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Synthesis of Heterobenzylic Fluorides

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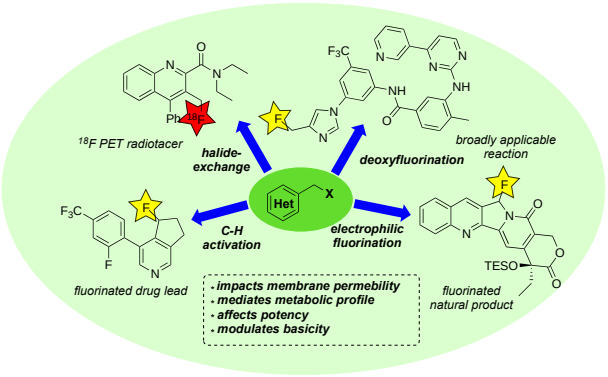

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Abstract Fluorination at heterobenzylic positions can have a significant impact on basicity, lipophilicity, and metabolism of drug leads. As a consequence, the development of new methods to access heterobenzylic fluorides has particular relevance to medicinal chemistry. This Short Review provides a survey of common methods used to synthesize heterobenzylic fluorides and includes fluoride displacement reactions of previously functionalized molecules (e.g., deoxyfluorination and halide exchange) and electrophilic fluorination of resonance stabilized heterobenzylic anions. In addition, recent advances in the direct fluorination of heterobenzylic C(sp^3)-H bonds and monofluoromethylation of heterocyclic C(sp^2)-H bonds are presented.

Key words heterocycles, fluorination, medicinal chemistry, C-H functionalization, heterobenzylic fluoride

1. Introduction

Nitrogen-containing heteroaromatics are privileged scaffolds in both pharmaceutical and agrochemical research.[1] In fact, roughly 60% of FDA approved drugs incorporate a nitrogen-containing heterocycle, of which pyridines, thiazoles, and imidazoles are among the most common.[1e] The prevalence of these heterocycles in approved pharmaceuticals has inspired significant advances in both their synthesis[2] and functionalization[3] that enable the fine-tuning of potency and physicochemical properties of drug leads. Thus, through the careful choice and positioning of substituents, features such as basicity (Figure 1; **1**[4]), inter- and intramolecular hydrogen bonding (Figure 1; **2**[5]), and π-stacking interactions (Figure 1; **2**[5]) can be optimized for ligand-target binding.[1c]

Notably, owing to the small size of fluorine atoms, the polarized nature of carbon-fluorine bonds and consequent impact on compound lipophilicity, hydrofluorocarbon substituents (e.g., CF_3 and CH_2F) can have profound effects on biological activity.[6-8] In addition, fluorine is also an isostere for both hydrogen and hydroxyl groups,[6-8] and strategic fluorination at metabolically labile sites is a common tactic employed to mediate enzymatic degradation and adjust pharmacokinetic properties.[6] For example, installation of the aryl fluoride in the anti-cancer drug gefitinib (**4**) markedly prevents metabolism at this position, resulting in an increased *in vivo* half-life (Figure 1).[10] Owing to their relatively weak C-H bond strength, heterobenzylic C-H bonds are also prone to metabolism (see **1** and **3**[9] Figure 1). Thus, strategic fluorination at these centers provides unique opportunities to modulate basicity and metabolism. However, heterobenzylic fluorination, especially at a late-stage in a synthesis or on structurally complex and functional group-rich drug leads, remains a significant synthetic challenge.[8]

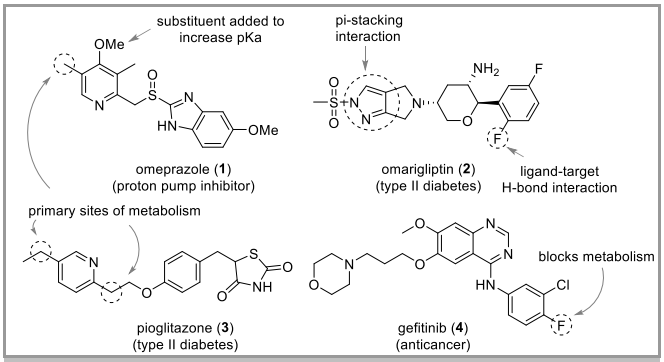


Figure 1. Primary sites of metabolism in omeprazole (**1**) and pioglitazone (**3**) and the effects of heterocycles and fluorine on physicochemical properties in omarigliptin (**2**) and gefitinib (**4**)

2. Heterobenzylic fluorides

Over the past decade several late-stage C-H fluorination strategies have been reported that enable the direct fluorination of benzylic C(sp^3)–H bonds.[11,12] These strategies are particularly useful tools for lead optimization and also present opportunities for the ^{18}F-labelling of ligands for positron-emission tomography (PET) imaging.[13] In contrast, however, there are very few examples of heterobenzylic fluorination. In fact, rarely have C(sp^3)–H fluorination reactions been demonstrated on molecules that include a heterocycle. While this may relate to fundamental incompatibilities between electrophilic fluorinating agents and nucleophilic heteroaromatics, there is a clear need for robust reactions that engender the synthesis of heterobenzylic fluorides. Previous reviews on late-stage C-H fluorination[8,12] have included examples of heterobenzylic monofluorination, however, there is no focused review on the topic. Here, we will provide a survey of methods available for the synthesis of heterobenzylic fluorides, summarize recent advances in this area and identify limitations that we hope will inspire further investigation.

2.1 Deoxyfluorination

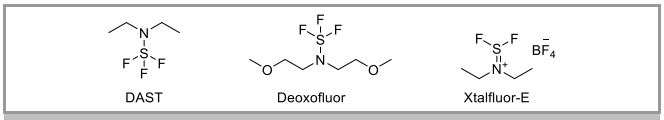


Figure 2. Common deoxyfluorination reagents

The most common strategy to access heterobenzylic fluorides is through deoxyfluorination.[14-24] While these processes are not late-stage transformations and require prior synthesis of a heterobenzylic alcohol, they have proven to be a valuable resource for medicinal chemists. Here, reagents such as DAST,[15b,16,17,18a] Deoxofluor,[15a] and Xtalfluor[21b] (Figure **2**), have enabled transformation of a broad range of heterobenzylic alcohols into the corresponding heterobenzylic fluorides. Mechanistically, these reagents function by activation of the hydroxyl group followed by nucleophilic displacement by fluoride.

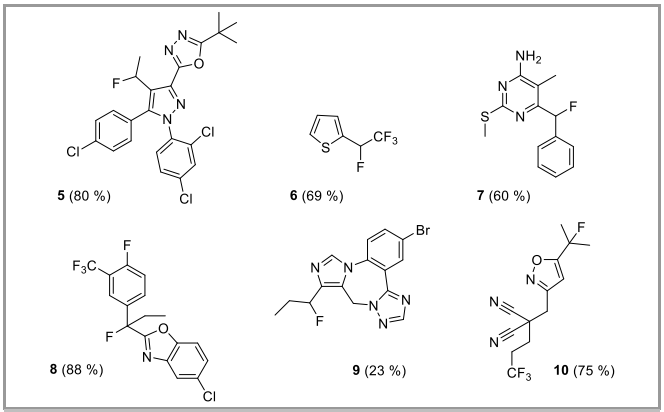
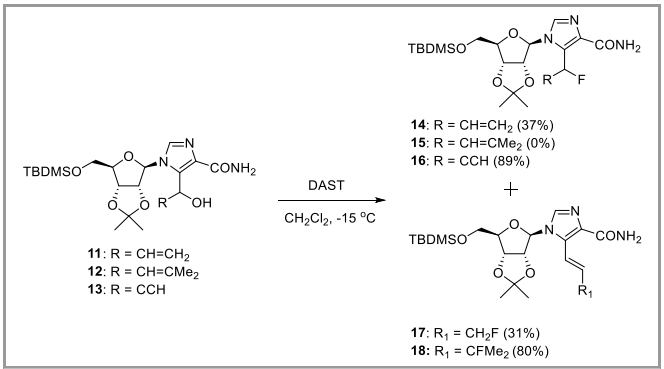


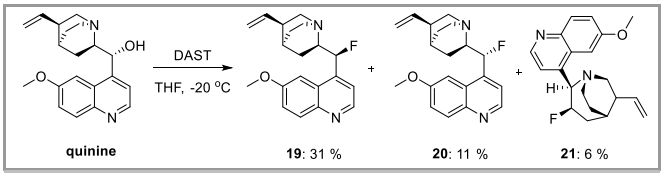
Figure 3. Deoxyfluorination is broadly applicable for the synthesis of heterobenzylic fluorides

Deoxyfluorination at the heterobenzylic position in quinoline-,[14] pyrazole-,[15] pyrimidine-,[16] thiophene-,[17] imidazole-,[18] thiazole-,[19] oxazole-,[20] pyridine-[21], and purine-containing[24] heterocycles, among others[22,23] have been described (for examples, see compounds **5**–**10**, Figure 3). Though deoxyfluorination is a robust and widely used transformation, it is fundamentally limited by a reliance on the prior formation of a heterobenzylic alcohol and can be complicated by the formation of by-products derived from elimination or isomerization processes.[12b] As illustrated in Scheme 1, Matsuda and co-workers were able to access the imidazolyl fluoride **14** using DAST in their synthesis of 3-deaza-3-fluoropurine ribonucleosides.[18a] However, in the case of the methylpropenol **12**, the corresponding fluoride **15** was not produced, and the formation of both **14** and **15** were complicated by the formation of isomeric allylic fluorides **17** and **18**.



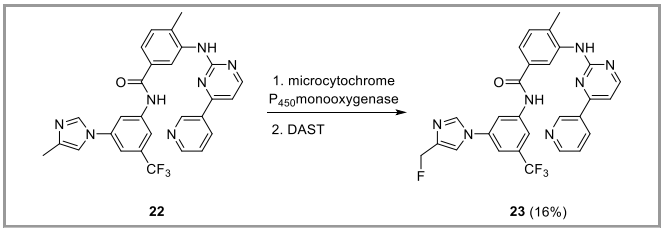
Scheme 1. Deoxyfluorinations of **11** and **12** were complicated by the formation of undesired rearrangement products **17** and **18**

In 2009, Gilmour and colleagues reported the deoxyfluorination of quinine alkaloids using DAST in THF at -20 °C as part of a broader medicinal chemistry campaign (Scheme 2).[14] Here, products derived from both stereochemical inversion **19** and retention **20** were produced in low to modest yield. In addition, the ring-expanded azepane **21** was produced via formation of an aziridinium intermediate.



Scheme 2. Deoxyfluorination of quinine led to inversion (**19**), retention (**20**), and rearrangement (**21**) products

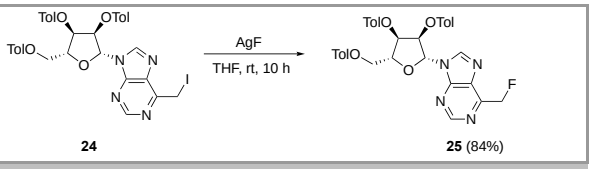
A recent and particularly interesting example of this transformation was reported by Huisman and co-workers, who introduced a heterobenzylic alcohol via the selective late-stage oxidation of **22** with microcytochrome P_{450} monooxygenase followed by deoxyfluorination, which provided access to the fluoromethyl imidazole **23** (Scheme 3).[25]



Scheme 3. Late-stage enzymatic oxidation enabled deoxyfluorination

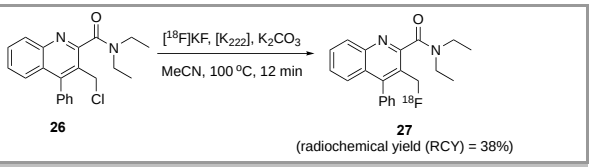
2.2 Halide exchange

Halide exchange reactions have also proven useful for the synthesis of heterobenzylic fluorides, and have been described for purines,[24] imidazoles,[26] oxazoles,[27] pyridines,[28] quinolines,[29] pyrimidines,[30] indoles,[31] benzofurans,[32] thiazoles,[33] triazoles,[34] and other heterocycles.[35] However, as with deoxyfluorination, the requirement for prior installation of a heterobenzylic halide limits the utility of these processes and their suitability as late-stage modifications for lead optimization.



Scheme 4. Halide-exchange reaction with silver fluoride

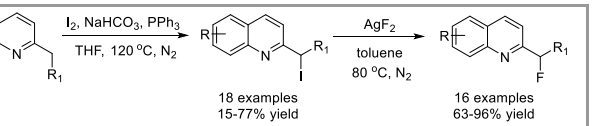
An excellent example of halide exchange was reported as part of an investigation into the cytostatic activity of 6-(fluoromethyl)purine nucleoside analogues. Here, Hocek and co-workers converted the protected 6-(iodomethyl)purine nucleoside **24** into its fluoromethyl derivative **25** using silver fluoride in THF (Scheme 4).[24]



Scheme 5. Halide-exchange reactions for the synthesis of ^{18}F radiotracer (**27**)

Silver fluoride, tetrabutylammonium fluoride (TBAF), potassium fluoride, cesium fluoride, and hydrogen pyridinium fluoride (Olah reagent) are common fluoride sources used in halide exchange reactions, and their efficient preparation as ^{18}F isotopes has provided opportunities for the synthesis of ^{18}F-labelled radiotracers for PET imaging.[29b,33,35] For example, Sutherland and colleagues have reported a radiotracer for imaging of the translocator protein. Here, K^{18}F in MeCN under moderate heating rapidly converted **26** into its ^{18}F-fluorinated derivative **27** in 38% radiochemical yield (Scheme 5).[29b]

Recently, Yan and co-workers reported a late-stage iodination of 2-alkyl quinolines with iodine and triphenylphosphine in the presence of sodium bicarbonate. Coupling this process with a subsequent halide exchange reaction using silver(II) fluoride provided a means to access 2-fluoroalkyl quinolines in excellent yield (Scheme 6).[29c]



Scheme 6. Late-stage C-H iodination and corresponding halide-exchange fluorination

2.3 Electrophilic fluorination of heterobenzylic anions

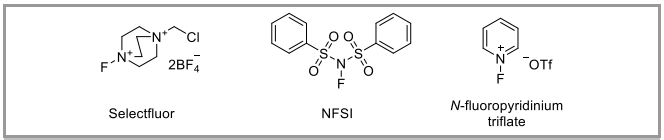
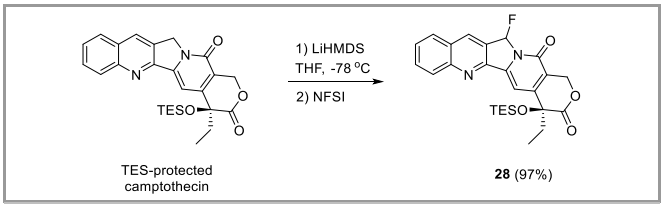


Figure 4. Electrophilic fluorinating reagents

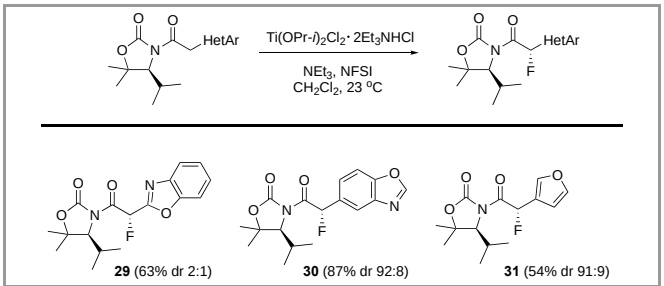
The deprotonation of a heterobenzylic methyl or methylene by strong base, followed by reaction with an electrophilic fluorinating agent (e.g., Figure 4) has also provided access to heterobenzylic fluorides. Here, however, the substrate scope is often limited to molecules with little additional functionality or relatively acidic heterobenzylic protons. Thus, to facilitate deprotonation, the heterobenzylic position is often adjacent to a carbonyl,[36] nitro,[37] or sulfonate group.[38] Notably, this strategy can also provide access to difluorinated adducts by simply employing an excess of base and fluorinating reagent.[39] While much less common, fluorination of unfunctionalized alkyl heterocycles have also been reported. For example, in 1991, Anders and co-workers investigated the deprotonation of 4-alkyl pyridines using LDA followed by reaction with various electrophiles, including NFSI, a process that delivered the corresponding pyridylic fluoride in modest yield.[40]



Scheme 7. Heterobenzylic fluorination of camptothecin

As a notable additional example, Varchi and co-workers utilized this sequence in their fluorination of the TES-protected natural product camptothecin (Scheme **7**).[41] Here, deprotonatation with LiHMDS at -78 ˚C in THF, and subsequent addition of NFSI, afforded **28** in excellent yield.

Controlling the absolute stereochemistry at the resulting heterobenzylic fluoromethine center remains a significant challenge.[42] A straightforward solution to this problem has been developed that involves use of chiral auxiliaries and provides heterobenzylic fluorides with good levels of diastereoselectivity.[43] For example, Zakarian and co-workers have described the diastereoselective fluorination of *N*-acyloxazolidinones with Ti(O^{i}Pr)$_2$Cl$_2$ and NFSI (Scheme 8). Among the reported examples were the heterocycles **29–31**.[43a]

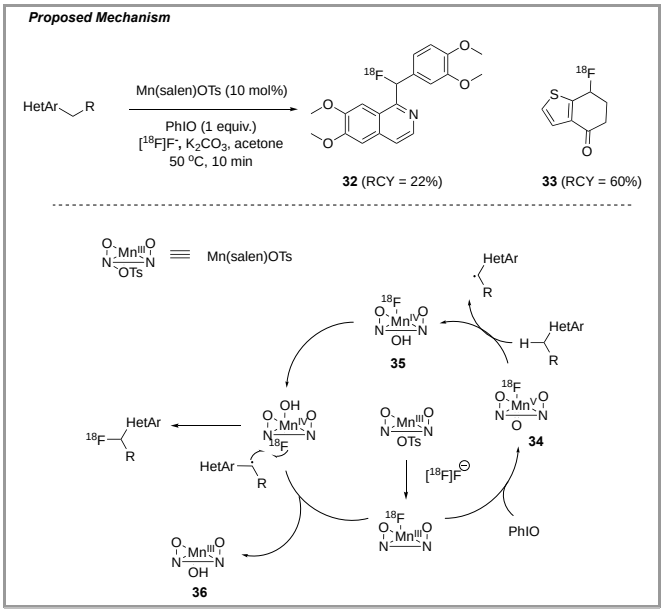


Scheme 8. Stereoselective installation of heterobenzylic fluorides using a

chiral auxiliary

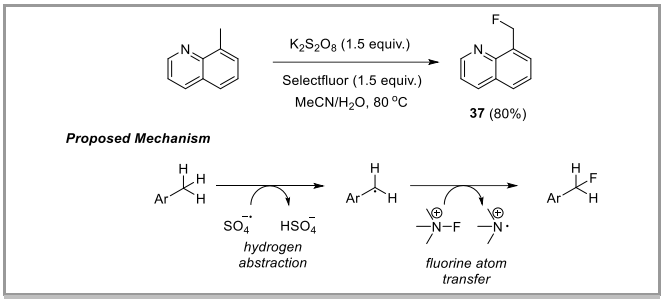
2.4 Late-stage C-H bond fluorination

Following Groves and co-workers pioneering report on the fluorination of unactivated C(*sp*^{3})-H bonds in 2012,[44a] several complimentary C-H fluorination strategies have been developed that provide access to aliphatic,[44] allyl,[45] or benzylfluorides.[11-13] Many of these processes take advantage of the observation made by Sammis and Paquin that electrophilic fluorinating agents such as NFSI and Selectfluor are capable of transferring a fluorine atom to an intermediate carbon-centered radical owing to their low N-F bond dissociation energies (Selectfluor BDE_{NF} = 62.2 kcal/mole in H_2O; NFSI BDE_{NF} = 63.5 kcal/mole in H_2O).[46] Unfortunately, as pointed out earlier by Crugeiras,[47] these reagents are often incompatible with basic amines. For example, the sulfonyl group in NFSI is readily attacked by pyridine, liberating an *N*-fluorosulfonamide.[48] Thus, the preponderance of reports on C-H fluorination that employ electrophilic fluorinating reagents lack examples of nitrogen-containing heterocycles. Uniquely, the C(*sp*^{3})-H fluorination reaction described by Groves relies instead on the *in situ* formation of a Mn(IV) species that is a competent fluorine transfer agent. It has also been demonstrated that this process is amenable to ^{18}F-fluorination of benzylic C-H bonds[13] including the two heterobenzylic C-H ^{18}F-fluorination reactions depicted in Scheme 9 (i.e., **32** and **33**). Mechanistically, it is proposed that Mn(salen)OTs undergoes ligand exchange with fluoride to afford the active catalyst Mn(salen)F, which is subsequently oxidized by iodosobenzene to the Mn(V) intermediate **34**. This later species functions as a hydrogen atom abstracting agent, generating a heterobenzylic radical and Mn(IV) species **35**. Fluorine atom transfer from **35** to the intermediate carbon centered radical affords the fluorinated product.



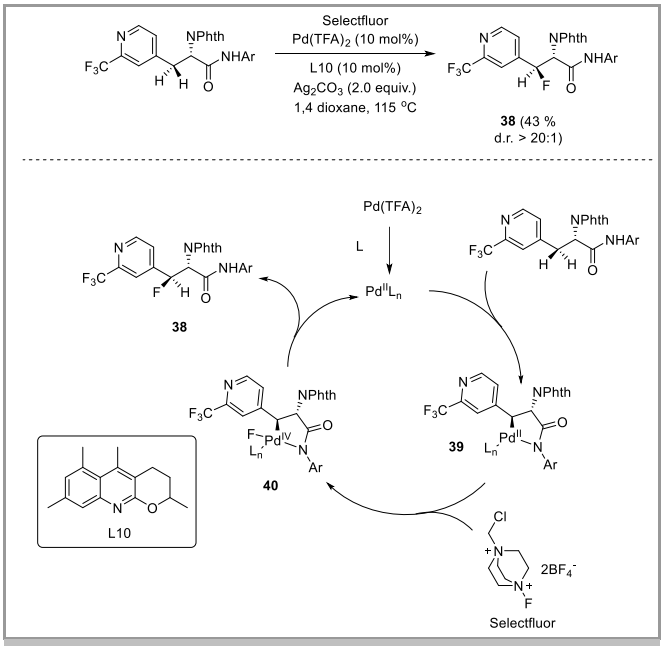
Scheme 9. Manganese-catalyzed C-H fluorination for the generation of ^{18}F radiotracers

In 2015, Yi and co-workers described a transition metal-free radical benzylic fluorination using potassium persulfate in combination with Selectfluor. It was also demonstrated that 8-(fluoromethyl)quinoline (**37**) could be produced in 80% yield using this process (Scheme 10).[11e] The authors proposed that thermal decomposition of persulfate generates a sulfate radical that abstracts a benzylic hydrogen atom. Subsequent fluorine atom transfer from Selectfluor[46] provides the fluorinated adduct. Interestingly, an additional 1.5 equiv. of both potassium persulfate and Selectfluor led to selective difluorination. The authors also noted a competitive benzylic oxidation reaction that predominated at lower temperatures.



Scheme 10. Transition metal-free radical C-H fluorination

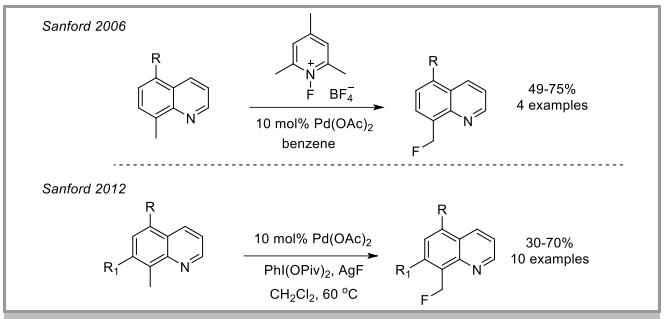
Transition metal catalyzed stereocontrolled fluorinations have also been employed for the synthesis of enantiopure heterobenzylic fluorides.[49,50] The Pd-catalyzed β-C(*sp*^{3})-H directed fluorination reported by Yu and co-workers for the synthesis of enantiopure *anti*-β-fluoro-α-amino acids provided **38** in 43 % yield and excellent diastereoselectivity (Scheme 11).[49] Here, it was proposed that the active catalyst ($Pd^{II}L_n$) is formed *in situ* from the quinoline ligand coordinating to $Pd(TFA)_2$. A *trans*-substituted 5-membered palladacycle **39** derived from C(*sp*^{3})-H activation undergoes oxidative addition with Selectfluor to generate a Pd(IV) fluoride intermediate **40**. Reductive elimination then affords the pyridylic fluoride **38**.



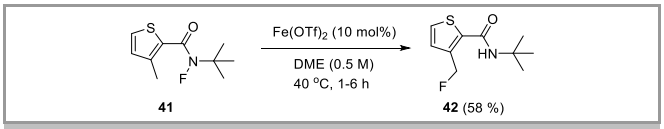
Scheme 11. Palladium-catalyzed diastereoselective C-H fluorination

In 2006, the palladium-catalyzed directed C-H fluorination of both heterobenzylic and aryl C-H bonds was reported by Sanford

and co-workers and represents the first example of metal-catalyzed heterobenzylic fluorination (Scheme 12).[51] Here, following generation of an intermediate 5-membered palladacycle, oxidation by *N*-fluoropyridinium triflate to Pd(IV) and a subsequent reductive elimination generates a new C-F bond. In 2012, Sanford and co-workers described an important advance by demonstrating that the palladium-catalyzed C-H fluorination could also be effected using nucleophilic fluoride (Scheme 12).[52] Here, a hypervalent iodine source is responsible for oxidation of Pd(II) to Pd(IV), which upon ligand exchange with silver fluoride and subsequent reductive elimination generates 8-(fluoromethyl)quinolines.

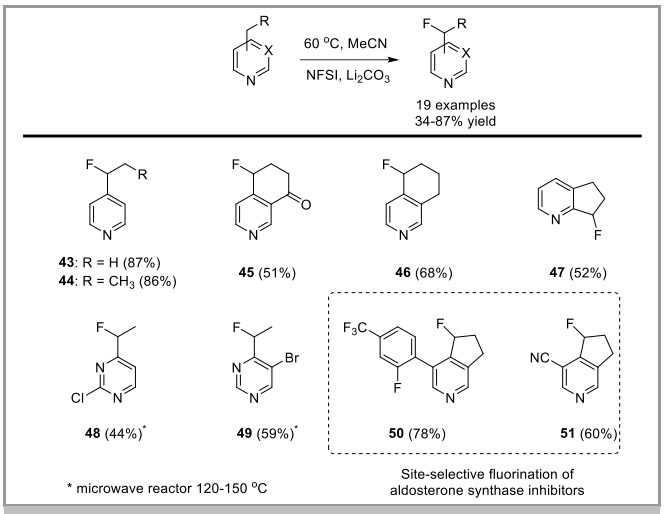


Scheme 12. Palladium-catalyzed C-H fluorination using electrophilic and nucleophilic fluorine sources



Scheme 13 Iron-catalyzed fluoroamide-directed fluorination

While directed C-H fluorination methods have generally relied on palladium catalysis,[49,51,52,53] Cook and co-workers have recently reported an iron-catalyzed fluoroamide-directed fluorination of benzylic, allylic, and unactivated C-H bonds.[54] This study included the fluorination of thiophene **41**. Interestingly, mechanistic studies suggest that iron-mediated homolytic cleavage of the N-F bond generates a nitrogen-centered radical that engages in hydrogen abstraction to afford the corresponding (hetero)benzylic radical. C-F bond formation then involves either a free radical process whereby intermolecular fluorine atom transfer from a second molecule of fluoroamide occurs, or an $Fe^{III}F$ intermediate. Crossover experiments using the corresponding chloroamide as well as DFT calculations supported the latter organometallic pathway.



Scheme 14 Late-stage fluorination of pyridylic C-H bonds and aldosterone synthase inhibitors **50** and **51**

Recently, we reported a late-stage C-H fluorination of 2- and 4-alkyl pyridines with *N*-fluorobenzenesulfonimide (NFSI),[48] a reaction that was discovered serendipitously while examining the utility of our decatungstate-catalyzed C-H fluorination reaction[11d,44b,44c,55] on nitrogen heterocycle-containing molecules. Notably, this work builds on an earlier report by DesMarteau and co-workers who noted that 2- and 4-picolines reacted with $(CF_3SO_2)_2NF$ (a more reactive fluorination reagent than NFSI) to produce mixtures of mono/difluorinated picolines.[56] We demonstrated that simply heating mixtures of 2- or 4-alkylpyridines with NFSI and Li_2CO_3 in MeCN resulted in good to excellent yield of pyridylic fluorination products (see Scheme 14; **43-47**, **50, 51**). Importantly, this reaction proved remarkably tolerant to functional groups and pyridylic fluorination occurs exclusively even in the presence of enolizable carbonyls (e.g., **45**). This operationally straightforward reaction was also exploited in the late-stage fluorination of the annulated pyridines **50** and **51**, both of which are aldosterone synthase inhibitors and potential leads for the treatment of hypertension.[57] A particularly appealing feature of this reaction is its complementarity to our previously reported decatungstate-catalyzed C-H fluorination reaction. For example, it was demonstrated that selective fluorination at benzylic or branched positions in **52** and **53** could be accomplished using our photocatalyzed decatungstate fluorination reaction on the corresponding TFA salts,[44c] while pyridylic fluorination could be readily effected by simply heating either substrate with NFSI and Li_2CO_3 in MeCN (Figure 5).

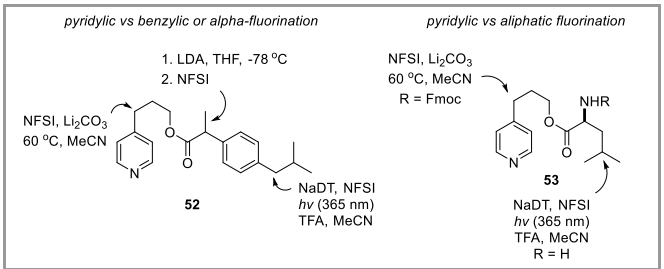
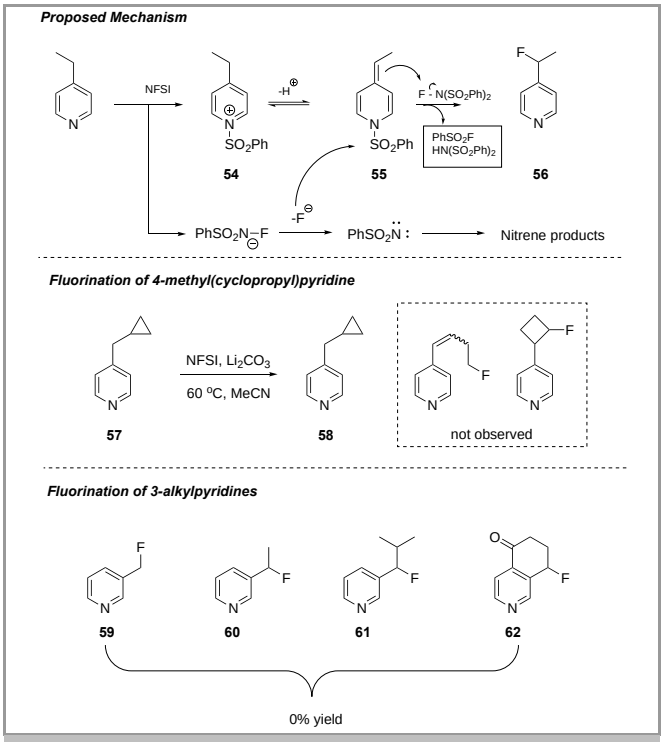


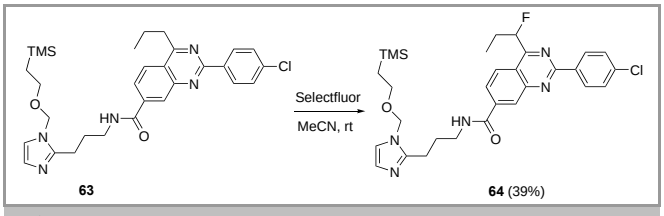
Figure 5. Site-selective C-H fluorination of benzylic-, aliphatic-, α-carbonyl-, and pyridylic- positions

Mechanistically,[47] we proposed that initial formation of an *N*-sulfonylpyridinium salt **54** serves to increase the acidity of the pyridylic proton (Scheme 15). Following deprotonation, the resonance-stabilized extended enamine **55** reacts with the electrophilic fluorinating reagent NFSI to provide adduct **56.** This mechanism is consistent with the observation that 3-alkyl pyridines (e.g., **59**–**62**) do not undergo fluorination. Given the relatively low BDE of pyridylic C-H bonds we also considered a radical process, however, fluorination of the cyclopropylmethyl pyridine **57** gave only the pyridylic fluoride **58** in good yield.



Scheme 15. Mechanistic proposal and the fluorination of 4-methyl(cyclopropyl)pyridine and 3-alkylpyridines

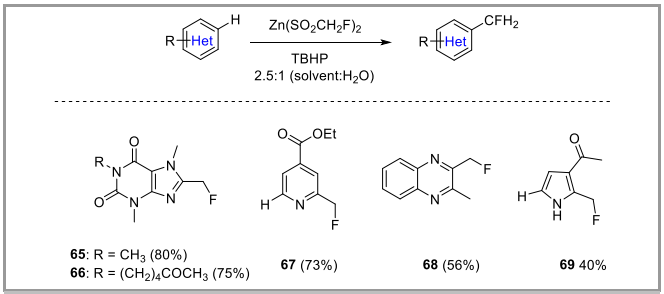
In the same year, Freeze and collegues described the heterobenzylic fluorination of quinazoline **63** with Selectfluor in their synthesis of nicotinamide phosphoribosyltransferase inhibitors (Scheme 16; **64**).[58] Given these mild conditions, this simple reaction may well prove useful for the the late-stage fluorination of other heterobenzylic C-H bonds.



Scheme 16. Fluorination with Selectfluor

2.5 Monofluoromethylation of C(sp^2)-H bonds

In 2012, Baran and co-workers reported an efficient and complementary synthesis of heterobenzylic fluorides by demonstrating that these compounds could be accessed through the direct functionalization of heteroaromatic C(sp^2)–H bonds (Scheme 17).[59] Here, it was shown that a zinc monofluoromethane sulphinate, in the presence of an oxidant, effected the direct monofluoromethylation of xanthines (**65**, **66**), pyridines (**67**), quinoxalines (**68**), and pyrroles (**69**). Notably, in cases such as **67** and **69** where multiple monofluoromethylation events are possible, single products were observed with excellent regioselectivity. Mechanistically, it was proposed that the reaction involves a Minisci-like radical process, whereby a zinc monofluoromethane sulphinate generates a nucleophilic CH_2F radical. Through the use of alternative zinc sulphinate salts it was also shown that heterocycles could be readily modified by addition of CF_3, CF_2H, and CH_2CF_3.



Scheme 17. Monofluoromethylation of xanthines, pyridines, quinoxalines, and pyrroles.

3. Conclusions

In summary, several strategies have been developed for the synthesis of heterobenzylic fluorides. Deoxyfluorination and halide exchange reactions have been broadly utilized and applied to both lead optimization in medicinal chemistry and ^{18}F-radiotracer development. However, these reactions require prior synthesis of a heterobenzylic alcohol or halide and thus there has been considerable recent attention focused on the direct fluorination of heterobenzylic C(sp^3)–H bonds. While these processes can suffer from substrate/reagent incompatibilities, several advances have demonstrated that heterobenzylic fluorination can indeed serve as an enabling tool for medicinal chemists and provide unique opportunities for late-stage optimization of drug leads. Given that only a limited number of aromatic heterocycles are represented in these examples (i.e., pyridine, quinolone, quinazoline, pyrimidine) we expect that this area of research will continue to flourish and that new strategies and tactics will extend the utility of this approach to other heteroaromatics that are particularly important in medicinal chemistry (e.g., thiazole, imidazole, oxazoles, indoles).

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Biosketches

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