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Iron-Catalyzed, Fluoroamide-Directed C–H Fluorination

Brian J. Groendyke, Deyaa I. AbuSalim, and Silas P. Cook*

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405-7102, United States

Supporting Information

ABSTRACT: This communication describes a mild, amide-directed fluorination of benzylic, allylic, and unactivated C–H bonds mediated by iron. Upon exposure to a catalytic amount of iron(II) triflate ($Fe(OTf)_2$), *N*-fluoro-2-methylbenzamides undergo chemoselective fluorine transfer to provide the corresponding fluorides in high yield. The reaction demonstrates broad substrate scope and functional group tolerance without the use of any noble metal additives. Mechanistic and computational experiments suggest that the reaction proceeds through short-lived radical intermediates with F-transfer mediated directly by iron.

Due to its unique properties, fluorine offers unparalleled opportunities in drug discovery,[1] crop sciences,[2] and materials[3] research. However, fluorine incorporation remains challenging; the most common strategy employs fluorinated building blocks in the established synthesis of a given target. This approach is limited by the availability of fluorinated building blocks and the complexity of the synthesis. In this context, late-stage fluorination provides a powerful strategy to access fluorinated analogs of lead compounds.[4] While standard fluorination chemistry uses a preactivated position in the form of an alcohol[5] or tin derivative,[6] the directed fluorination of resident C–H bonds promises a particularly attractive approach to late-stage fluorination.

The current Csp^3–H fluorination methodology can be divided into directed and undirected categories (Figure 1a–b). The reported undirected fluorination reactions generally proceed through carbon-based radical intermediates and have been demonstrated with iron,[7] copper,[8] manganese,[9] uranium,[10] tungsten,[11] silver,[12] or organocatalysts[13] (Figure 1a). A current limitation of the existing radical C–H fluorination technology is the inherent preference for the weakest C–H bond,[14] which may not provide the desired product. Directed fluorination can overcome this shortcoming, yet current reports remain limited in scope and still use palladium.[15]

While directed C–H functionalization has developed quickly over the past 15 years,[16] strict steric and electronic requirements imposed by the transition-metal mediated C–H-activation step has limited extension of this strategy to Csp^3–H bonds. Here, we propose a *directed*, radical C–H fluorination reaction that can overcome such limitations and enable a late-stage fluorination.

The Hofmann–Löffler–Freytag (HLF) reaction is the earliest example of a selective C–H functionalization.[17] We hypothesized that, by harnessing the facile 1,5-H atom abstraction observed in the HLF reaction, we could provide a general solution to the functionalization of primary, secondary, and

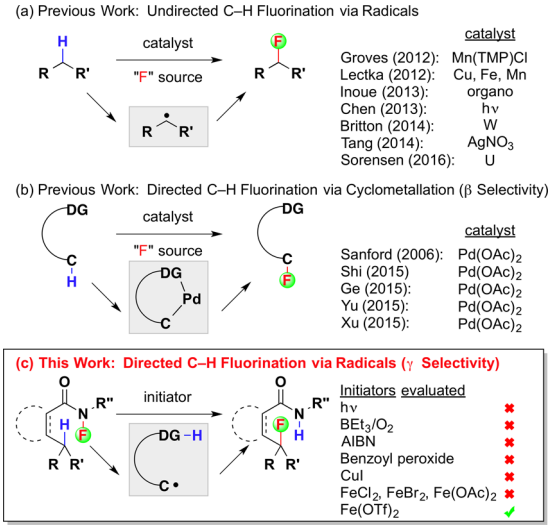

Figure 1. Directed radical chemistry as a route to Csp^3–H fluorination.

tertiary C–H bonds (Figure 1c). Controlling the fate of radicals is a well-documented phenomenon[18] that is underutilized in modern C–H functionalization approaches. To implement this strategy, we envisioned creating a high-energy, heteroatom-based radical that could abstract a hydrogen atom. The newly formed carbon-based radical could then be fluorinated under suitable conditions.

To test the hypothesis, fluoroamide **1a** was prepared from the treatment of the parent amide with *n*-butyllithium and NFSI.[19] Currently, our protocol for N-fluorination is limited to *N-tert*-butyl amides since less-hindered amides undergo N-sulfonation when treated with NFSI.[20] While *N*-fluoroamides have been studied extensively as a source of F^+,[21] their stability in the context of other synthetic manipulations is poorly understood. In general, compounds **1** are clear oils that are thermally stable to at least 80 °C, as well as air- and silica-stable. They can be stored at room temperature for several months and are stable to a variety of reaction conditions (see Supporting Information, SI, for full details). Exposure of compound **1a** to a variety of initiators revealed the surprising stability of the fluoroamide moiety, with most reactions returning unadulterated starting material (Figure 1c and SI). Interestingly, $Fe(OTf)_2$ in acetonitrile at 80 °C converted compound **1a** to desired product **2a** in 17% yield (entry 1, Table 1). Among all iron(II) and (III) salts tested, $Fe(OTf)_2$ was uniquely effective in promoting the fluorine transfer (see SI for detailed optimization). Changing the solvent

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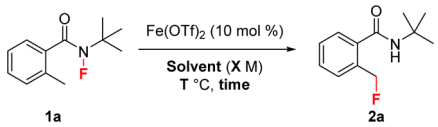
Table 1. Optimization of Pertinent Reaction Parameters



entry	solvent	temp (°C)	concn (M)	time (h)	yield[a] (conv)
1[b]	MeCN	80	0.1	16	17% (73%)
2[b]	DME	80	0.1	16	32% (71%)
3	DME	rt	0.5	1	69% (78%)
4	**DME**	**40**	**0.5**	**1**	**92% (96%)**

[a]Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [b]Run with 20 mol % Fe.

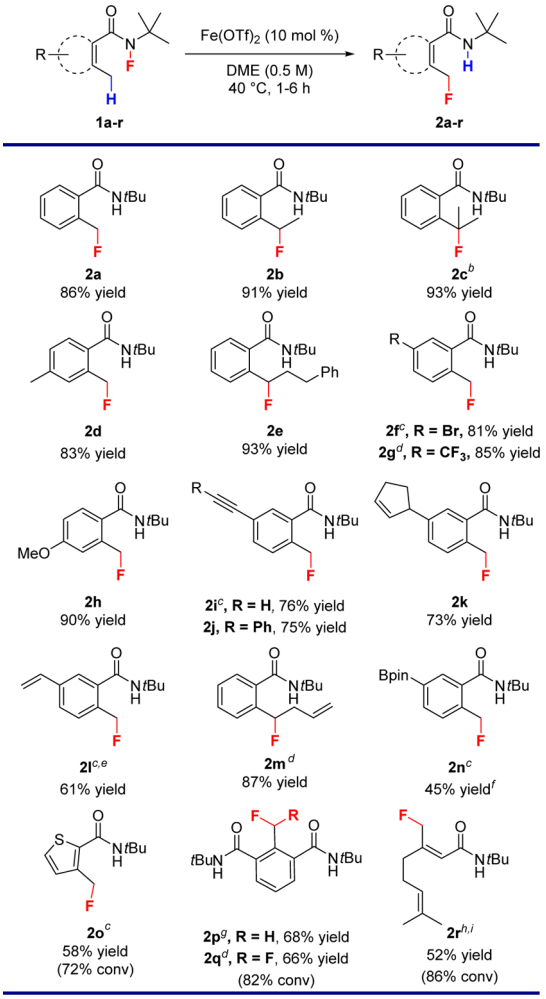
to 1,2-dimethoxyethane (DME) nearly doubled the reaction yield (entry 2, Table 1). By reducing the catalyst loading to 10 mol % and shortening the reaction to 1 h, we increased the reaction yield and achieved much cleaner conversion to product (entry 3, Table 1). Finally, by running the reaction at 40 °C, the desired product could be obtained in 92% NMR yield and 86% isolated yield (entry 4, Table 1). The reaction is iron mediated and not promoted by visible light. $Fe(OTf)_2$ or $Fe(acac)_2$ does not catalyze benzylic fluorination of the free *tert*-butyl amide with NFSI or Selectfluor (see SI).

With this unique directed Csp^3–H fluorination, we next evaluated the performance of the reaction across a number of substrates. The reaction is seemingly unaffected by the steric environment at the benzylic carbon; primary, secondary, and tertiary substrates perform well (**2a–c**, Table 2). Tertiary fluoride **2c** is prone to a small amount of HF elimination (5–10%) under the reaction conditions, and the product was purified on neutralized silica to minimize further elimination. Fluorine transfers with complete chemoselectivity when multiple benzylic C–H bonds are present, as demonstrated by **2d** and **2e**. The electronic properties of the aromatic ring had a small but noticeable effect on the reaction.

For example, while both electron-deficient and electron-rich aryl rings provided products in good yield (**2f–h**, Table 2), electron-deficient substrates react slower and require a longer reaction time for full conversion. The reaction proceeds well in the presence of internal and terminal alkynes and alkenes (**2i–m**), which often can be problematic functional groups in fluorination chemistry. In the case of styrenyl substrate **1l**, significant polymerization unrelated to the F transfer is observed but can be mitigated by the addition of 0.5 mol % 3,5-di-*tert*-butylcatechol. Arylboronic ester **1n** provides the benzyl-fluoride product **2n** in near-quantitative yield before chromatography. Notably, the reaction proceeds well even when the C–H bond is distanced from the fluoroamide functionality and in the presence of a Lewis basic sulfur as evidenced by thiophene product **2o**.

Since difluoromethyl moieties often display enhanced physiological properties relative to their fluoromethyl counterpart,[1b,22] exploring whether a fluoromethyl can undergo a second fluorination warrants investigation. To that end, both mono- (**1p**) and difluoro-2-methylisophthalamide were prepared and subjected to the reaction conditions.[23] Satisfyingly, **1q** undergoes difluorination to provide **2q** as the major product (5:1 **2q**:**2p**). Additionally, the reaction conditions allow directed allylic fluorination as demonstrated by the selective allylic fluorination of **1r** with four competing allylic sites. Interestingly, a small amount of α-fluorination is observed, likely due to isomerization of the presumed intermediate allylic radical.

Table 2. Substrate Scope for Fluorine Transfer[a]

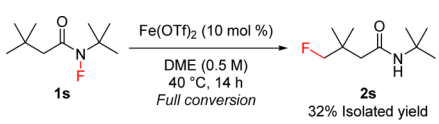


[a]All reactions were run on 0.5 mmol scale unless otherwise noted. Isolated yield. [b]Isolated an 8:1 mixture of 3° fluoride/styrene. [c]3 h reaction time. [d]6 h reaction time. [e]With 0.5 mol % 3,5-di-*tert*-butylcatechol to minimize polymerization. [f]Product unstable to silica, NMR yield > 95%. [g]2 h reaction time. [h]0.37 mmol scale. [i]Isolated a 5:1 mixture of **2r**: α-fluorination; observe 18% of other fluorinated products.

Unfortunately, 2,6-disubstituted substrates provide only trace product and extensive decomposition of the N–F bond (see SI). While not obvious from conformational analysis, the presence of a resident ortho substituent apparently prevents or slows H atom abstraction, thereby allowing off-cycle pathways. Counterintuitively, known intermolecular C–H fluorination methods provide lower yields for benzylic substrates relative to unactivated C–H bonds.[7–10] The work here is notable for faster reaction times, efficacy with electron-rich arenes, and its selective fluorination in the presence of competing activated sites.

Next, we attempted to extend the reaction to unactivated C–H bonds. Delightfully, aliphatic **1s** transfers fluorine selectively to

Scheme 1. Fluorination of an Unactivated C–H Bond



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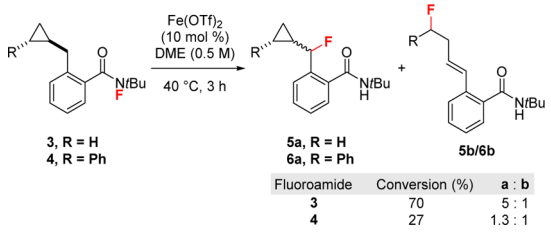
form primary fluoride **2s** albeit in 32% isolated yield, with 7% of the unfluorinated secondary amide as a side product (Scheme 1).

The presumption of a radical-transfer mechanism guided the conceptual development of this fluorination reaction. To test this mechanistic hypothesis, experiments were conducted to uncover evidence for the presence of radical intermediates. Interestingly, *the reaction proceeds well in the presence of 1 equiv of BHT with only slightly lower conversion and yield.* The reaction does not proceed with 0.5 equiv of TEMPO, and the addition of TEMPO to the reaction in progress immediately stops any further conversion. When TEMPO is used to quench a reaction, approximately 3% of the benzylic TEMPO-substituted product can be detected by ^{1}H NMR. Although the TEMPO results ostensibly suggest a radical pathway, they cannot offer conclusive evidence since the *N*-oxyl radical can be reduced by iron(II) to generate a nitroxide anion.[24]

Next, *ortho*-cyclopropylmethyl substrate **3** was synthesized and subjected to the reaction conditions. Surprisingly, we observed secondary fluoride **5a** as the major product, instead of the expected ring-opened product **5b** (Scheme 2), suggesting a

Scheme 2. Radical-Clock Experiments

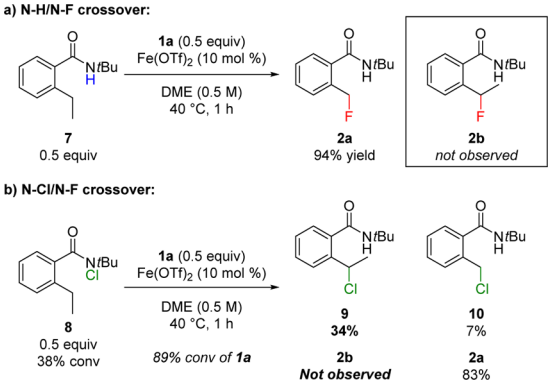


Fluoroamide	Conversion (%)	a : b
3	70	5 : 1
4	27	1.3 : 1

relatively short-lived radical intermediate. Although the primary cyclopropylmethyl radical rearrangement is exceptionally fast (1.3×10^8/s),[25] benzylic stabilization likely increases the lifetime of this radical. To mitigate the benzylic rate attenuation, we employed *trans*-phenyl-substituted **4**, which provided a 1.3:1 mixture of unopened and opened fluorides. With benzylic stabilization at both sides of the cyclopropyl, these experiments provide strong evidence for an intermediate carbon-based radical with a lifetime close to 1×10^8/s.

To gain additional support for an intramolecular, directed mechanism, several crossover experiments were conducted (Scheme 3). As expected, no crossover was observed when fluoroamide **1a** reacted in the presence of 0.5 equiv of a free amide **7** (Scheme 3a). When a 1:1 mixture of fluoroamide **1a** and chloroamide **8** was subjected to the reaction, a small amount of crossover product **10** was detected (7%), but secondary fluoride

Scheme 3. Crossover Experiments



2b, the other possible crossover product, was not detected by ^{1}H or ^{19}F NMR (Scheme 3b). *This surprising result is inconsistent with a free-radical, atom-transfer mechanism initiated by iron.*

Counterintuitively, the weaker N–Cl bond reacts more slowly than the N–F bond (38% vs 89% conversion at 1 h). The high fidelity of the atom transfer is consistent with a mechanism wherein the iron is involved in C–X bond formation. The discrete Fe–X intermediate formed after halogen abstraction may react directly with the newly formed benzylic radical or be responsible for C–H bond cleavage. The small amount of chloride crossover may be the result of Fe–F/Fe–Cl mixing in an off-cycle dimeric species, or from the interception of an $Fe(OTf)_2Cl$ intermediate.

To compare the energetics of a free-radical mechanism to an organometallic pathway, we computed the reaction profile using DFT (Figure 2; see SI for computational details). Upon cleavage

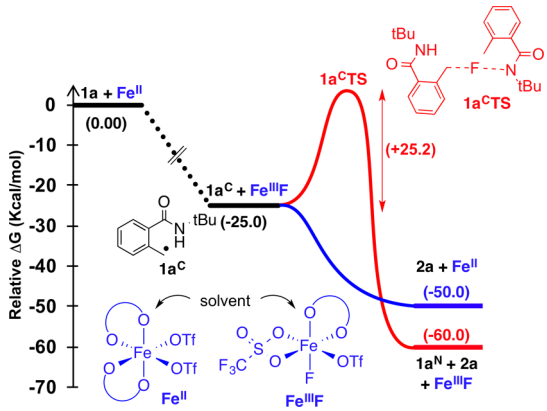


Figure 2. Computed (with uM06/cc-pVTZ(-f)–LACV3P**//uM06/LACVP** level of theory) relative Gibb's free energies for key intermediates along the reaction pathway (for complete reaction coordinate, see SI).

of the N–F bond by iron, the resulting N-based radical (not shown) undergoes 1,5-hydrogen atom abstraction to form $\mathbf{1a}^{C}$. From benzylic radical $\mathbf{1a}^{C}$, F-atom abstraction could occur from either starting fluoroamide **1a** or $\mathbf{Fe}^{III}\mathbf{F}$. The free-radical atom transfer pathway provides transition state $\mathbf{1a}^{C}\mathbf{TS}$ with a 25.2 kcal/mol barrier. Interestingly, removing the F atom directly from $\mathbf{Fe}^{III}\mathbf{F}$ converges to product **2a** without an energetic barrier. This result is consistent with the crossover experiments in Scheme 2 and suggests an organometallic pathway, and not a free-radical atom transfer, is operative for this reaction. Such a mechanism would also explain the lack of reactivity with light or other radical initiators (Figure 1). An alternative mechanism, involving oxidation to the benzylic cation, was ruled out due to lack of lactam formation and high energies observed computationally.

To probe the C–H cleavage step, monodeuteromethyl fluoroamide **d-1a** and trideuteromethyl fluoroamide $\mathbf{d_3}$**-1a** were prepared for kinetic-isotope-effect (KIE) analysis (Scheme 4). With **d-1a**, a striking intramolecular KIE of 3.3 indicates that C–H cleavage is very nearly complete in the transition state.[26] The intermolecular reaction with **1a** and $\mathbf{d_3}$**-1a** was run to 3% conversion. In this case, a primary KIE of 1.6 again is consistent with C–H cleavage, or some prior event, as the turnover-limiting step.[27]

While benzylic fluorides are attractive for a number of applications, conversion of the *tert*-butyl amide directing group would offer greater versatility of the products. Gratifyingly, the

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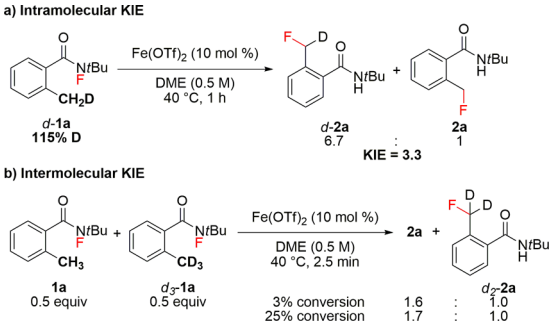
Scheme 4. Kinetic Isotope Effect



benzyl fluoride products can be reduced to the 2-(fluoromethyl)-benzyl alcohol or benzaldehyde selectively upon treatment with Schwartz's reagent (see SI).[28] To date, very few compounds of this type exist in the literature.[29]

In conclusion, we developed a mild, directed C−H fluorination reaction catalyzed by low-cost Fe(II) triflate. The reaction proceeds in high yield, with broad functional-group tolerance, under simple reaction conditions. Notably, the methodology enables the direct fluorination of a cyclopropylmethyl group and provides access to 2-fluoromethylbenzyl alcohols. Additionally, we have shown that the *N*-fluoroamide is a robust, kinetically stable oxidant/functional group, despite its high potential energy. Although the exact mechanism is currently uncertain, the reaction most likely proceeds through short-lived radical intermediates. Control and crossover reactions suggest that the reaction is directed by the amide group and proceeds via an intermediate Fe−F complex. Crossover and DFT experiments suggest that an organometallic pathway is more likely than a free-radical mechanism. Efforts to extend this methodology to the fluorination of other substrate scaffolds are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08171.

Experimental details and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*sicook@indiana.edu

Notes

The authors declare no competing financial interest.

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