Fluorination

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A Convenient Late-Stage Fluorination of Pyridylic C–H Bonds with *N*-Fluorobenzenesulfonimide

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Abstract: *Pyridine features prominently in pharmaceuticals and drug leads, and methods to selectively manipulate pyridine basicity or metabolic stability are highly sought after. A robust, metal-free direct fluorination of unactivated pyridylic C–H bonds was developed. This convenient reaction shows high functional-group tolerance and offers complimentary selectivity to existing C–H fluorination strategies. Importantly, this late-stage pyridylic C–H fluorination provides opportunities to rationally modulate the basicity, lipophilicity, and metabolic stability of alkylpyridine drugs.*

Nitrogen-containing heterocycles are perhaps the most important scaffold components in agrochemicals and pharmaceuticals,[1] and they are found in roughly 60% of FDA-approved drugs. Among these heterocyclic drugs (e.g., **1**[2] and **2**;[3] Figure 1), the pyridine ring system features prominently[4] and is an essential fragment in medicinal chemistry and drug discovery efforts. Owing to its privileged status, methods for pyridine synthesis[5] or functionalization strategies[6] that enable rational manipulation of potency (e.g., in **4**[7] and **6**[8]), toxicity (e.g., CYP or hERG inhibition),[9] or other physiochemical properties (e.g., Log*P*, pK_a, lipophilicity)[3b,10] are of immense value. For example, attenuating the metabolism of relatively weak pyridylic C–H bonds (bond dissociation energy (BDE) ≈ 87 kcal mol^{-1})[11] through late-stage fluorination is particularly appealing. Unfortunately, the synthesis of pyridylic fluorides is challenging and relies largely on the introduction of a leaving group at the pyridylic position, followed by fluoride displacement.[7,8] Thus, despite recent advances in the fluorination of unactivated C(sp^3)–H bonds,[12] including benzylic C–H,[13] these strategies have not translated broadly to pyridylic fluorination[14] or indeed the fluorination of other heteroarylmethanes, thus limiting their impact in late-stage lead optimization. In an effort to expand the utility of our own photocatalytic C–H fluorination[15] to include heterocyclic molecules, we have identified a convenient and orthogonal process for pyridylic C–H fluorination. Notably, this predictable, regioselective, and transition-metal-free monofluorination reaction tolerates a wide range of functional groups and should be a useful tool for medicinal chemistry and potentially for [^{18}F]-radiotracer synthesis for PET imaging applications.

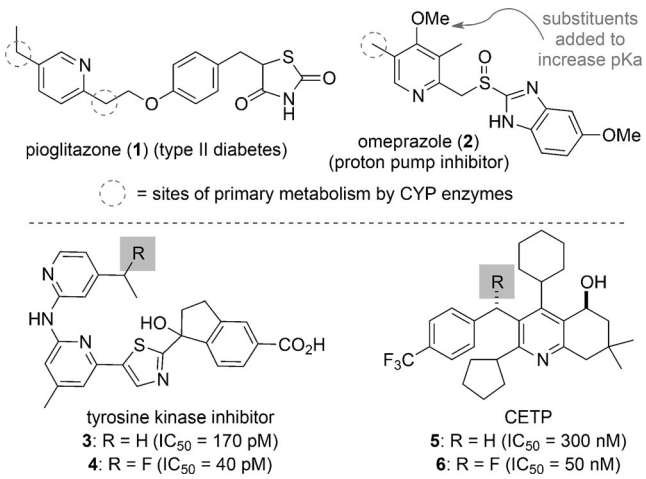

Figure 1. Metabolism of the alkylpyridine drugs pioglitazone (**1**) and omeprazole (**2**), and the effect of pyridylic fluorination on inhibitory activity in two series of drug leads.

We have recently reported the direct fluorination of unactivated C–H bonds using the unique combination of a decatungstate photocatalyst and *N*-fluorobenzenesulfonimide (NFSI).[15] Considering our prior success in the fluorination of aliphatic,[15a,c] acyl,[15a] and benzylic[15b] C–H bonds, we endeavoured to expand the reaction scope to include the fluorination of relatively weak pyridylic C–H bonds (4-picoline BDE (CH$_3$) ≈ 87 kcal mol^{-1} vs. toluene BDE (CH$_3$) ≈ 90 kcal mol^{-1}).[16] As a significant complicating factor, however, Crugeiras has reported[17] that several amine bases react with NFSI at the sulfonyl group (and not the electrophilic fluorine) and decompose this reagent. In an effort to prevent such undesired sulfonyl transfer reactions, we initiated our investigation by exploring the fluorination of N-oxides and various Brønsted acid salts of 4-ethylpyridine (**7**) and 4-isobutylpyridine (**8**) under our standard decatungstate/NFSI reaction conditions.[15a] As summarized in Table 1 (entries 1–4), while we were unable to effect the fluorination of salts of 4-ethylpyridine, 4-isobutylpyridine·TFA was fluorinated selectively at the branched aliphatic position (entry 4). While encouraging, this result suggested that protonation disfavours formation of the intermediate pyridylic radical. The addition of Lewis acids of varying strength was also explored and we were delighted and surprised to find that pyridylic fluorination of 4-ethylpyridine occurred only in the presence of AlF$_3$ (entry 5), a relatively weak and largely

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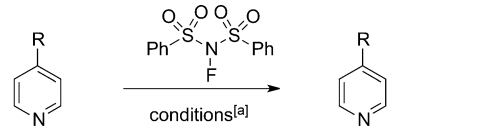
Table 1: Fluorination of 4-alkylpyridines using NFSI.



7: R = CH_2CH_3
8: R = $CH_2CH(CH_3)_2$

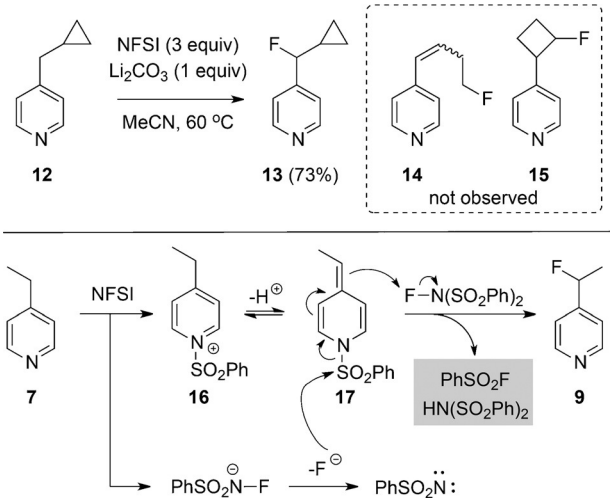
9: R = $CHFCH_3$
10: R = $CH_2CF(CH_3)_2$
11: R = $CHFCH(CH_3)_2$

Entry	Conditions (pyridine)	Solvent	Additive (1 equiv)	*t* (h)	Product (% yield[b])
1	A (**7**)	MeCN	HCl	24	**9** (0)
2	A (**7**[c])	MeCN	none	24	**9** (0)
3	A (**7**)	MeCN-H_2O[d]	HCl	24	**9** (0)
4	A (**8**)	MeCN-H_2O[d]	TFA	36	**10** (38)
5	A (**7**)	MeCN	AlF_3	18	**9** (26)
6	B (**7**)	MeCN	AlF_3	18	**9** (32)
7	B (**7**)	MeCN	none	18	**9** (29)
8	C (**7**)	MeCN	none	18	**9** (79)
9	D (**7**)	MeCN	none	15	**9** (87)
10	D (**7**)	benzene	none	18	**9** (81)
11	D (**7**)	EtOAc	none	18	**9** (90)
12	D (**8**)	MeCN	none	18	**11** (61)

[a] A: NaDT (2 mol%), NFSI (3 equiv), MeCN, hν (365 nm), RT; B: NFSI (3 equiv), RT; C: NFSI (3 equiv), 60°C; D: NFSI (3 equiv), Li_2CO_3, 60°C. [b] Determined by analysis of ^{1}H NMR spectra recorded on crude reaction mixture with internal standard. [c] The N-oxide of **7** was used. [d] MeCN/H_2O = 3:1. NaDT = sodium decatungstate; NFSI = *N*-fluorobenzenesulfonimide.

insoluble Lewis acid. To assess the individual roles of the various reagents now present, the reaction was repeated without the decatungstate or photoirradiation, and a similar outcome was observed (entry 6), thus clearly indicating that the photocatalyst was not a participant. Furthermore, removal of AlF_3 also had no effect on the reaction outcome (entry 7). In fact, simply stirring 4-ethylpyridine with an excess of NFSI in MeCN led cleanly to 4-(1-fluoroethyl)pyridine (**9**). Remarkably, only a single related example of this operationally straightforward process has been reported; in 1996 DesMarteau found[18] that 2- and 4-picoline react with the highly reactive fluorinating agent $(CF_3SO_2)_2NF$ (fluorine plus detachment (FPD) = 200.5 kcal mol^{-1} in CH_3CN vs. 229.6 kcal mol^{-1} for NFSI)[19] and base in CH_2Cl_2 to provide fluoromethyl-picolines, along with lesser amounts of difluoromethyl and fluoropyridine products. Quite distinctly, in the present reaction, the addition of base ($NaHCO_3$ or Li_2CO_3) had little effect on the outcome (entries 8 and 9), and the reaction proceeds equally well in C_6H_6 and EtOAc (entries 10 and 11) but gives poorer results in CH_2Cl_2 and THF. Optimally, simply heating a mixture of 4-ethylpyridine and NFSI in MeCN at 60°C afforded 4-(1-fluoroethyl)pyridine (**9**) in excellent yield (87%, entry 9). Gratifyingly, reaction of 4-isobutylpyridine (**8**) under the same conditions afforded the pyridylic fluorination product **11** (entry 12), with selectivity complimentary to that observed in the photocatalytic C–H fluorination of the same substrate (entry 4).

Our previous studies[15b] have shown that benzylic fluorination can involve radical propagation by NFSI, and we questioned whether radical intermediates are involved in the present pyridylic fluorination. When the reaction of 4-ethylpyridine with NFSI (Table 1, entry 9) was repeated with addition of the galvinoxyl free-radical trap,[20] the yield of 4-(1-fluoroethyl)pyidine (**9**) was not affected. Moreover, fluorination of 4-(cyclopropylmethyl)pyridine (**12**)[21] with NFSI delivered only the pyridylic fluoride **13** in excellent yield (Scheme 1). The absence of rearrangement products **14** or **15**



Scheme 1. Fluorination of 4-(cyclopropylmethyl)pyridine (**12**) and a mechanistic proposal for the formation of **9** and decomposition products of NFSI.

suggests this reaction does not proceed via a pyridylic radical or cation generated through a SET process.[22] Further investigation of the fluorination of 4-ethylpyridine provided additional insight. For example, when NFSI was replaced with *N*-fluoropyridinium triflate, an equally reactive fluorinating agent,[19] only unreacted starting materials were recovered, thus suggesting that NFSI plays a critical role. Moreover, the major byproducts produced in the 4-ethylpyridine fluorination were found to be benzenesulfonamide, phenylsulfonyl fluoride, dibenzenesulfonimide and, to a lesser extent, products apparently derived from phenylsulfonyl nitrene[23] (Scheme 1). Based on these findings and the propensity of nitrogen nucleophiles to react with NFSI at the sulfur,[17] we posit that this pyridylic fluorination involves a transient reaction between pyridine and NFSI to generate *N*-sulfonylpyridinium salt **16** and a nitrene.[23] Loss of an α-methylene proton from the pyridinium then affords the resonance-stabilized tautomer **17**, which can subsequently react with NFSI to provide the fluoroalkylpyridine **9**. Phenylsulfonyl fluoride, which is generated in this reaction, may also play a role and serve as the key sulfonylating reagent. While it is conceivable that this process could be initiated by transient fluorination of the pyridine nitrogen, when a mixture of pyridine and NFSI was heated in MeCN-d_3, the expected *N*-fluoropyridinium salt was not detected by ^{1}H or ^{19}F NMR spectroscopy. A corollary of this mechanistic proposal is that pyridylic fluorination is restricted to 2- and 4-substituted pyridines, where deprotonation results in a resonance-stabilized carbanion. As detailed below, 3-substituted pyridines fail to engage in productive reactions with NFSI.

In order to evaluate the regioselectivity and scope of this reaction, we investigated the fluorination of a structurally diverse collection of alkyl pyridines (Figure 2). In general, the direct C–H fluorination of 2- and 4-alkyl pyridines and annulated pyridines proceeds in good to excellent yield. Notably, the reaction is highly tolerant to common functional groups, including amides, esters, ketones, imidazolidinones, tertiary alcohols, and sulfonamides. While conceptually, fluoroalkyl pyridines could be accessed from the deprotonation of alkyl pyridines using a strong base, followed by reaction with NFSI, the reaction of 4-ethylpyridine with LDA[24] followed by NFSI optimally provided the fluoroethyl pyridine **9** in inferior yield (57%). Moreover, the reaction of 5,6,7,8-tetrahydroisoquinoline with LDA followed by NFSI delivered none of the fluorinated adduct **23**, and these conditions only effected α-fluorination of carbonyl-containing substrates (see the Supporting Information). Conversely, fluorination of 5,6,7,8-tetrahydroisoquinoline using our optimized method (Table 1, entry 9) provided **23** in good yield and with complete selectivity for fluorination at C5. Likewise, fluorination of 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine[25a] afforded the 7-fluoro adduct **22** exclusively. This selectivity is consistent with the mechanistic proposal outlined above and the fact that other 3-alkylpyridines (e.g., 3-ethyl- and 3-isobutylpyridine) failed to undergo fluorination. Importantly, this predictive selectivity creates opportunities for site-selective fluorination in more complex or annulated pyridines[5,25] (e.g., **22**–**25, 34**, and **36**), thus making this method a potentially powerful tool for the late-stage modification of drug leads. Substrates containing acid-sensitive functionalities were also well tolerated under the mild reaction conditions, which enabled access to the tertiary alcohols **26** and **28**. Interestingly, pyridylic fluorination occurs in preference to fluorination at the α-carbon of ketones, amides, and esters (e.g., **24**, **25**, and **30**), which further highlights the enhanced acidity of the pyridylic proton following activation (Scheme 1) and the distinctness of this process from classical deprotonation/fluorination strategies. It was also found that this simple reaction is capable of delivering the fluorinated alkylpyrimidines **31** and **32**, albeit at significantly higher reaction temperatures (120–150 °C) in a microwave reactor. With an interest in exploring the reliability of this transformation for medicinal chemistry purposes, the potent ($IC_{50} < 10$ nM) aldosterone synthase (CYP11B2) inhibitors **33** and **35**[25b] were also reacted with NFSI to afford the fluorinated analogues **34** and **36** in good yield and with complete regioselectivity for the position indicated. It is notable that this simple modification should have a measurable influence on both the acidity ($\Delta pK_a \approx 1.4$)[26] and metabolic stability of these drug leads.

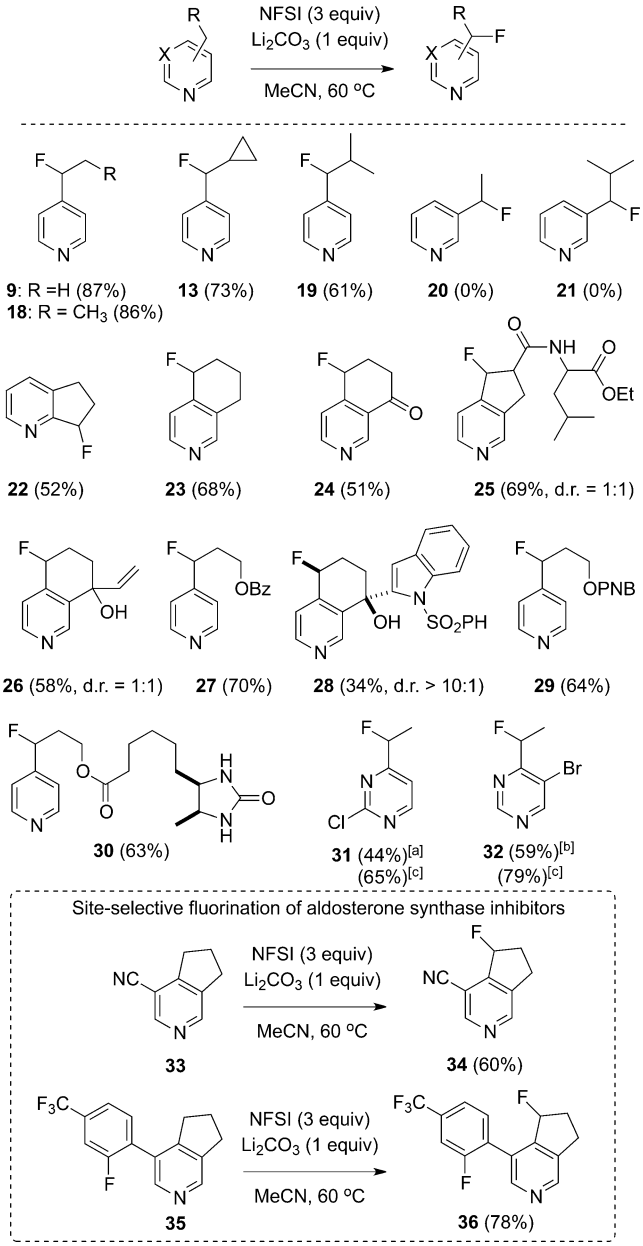
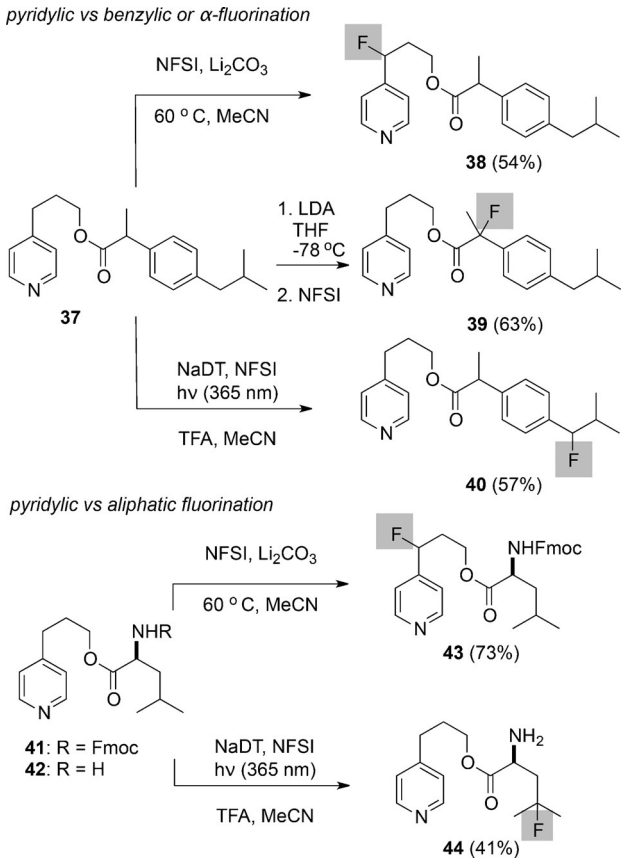


Figure 2. Selective pyridylic fluorination of C–H bonds and direct fluorination of the potent aldosterone synthase inhibitors **33** and **35**. [a] Reaction temperature: 150 °C (microwave reactor). [b] Reaction temperature: 120 °C (microwave reactor). [c] Yield based on unreacted starting material. PNB = *p*-nitrobenzoyl; Bz = benzoyl.

Finally, to demonstrate the utility of this advance within the context of site-selective late-stage C–H fluorination, we explored the fluorination of esters derived from ibuprofen and leucine (Scheme 2). When employing our photocatalytic decatungstate reaction conditions[15a] with the TFA salts of **37** and **42**, we observed complete selectivity for the expected[15] benzylic or aliphatic fluorination products **40** and **44**, respectively. Conversely, simply heating the esters **37** and **41** with NFSI in MeCN delivered the corresponding pyridylic fluorides **38** and **43** in good yield. Notably, treatment of **37** with LDA followed by NFSI provided complimentary selectivity and afforded the α-fluoroester **39** as the exclusive product.

In summary, we have developed a convenient and regioselective fluorination reaction that enables the late-stage fluorination of pyridylic C–H bonds. This reaction tolerates a wide variety of functional groups and offers selectivity complementary to decatungstate-catalyzed C–H fluorination. Importantly, this process provides a means to directly modulate basicity, improve lipophilicity, and alter the metabolic profile of 2- and 4-alkylpyridines. Considering that pyridines are prominent scaffolds in small-molecule drugs,



Scheme 2. Site-selective late-stage fluorination of pyridylic, benzylic, or aliphatic C–H bonds, contrasted with classical α-fluorination.

this simple reaction may well serve as an enabling tool in medicinal chemistry. Further optimization aimed at decreasing reaction times (e.g., in continuous flow) may expand the utility of this process to include radiotracer synthesis using [^{18}F]NFSI[27] (^{18}F $t_{1/2} \approx 110$ min). The C–H fluorination of aliphatic groups attached to other heterocycles (e.g., imidazoles, quinolines, pyrazines) and additional pyrimidines using this simple strategy is currently under investigation.

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