-fluorination of the starting compound inhibits desired functionalization,[18] instead leading to *N*-oxidized products through a putative iminium intermediate.[19] We gathered that a compound in which the presence of a carbonyl in concert with lowered basicity of the nitrogen (e.g., through amide resonance) would be primed for fluorination, such as **1h**. Indeed, **1h** proved most amenable providing fluorinated **2h** in 41%.

Future studies will seek to elucidate the mechanism of this reaction through kinetic, isotopic, and spectroscopic analysis. Additionally, efforts will be made in the way of rendering the reaction enantioselective, an important goal in direct fluorination methods, and determining the role of carbonyls as potential directing groups for fluorination.

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Supporting Information Available. Synthetic procedures and the characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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