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Benzylic Fluorination of Azaheterocycles Induced by Single Electron Transfer to Selectfluor®

*Kelley E. Danahy, Julian C. Cooper, and Jeffrey F. Van Humbeck**

Abstract: *We have investigated a selective and mild method for the benzylic fluorination of aromatic azaheterocycles with Selectfluor®. These reactions take place via a previously unreported mechanism, in which electron transfer from the heterocyclic substrate to the electrophilic fluorinating agent Selectfluor® eventually yields a benzylic radical, leading to the desired C–F bond formation. This mechanism enables high intra and intermolecular selectivity for azaheterocycles over other benzylic components with similar C–H bond-dissociation energies.*

Aromatic azaheterocycles and carbon-fluorine bonds are key building blocks in small molecules designed for medicinal chemistry. As of 2014, over 250 FDA approved medicines contained aromatic azaheterocycles (Figure 1),[1,2] demonstrating why methods to selectively modify these substructures remain in demand. Likewise, the unique properties and increasing prevalence of fluorine in pharmaceuticals and radiotracers have led to its inclusion in 20% of pharmaceutical small molecules and 30–40% of agrochemicals, [3,4] and consequently, the development of new fluorination methods is an active area of research.

While several notable methods to add difluoroalkyl[4] and trifluoromethyl[5] groups to heterocycles are known, direct addition of monofluoroalkyl groups has so far remained limited to α-fluorocarbonyl fragments.[6] Heterobenzylic monofluorination of an unactivated alkyl group has been rarely reported, most notably in Sanford's palladium-catalyzed fluorination of 8-methylquinoline, Groves' ^{18}F manganese-salen catalyzed fluorination of papaverine, and recently Britton's *N*-fluorobenzenesulfonamide (NFSI) promoted fluorinations of pyridines and pyrimidines.[7] Britton's work, the most comprehensive to date, used NFSI to activate heterocycles by *N*-sulfonylation. C–F bond formation then follows an ionic mechanism, in which the increased acidity at the heterobenzylic position allows deprotonation by mild bases. Pyridine substrates were efficiently monofluorinated under mild conditions (60 ºC, MeCN). The requirement for *N*-sulfonylation makes other substrates challenging, however: pyrimidine substrates required 120-150 ºC to provide significant conversion.

We questioned whether radical mechanisms could expand the scope of azaheterocycle fluorination. C–F bond forming methods

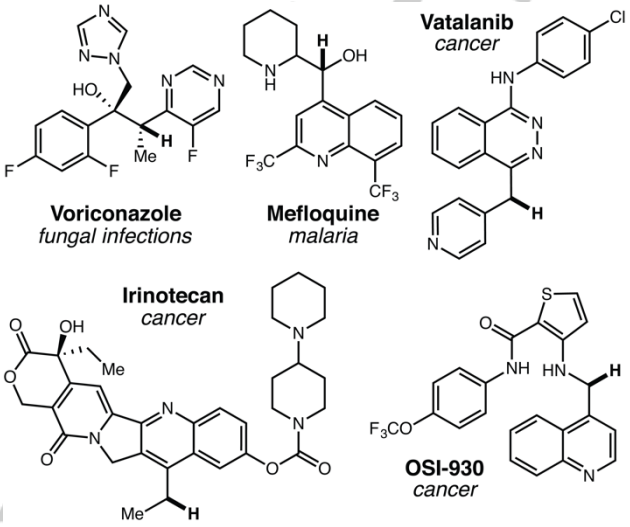

Figure 1. Examples of medically relevant 4-alkyl-*N*-heterocycles.

are typically divided into three categories: electrophilic,[8] nucleophilic,[9] and radical.[10] The latter emerged recently with Sammis' demonstration that 'electrophilic' fluorine sources, such as NFSI and Selectfluor®, can function as radical fluorine sources.[10a] Since their seminal work, numerous examples of radical fluorination have been reported.[10] However, attempts to use radical mechanisms for C-H fluorination adjacent to azaheterocycles face a significant challenge: even modestly complex molecules may feature multiple reactive C–H bonds (*e.g.* benzylic). Thus, reactions selective for heterobenzylic C–H bonds over other weak bonds are needed to allow for predictable fluorination in advanced intermediates.

Based on our recent studies on site selective methylene oxidation,[11] we speculated that abundant Lewis acids such as copper and iron might alter the radical reactivity of coordinated heterocycles. Our initial investigations pitted 4-ethylpyridine (**1**) against ethylbenzene (**2**), and used known radical initiators (*e.g.* VAZO™ 88, NHPI) (Table 1). We were excited to see selective fluorination with both metals, albeit in low yield (entries 1 and 2). However, our control experiments revealed that the selective fluorination of pyridine was optimal with merely a slight excess of Selectfluor® (**5**) and no other additives, resulting in ≤10% overreaction to difluorinated products. Addition of base, or modification of our fluorine source, proved detrimental to the yield (entries 4–8). We were pleased to find that these conditions delivered complimentary results to those reported using NFSI (Figure 2). Alkylpyridines are reactive towards Selectfluor® at room temperature, though they generally deliver slightly lower yields than those reported by Britton.[7c] Importantly, we observe different behavior in the case of electron-poor heterocycles. Pyrimidines, quinazolines, and purines, including an electron-poor pyrimidine

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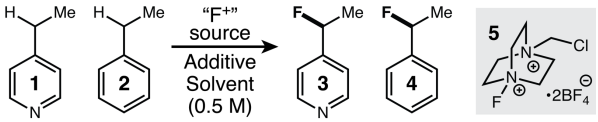
Table 1. Conditions screened for radical fluorination on *N*-heterocycles.



Entry	Additive	Solvent	"F+" source	Yield (%)	3:4 Ratio
1	$Cu(OTf)_2$[a]	MeCN-d_3	Selectfluor®	28	>99:1
2	$FeCl_3$[b]	MeCN-d_3	Selectfluor®	25	>99:1
3	None	DMF-d_7	Selectfluor®	20	>99:1
4	**None**	**MeCN-d_3**	**Selectfluor®**	**67**	**>99:1**
5	DABCO[c]	MeCN-d_3	Selectfluor®	50	>99:1
6	Li_2CO_3[c]	MeCN-d_3	Selectfluor®	50	>99:1
7	None	MeCN-d_3	Selectfluor®[d]	53	>99:1
8	None	MeCN-d_3	NFSI	44	>99:1

[a] 5 mol% copper and 5 mol% 1,1'-azobis(cyclohexanecarbonitrile) as a radical inititator; [b] 5 mol% iron and 5 mol% *N*-hydroxyphthalimide as a radical initiator; [c] 1 equiv. of base; [d] 2 equivalents Selectfluor®. All reactions were at 25 ºC.

(**15**), proved to be reactive at only 40 ºC. We found that the inclusion of catalytic amounts of the iron(III) complex $[FeCl_4][FeCl_2(dmf)_3]$ provided increased yields, through a currently unknown effect. In all cases where another benzylic position was present (**11**, **14**, **17**), selective fluorination adjacent to the azaheterocycle was observed.

We initially suspected an ionic mechanism given that transition metals and radical initiators were not needed to observe reactivity. An analogous mechanism to that proposed for NFSI[7c] is shown in Scheme 1. Acidification of the benzylic position due to pyridinium cation formation (**19**) would allow for deprotonation and dearomatization (**20**). Then, attack by the now–nucleophilic benzylic position onto another equivalent of electrophilic fluorine would yield our desired C–F bond (**21**). Pyridinium **21** could then transfer fluorine to another equivalent of substrate, delivering the observed product and regenerating the pyridinium intermediate **19**.

However, several observations called this mechanism into question. During our optimization studies, we had observed the complete failure of both *N*-fluorocollidinium (**22**) and *N*-fluoropyridinum (**23**) to promote the desired transformation. Given that an ionic mechanism using Selectfluor® demands fluorine transfer between *N*-fluoropyridiniums, the failure of these reagents strongly suggests that the presented ionic mechanism does not occur. Additionally, no pyridinium fluoride peaks (from **19** or **21**) were observed during NMR studies. Furthermore, the successful fluorination of 4-alkylpyrimidines under mild conditions would be unusual for an ionic mechanism, as the formation of pyrimidinium fluorides typically requires both harsh fluorinating reagents like hypofluorites, as well as oxidation to the pyrimidinone state.[12]

A mechanistic insight appeared during the fluorination of 4-benzylpyridine **24** (Scheme 2). Though the primary product was the expected monofluorinated structure (**9**), dimeric byproduct **25** was

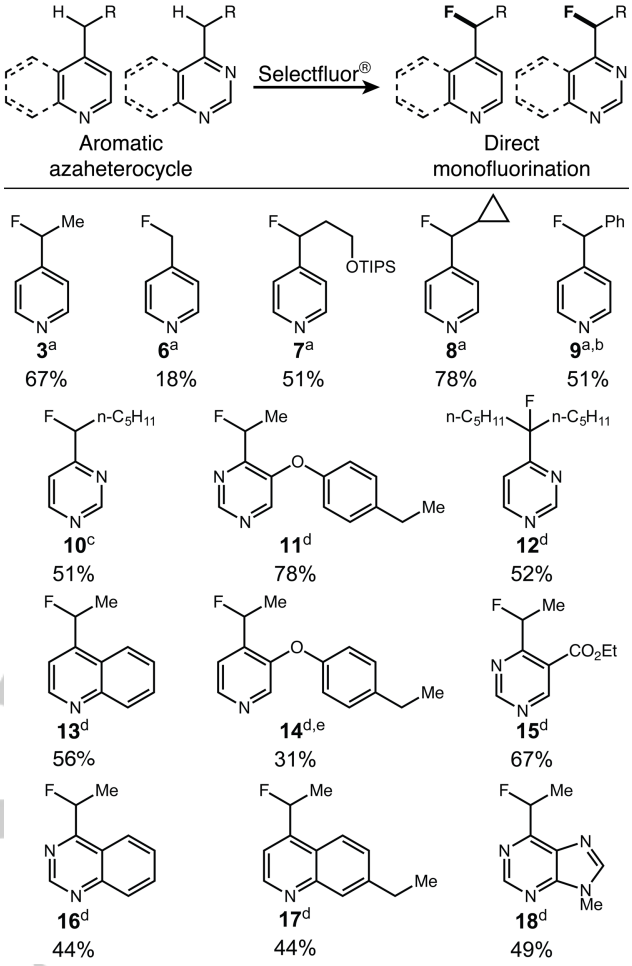


Figure 2. Substrate scope for benzylic fluorination. Conditions: a) acetonitrile, 1.2 equiv. Selectfluor®, 25ºC; b) 5% dimer observed – see Scheme 3; c) DMF, 2.5 mol% $[FeCl_4][FeCl_2(dmf)_3]$, 1.5 equiv. Selectfluor®, 40 ºC d) DMF, 2.5 mol% $[FeCl_4][FeCl_2(dmf)_3]$, 1.2 equiv. Selectfluor®, 40ºC. e) With 2% starting material.

observed via GC/MS, and confirmed by independent synthesis. The alkene stereochemistry was confirmed as *E* by hydrogenation to the known racemic dipyridyldiphenylethane **26**.[13] In our reaction, with only Selectfluor®, substrate, and acetonitrile present, it is difficult to explain the formation of this dimer without invoking radical **27**. As radical dimerization would lead to the saturated product **26**, we then confirmed that Selectfluor® is able to further oxidize the saturated intermediate to the observed product.

To reconsider a radical mechanism, we had to contend with the failure of substrate **8** (Figure 2) to rearrange as a radical clock. However, radical clocks have often failed to provide evidence for radical intermediates in transformations with Selectfluor®, yet ESI-MS has observed radical cation intermediates that implicate a radical mechanism despite a lack of rearranged products.[14,15] Thus, in regards to **8**, two possible explanations exist. First, radical fluorination may outcompete opening of the cyclopropane. Second, while cyclopropyl*methyl* radical clocks are known to yield rearranged products, the rate of ring *closure* for *aryl* cyclopropylmethyl radical clocks ($k = 5.4 \cdot 10^6\ s^{-1}$) is faster than the rate of opening ($k = 6.1 \cdot 10^4\ s^{-1}$).[16] This suggests an equilibrium favoring the closed form of the cyclopropane ring. As a result, the

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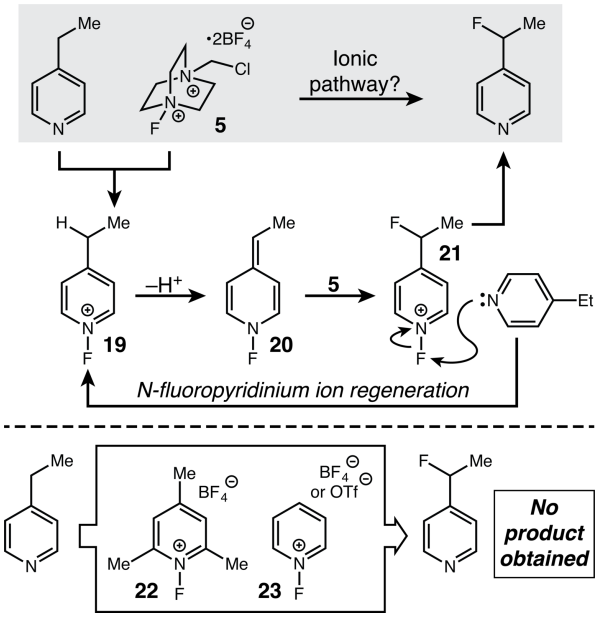
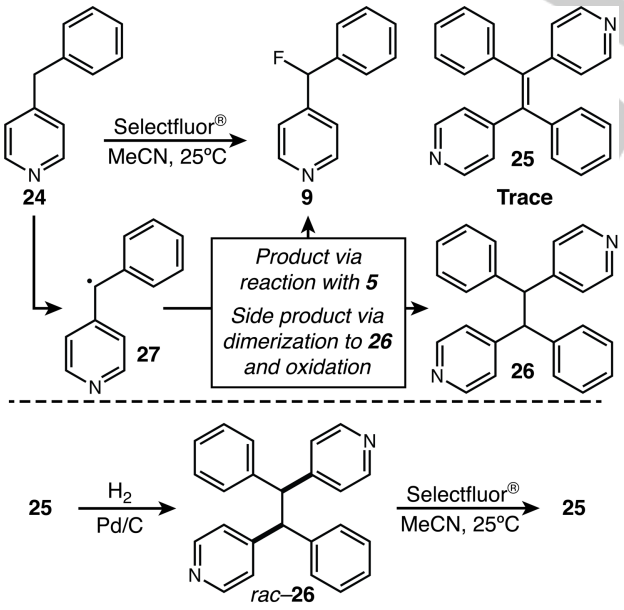


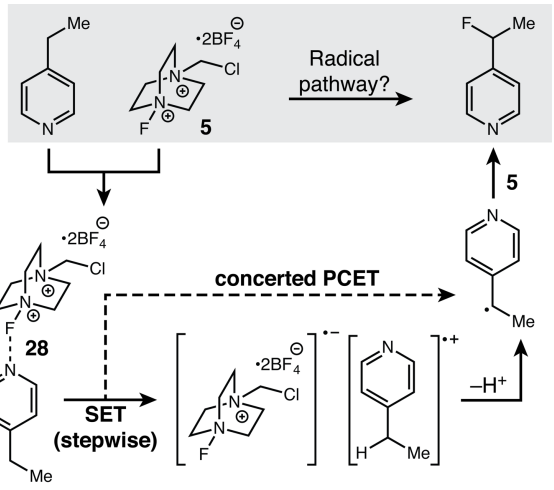
Scheme 1. Top: Proposed ionic mechanism for pyridylic fluorination with Selectfluor®. Bottom: Failure of *N*-fluoropyridinium reagents.

closed cyclopropane ring of **8** does not confirm or oppose either mechanistic pathway.

Previous studies have suggested that fluorination with Selectfluor® may proceed via single-electron transfer (SET) preceded by the formation of a charge-transfer complex. Calculations by Liu and coworkers predict that even simple electrophilic aromatic substitution with Selectfluor® should not follow the classic two-electron mechanism.[17] And, moving beyond theory, Ritter and coworkers recently found that charge-transfer



Scheme 2. Proposed radical mechanism for the formation of dimer **25**.



Scheme 3. Proposed radical mechanism for fluorination with Selectfluor®.

complexes between aromatic groups and Selectfluor® allowed for highly para-selective C-H functionalization via a radical pathway.[18]

We reconsidered a radical mechanism for this transformation (Scheme 3). First, we needed to address the high chemoselectivity in our system. Pyridine itself is more easily oxidized in acetonitrile than benzene ($E_{1/2}$ vs. $Ag/AgNO_3$: 1.82 V for pyridine, 2.04 V for benzene),[19] and so selective electron transfer may naturally follow. However, substrates such as **14** contain an anisole-type fragment, which should be much more easily oxidized in acetonitrile ($E_{1/2}$ vs. $Ag/AgNO_3$: 1.40 V for anisole,[19] 1.30 V for diphenyl ether[20]), and yet do not deliver C–F bond formation adjacent to the anisole-type ring. In these cases, we speculated that formation of a charge transfer complex (**28**) may lead to the observed selectivity—either through a stepwise electron transfer/deprotonation pathway or a concerted proton-coupled electron transfer (PCET) pathway.

We evaluated the formation of a pyridine-Selectfluor® charge transfer complex in solution using UV/Vis spectophotometry (Figure 3). At identical concentrations, a 4-ethylpyridine solution showed a maximum absorbance at 255 nm, but an identically concentrated reaction sample showed an absorbance nearly two-and-a-half times as intense, although its wavelength (252 nm) was nearly identical to the pyridine maximum. Further, a broad shoulder began around 270 nm and tailed to nearly 350 nm. These spectra contain all three characteristics (intensity, overlap of pyridyl charge-transfer absorbances with the uncomplexed pyridine absorbance, and tailing) also seen in the well-studied pyridine-I_2 and pyridine-Br_2 charge-transfer complexes.[21]

In an attempt to distinguish between PCET and a stepwise mechanism, we analyzed the kinetic isotope effect in an intermolecular competition between protonated and deuterated 4-ethylquinoline. ^{1}H NMR results indicated a primary k_H/k_D of 3.0, consistent with either concerted PCET or reversible SET, followed by irreversible deprotonation.[22] Detailed studies are required to differentiate between these two pathways.

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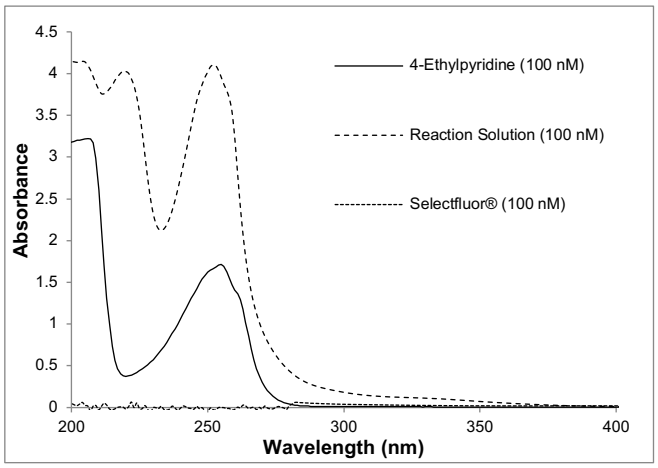

Figure 3. Qualitative UV/Vis spectra for pyridine, Selectfluor®, and a diluted aliquot of reaction solution.

In summary, we have observed the ability of Selectfluor® to directly fluorinate sp^3 C–H bonds adjacent to heterocycles. The formation of substrate dimers such as **25** suggest a radical mechanism, and the formation of charge transfer complexes may explain site-selectivity in cases where oxidation potentials do not predict the correct position of reaction. No additive is required for selectivity, though a catalytic amount of iron(III) may be added for optimum yield. This approach, which seems to be mechanistically distinct from NFSI-based reactions, provides a complementary substrate scope that includes heterocycles that are less likely to form *N*-sulfonylated intermediates, such as medically relevant pyrimidines and quinazolines.

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Keywords: fluorine • nitrogen heterocycles • charge transfer • C–H activation • regioselectivity

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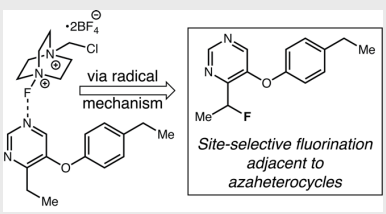
We have investigated a selective and mild method for the benzylic fluorination of aromatic azaheterocycles. These reactions take advantage of the oxidizing power of the electrophilic fluorinating agent Selectfluor®. Either proton-coupled electron-transfer or single-electron transfer—followed by deprotonation—yields a benzylic radical adjacent to the heterocycle, leading to selective C–F bond formation.



*Kelley E. Danahy, Julian C. Cooper, Prof. Dr. Jeffrey F. Van Humbeck**

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Benzylic Fluorination of Azaheterocycles Induced by Single Electron Transfer to Selectfluor®

Layout 2:

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