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Synthesis and Late-Stage Functionalization of Complex Molecules through C–H Fluorination and Nucleophilic Aromatic Substitution

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Supporting Information

ABSTRACT: We report the late-stage functionalization of multisubstituted pyridines and diazines at the position α to nitrogen. By this process, a series of functional groups and substituents bound to the ring through nitrogen, oxygen, sulfur, or carbon are installed. This functionalization is accomplished by a combination of fluorination and nucleophilic aromatic substitution of the installed fluoride. A diverse array of functionalities can be installed because of the mild reaction conditions revealed for nucleophilic aromatic substitutions (SNAr) of the 2-fluoroheteroarenes. An evaluation of the rates for substitution versus the rates for competitive processes provides a framework for planning this functionalization sequence. This process is illustrated by the modification of a series of medicinally important compounds, as well as the increase in efficiency of synthesis of several existing pharmaceuticals.

INTRODUCTION

Pyridines and diazines are among the most prevalent heterocycles in biologically active compounds. They are found in 2 of the 5 top-selling pharmaceuticals8 and 6 of the 23 small molecules approved by the FDA in 2013.3 Of course, the groups appended to the heteroarene and the heteroarene core together affect the activity of the molecule, not just the heteroarene itself. Thus, studies of the structure−activity relationships (SAR) require derivatives containing a range of substituents attached to pyridines and diazines. One potential method to create these derivatives is C−H bond functionalization of the heteroarene. Yet, few C−H bond functionalization reactions are amenable to late-stage functionalization of heteroarenes. Instead, multistep syntheses are typically conducted to study the effects of substituents on the heteroarene units.

Some C−H bond functionalization reactions of heteroarenes have been developed that exploit a directing group, but methods for site-selective functionalization without the influence of such groups would allow modifications at different positions and without the need to install and remove such groups.

Three major classes of reactions lead to the functionalization of C−H bonds in pyridines and diazines without the influence of directing groups. The first class comprises Minisci-type reactions, which involve the addition of carbon-centered radicals to heteroarenes (Scheme 1A).3,4 These reactions are versatile, but mixtures of isomers are formed in most cases, and the regioselectivity depends on the steric and electronic properties of both the heteroarene and the radical partner.3,5

A second class of heteroarene C−H bond functionalization reactions includes additions of nucleophiles to pyridine N-oxides in combination with a reagent to activate and dehydrate the pyridine N-oxide (Scheme 1B). Reactions of this type have been developed to install Br, Cl, CN, amino, phenoxy, and nucleophiles derived from reagents containing acidic C−H and N−H bonds (pKₐ range of ∼10−20).6 In most cases, the scope of the pyridine N-oxides that undergo these reactions is limited to those containing ether, ester, and nitrile substituents or halides at positions not reactive toward SNAr. In general, functionalization occurs at the 2-position, but competing functionalization at the 4-position or on pendant alkyl groups is often observed. In addition to these issues of functional group compatibility and site selectivity, the need to prepare and isolate the N-oxides limits the use of these reactions.

Most closely related to the work reported here, C−H functionalization reactions at the 2-position of pyridines and pyridine N-oxides have been developed with transition metal catalysts.7 However, these reactions are limited to the formation of C−C bonds, and the reaction conditions and scope suggest that these reactions are not suitable for complex substrates.8 Other functionalizations of heteroaryl C−H bonds involve

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Scheme 1. Strategies for C−H Functionalization of Pyridines

A: Radical addition reactions

B: Nucleophilic addition to pyridine N-oxides

C: This work

not isolated

NuH Base SNAr

Nu = OR, NR₂, SR, CN

Nu = OR, NR₂, SR, CN
cross-coupling at the most acidic C–H bond; these methods occur most commonly with five-membered ring heteroarenes.7a–c

Finally, C–H borylation reactions catalyzed by transition metal complexes provide a means to install substituents onto heteroarones by conversion of the heteroarene to the corresponding heteroarylborate ester and subsequent transformations of the C–B bond.9 However, borylations of pyridines occur predominantly at the 3- and 4-positions and, therefore, are complementary to the reactions at the 2-position described here.

We aimed to develop a method for the late-stage functionalization of pyridines and diazines that would address the limitations of the regioselectivity and scope of C–H functionalizations of heteroarones. Our approach was inspired by the value of borylation reactions developed in the authors’ laboratory to create synthetic intermediates that can be converted to a variety of functionalized products.9b We considered that the C–H fluorination of pyridines and diazines10 at the position α to nitrogen with AgF2 we developed recently could be used for the late-stage functionalization of medicinally relevant compounds because pyridines and diazines are contained in many such compounds and the 2-fluor group could be replaced with a wide range of nucleophiles.

Herein, we report mild conditions for the S_NAr reaction of fluoroheteroarenes, an assessment of the potential of the fluorination and S_NAr reactions to be conducted with complex structures, and the application of these findings to the development of late-stage functionalizations of complex heterocyclic compounds by the combination of C–H fluorination and S_NAr reactions (Scheme 1C). In addition to revealing the potential of this reaction for the functionalization of complex heteroarenes, we demonstrate how the combination of C–H bond fluorination and S_NAr creates routes to several active pharmaceutical ingredients that occur in higher yields and fewer steps than previously reported syntheses of these molecules.

\section*{RESULTS AND DISCUSSION}

\textbf{Conditions for the Nucleophilic Aromatic Substitution of 2-Fluoropyridines.} S_NAr reactions of 2- or 4-haloarylpyridines comprise a site-specific method to synthesize substituted pyridines.11 However, this approach requires initial synthesis and isolation of halogenated pyridines that are typically prepared from pyridine N-oxides or hydroxyarylpyridines with neat POX₃ (X = Br, Cl) at high temperatures.

The majority of S_NAr reactions with halopyridines have been performed with chloropyridines. Chloropyridines are more available commercially than other halopyridines, but the reactions of fluoropyridines are likely to be faster than those of chloropyridines. As for S_NAr reactions of arenes, the S_NAr reactions of pyridines and diazines are likely to be accelerated by the high electronegativity of fluorine. Indeed, the reaction of 2-fluoropyridine with NaOEt in EtOH is 320 times faster than the reaction of 2-chloropyridine.12 This higher reactivity of fluoropyridines could allow S_NAr reactions to occur under conditions that are mild enough to allow this class of reaction to occur on complex molecules; however, a more detailed assessment of the rates and yields for the S_NAr reactions of fluoropyridines and diazines would be needed to predict the scope of the S_NAr process and a method to create the 2-fluoropyridines and diazines that could be conducted in a typical laboratory on complex pyridines and diazines would be required.

Thus, to develop a sequence of C–H bond fluorination and S_NAr, we first evaluated conditions to conduct S_NAr reactions of 2-fluoropyridines. Although S_NAr reactions of electron-deficient fluoroarenes and chloropyridines are commonplace,11 few studies have been performed on S_NAr reactions of fluoropyridines.13 The majority of the published reactions of 2-fluoropyridines have been conducted with unsubstituted 2-fluoropyridine; a few examples were conducted with 2-fluoropyridines containing a single bromide substituent. Moreover, these reactions were performed under conditions involving strong nucleophiles and bases at high temperatures (up to 130 °C), neat reagents, microwave heating, strong reducing agents (LiBH_3NR₂), or toxic solvents (HMPA), and these conditions are unlikely to tolerate the functional groups found in complex molecules relevant to medicinal chemistry. Several S_NAr reactions of 2-fluoropyridines have been reported in the patent literature on both simple and complex substrates. However, the reactions described in these documents for a given class of nucleophile occur under varying conditions. Therefore, the scope of each set of reaction conditions is unclear, and the S_NAr reactions were performed with activated 2-fluoropyridines in most cases. From this body of work, it was unclear whether mild and general S_NAr reactions with fluorohetero arenes could be developed and if selectivity could be obtained for substitution of fluoride over other halides. In fact, previous reports showed that the same forcing reaction conditions lead to substitution of F, Cl, Br, and I.

To identify conditions for the S_NAr reaction that would tolerate common functionality, we studied reactions of unactivated 2-fluoropyridines with nucleophiles derived from alcohols, phenols, amines, amides, N-heterocycles, cyanide, and thios under relatively mild conditions. The reaction conditions identified afforded quantitative conversion to the substitution products, as indicated by GC/MS and TLC (Table 1).

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
NuH & base & solvent & temp (°C) & time (h) & conv. (%) \\
\hline
1, 2, or 3° alcohol & KO'Bu & THF & 50 & 3 & 100 \\
ArOH & KO'Bu & DMF & 80 & 6 & 100 \\
1 or 2° amine & Pr₂NEt & DMSO & 120 & 18 & 100 \\
amide (N–H) & NaH & DMF & 100 & 3 & 100 \\
N-heterocycle & NaH & DMF & 100 & 1–3 & 100 \\
KCN (3 equiv) & DMSO & 120 & 18 & ~80 \\
NaSR & THF & 50 & 3 & 100 \\
\hline
\end{tabular}
\caption{Reaction Conditions for the S_NAr of 2-Fluoropyridines}
\end{table}

Reactions with KCN proceeded in approximately 80% yield. Variation of the cyanide source, stoichiometry, temperature, and solvent did not increase the yield, but the initial conditions did form the cyanopyridine product in a synthetically useful yield. Having developed a set of S_NAr reactions that occur under mild conditions, we explored the tandem fluorination–substitution process.

For the S_NAr reactions to occur in tandem with C–H fluorination, the MeCN and silver salts from the fluorination reaction needed to be removed. Filtering the fluorination reaction...
Reactions through a short silica-filled pipet and evaporating the solvent was sufficient to perform the subsequent SNAr reactions. Yields of the SNAr reactions conducted after filtering the fluorination reaction through Celite were low, due to the presence of soluble Ag salts.

**Convenient Protocols for Performing the Fluorination of Pyridines and Diazines.** For the fluorination−SNAr sequence to be used broadly, procedures for conducting the reaction without specialized equipment for excluding air and moisture are needed. AgF₂ is a hygroscopic solid that decomposes in the presence of water. Therefore, during our initial study, the fluorination reactions were assembled in a glovebox with rigorously dried MeCN. However, despite the water sensitivity of AgF₂, simple procedures can be followed for conducting the reactions without rigorous exclusion of air or moisture.

To assess the impact of water and oxygen on the yield of the fluorination reaction of complex molecules, we performed a series of experiments with (CO₂Me)-vismodesgib, a drug recently approved for the treatment of basal-cell carcinoma (Table 2). Assembling the fluorination reaction in a glovebox (Table 2). Assembling the fluorination reaction in a glovebox with rigorously dried MeCN. However, despite the water sensitivity of AgF₂, simple procedures can be followed for conducting the reactions without rigorous exclusion of air or moisture.

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| method of drying MeCN | dry vial | solids weighed | atmosphere | yield (%) (NMR) |
|-----------------------|----------|----------------|------------|-----------------|
| CaH₂ | yes | in glovebox | N₂ | 99 |
| CaH₂ | yes | in air | N₂ | 84 |
| molecular sieves | no | in air | air | 79 |
| none | no | in air | air | 65 |

Reactions were performed with 0.2 mmol of (CO₂Me)-vismodesgib with 2 mL of MeCN in 4 mL vials.

(oxygen and water content <1 ppm), in an oven-dried vial, with MeCN that had been rigorously dried over CaH₂, afforded the fluorinated vismodesgib derivative in 99% yield by ¹⁹F NMR spectroscopy.

Since the use of a glovebox is not practical for all chemists, we studied the effects of weighing the solid reagents in air and assembling the reaction using standard air-free techniques. A reaction was assembled by adding the pyridine substrate to a dry vial in air and adding MeCN that had been dried over CaH₂. AgF₂ was weighed quickly in air, added to the pyridine solution, and the vial was sealed under an atmosphere of N₂. The reaction assembled in this manner afforded a 2-fluoropyridine product in 84% yield, only a slight decrease in yield compared to the reaction assembled entirely in the glovebox. Performing the reaction in a similar manner with a non-dried vial and sealing the reaction under an atmosphere of air (2 mL of MeCN in a 4 mL vial; 2 mL headspace of air) resulted in a similar yield of the 2-fluoropyridine product (79%).

Acetonitrile dried with 5 wt. % of 3 Å molecular sieves for 24 h was a suitable solvent; the reaction of (CO₂Me)-vismodesgib with AgF₂ assembled by weighing the solid reagents in air afforded the fluorinated product in 85% yield. The water content in MeCN dried over 5 wt % molecular sieves for 24 h is near 4 ppm, and the water content further decreases with time.⁴ The water content of commercial “anhydrous” MeCN is below 10 ppm water and should be equally suitable for this reaction.

Finally, the same reaction was assembled in air with ACS grade MeCN directly from a commercial bottle that had been opened and used over the course of a year; a noticeable decrease in yield to 65% was observed, but a substantial amount of product was still formed. Together, these results demonstrate that these fluorination reactions can be conveniently assembled completely in air, without the use of a glovebox or air-free techniques, and with MeCN dried over molecular sieves, even though AgF₂ is sensitive to water and should be stored under an inert atmosphere. Reactions performed on the benchtop occur in yields that are comparable to those performed under rigorously anhydrous reaction conditions.

AgF₂ is supplied as a black, microcrystalline solid, which should be stored under an inert atmosphere. Because AgF₂ undergoes decomposition with moisture, a noticeable color change from black to yellow or brown is observed when it is stored in air. For all reactions reported here, and in our previous paper, AgF₂ was used as received from Alfa Aesar and stored under a nitrogen atmosphere in a plastic bottle. In our experience, reactions with AgF₂ supplied from Strem occurred in comparable rates and yields to those performed with AgF₂ purchased from Alfa Aesar.

**Scope of the Tandem C–H Fluorination and Nucleophilic Aromatic Substitution of Pyridines.** Having identified convenient methods for conducting both the fluorination and SNAr reactions and having developed a protocol to conduct the two reactions in sequence, we investigated the scope of the C–H bond fluorination−SNAr process. Representative examples illustrating the scope of the combined reactions are shown in Tables 3 and 4. Yields given are for isolated products starting from the heteroarene. The yields for the fluorination step are also shown to illustrate how the values for the two-step process compare to those of the first step.

A variety of pyridines that are sterically hindered (2, 4, 11, 12, 14, 15) and/or electronically deactivated (2, 9, 13, 15) toward SNAr reactions afforded the substitution products in good yields. Substrates containing alkyl groups in the 2-position reacted selectively at the 6-position (2, 4, 9, 14), while analogous reactions with pyridine N-oxides are known to result in substitution of a C–H bond on the alkyl group (Scheme 1B). A wide range of functional groups were tolerated, including ethers, halides, ketones, acetics, esters, amides, ethyl and t-butyl carbamates, nitriles, and sulfones. It is notable that the azetidine in 11 (Table 4) did not undergo ring opening, a competing reaction observed under acidic conditions.

The reactions of chloropyridines 7 and 11 revealed a high selectivity for substitution of a fluoride over a chlorine under conditions of the SNAr reactions shown in Table 1. This high selectivity, along with the high functional group compatibility, is attributed to the milder reaction conditions we developed for the SNAr reaction at the 2-fluoro position, relative to the conditions typically used to conduct substitutions with 2-fluoropyridines. In sum, this work shows that fluoropyridines undergo substitution reactions under conditions much milder than previously reported and can be performed in the presence of a wide range of functional groups, including those that are electrophilic.
Tandem C−H Fluorination and Nucleophilic Aromatic Substitution of Diazines. Six-membered heteroarenes containing two nitrogen atoms (diazines) are prevalent subunits in medicinal chemistry. Radical addition reactions to diazines are commonplace3 (Scheme 1A), but a single example of C−H bond functionalization by nucleophilic addition of a heteroatom to a diazine N-oxide (Scheme 1B) has been demonstrated.6c Like pyridines, diazines react with AgF2 with exclusive selectivity for fluorination adjacent to nitrogen.10 Thus, we considered that the combination of C−H bond fluorination and SNAr reactions could be conducted with these heterocycles to form functionalized diazine products.

Indeed, pyrimidines (5, 6) and pyrazines (8) reacted in the two-step sequence following the standard conditions we developed for the fluorination and SNAr reactions reported in Table 1. This sequence allowed several polysubstituted diazines to be prepared through C−H functionalization. Because the conditions for both the fluorination and the SNAr reactions with diazines are the same as those for pyridines, the tolerance of the reactions toward functional groups on pyridines and diazines should be comparable. This C−H fluorination−SNAr sequence was also applied to the synthesis of a reverse transcriptase inhibitor containing a tetra-substituted pyrimidine (vide infra).

Late-Stage Functionalization of Complex Molecules via Tandem C−H Fluorination and Nucleophilic Aromatic Substitution. With conditions established for the fluorination and SNAr reactions of pyridines and diazines, we evaluated this sequence for the late-stage functionalization of more complex molecules in medicinal chemistry. First, we used our tandem sequence to prepare several 2-substituted derivatives of (Boc-protected) betahistine (9), a histamine agonist used in the treatment of Ménière’s disease. Reaction of 9 with AgF2 formed the corresponding 2-fluopyridine in nearly quantitative yield (98%). This electronically deactivated fluoropyridine intermediate reacted with nucleophiles derived from butanol, morpholine, and indole to provide several 2-substituted analogues of betahistine. Although betahistine is a relatively simple compound that can be prepared in one step from 2-vinylpyridine, the synthesis of derivatives that are similar to those we report here would require 2-substituted 6-vinylpyridines. Few such pyridines are commercially available.16 Thus, our C−H bond fluorination−SNAr strategy for late-stage functionalization avoids lengthy synthetic sequences to prepare derivatives of betahistine.

We also conducted the fluorination of compound 10, the direct precursor to loratadine (Claritin) and desloratadine (Clarinex), two common antihistamines. Compound 10 is prepared in two steps from 3-methylpicolinic acid under relatively harsh reaction conditions (“BuLi, KOtBu for the first step; SOCl2, AlCl3 for the second step”).17 Therefore, the synthesis of 2-substituted derivatives of 10 would require access to the appropriately substituted 3-methylpicolinic acid, which could require several steps to prepare, and an additional two-step sequence to construct the tricycle for each derivative. We prepared various analogues of 10 more directly through fluorination and SNAr reactions to form the corresponding 2-alkoxy-, 2-amino-, and 2-pyrazolyl-substituted derivatives. It is worthy to note that the substituents we installed in 10a−10c would be unlikely to tolerate the conditions of a de novo synthesis of similar analogues of 10.
Our C–H functionalization method also gave access to a series of (Boc-protected) derivatives of tebanicline (11), a potent non-opioid analgesic that is structurally related to several nicotinic acetylcholine receptor agonists. As mentioned above, no ring opening of the azetidine or substitution of the chloride was observed. De novo syntheses of compounds similar to 11a–11c would require access to 2-substituted 3-hydroxy-6-chloropyridine substrates and an additional C–O bond-forming reaction to complete the synthesis of each derivative.

The sequence of C–H bond fluorination and S_{n}Ar also led to a convenient synthesis of 2-alkoxy and 2-amino analogues of roflumilast (12). Roflumilast is a recently approved PDE-4 inhibitor used in the treatment of chronic obstructive pulmonary disease. The reported syntheses of this compound involve amide bond formation with 3,5-dichloro-4-amino-pyridine. Thus, the syntheses of the 2-substituted analogues we report would require access to 2-alkoxy or 2-amino-3,5-dichloro-4-aminopyridine, for which none are commercially available. Therefore, preparing derivatives of roflumilast would mandate multistep syntheses of the appropriate pyridine, in addition to performing the subsequent amide bond formation for each derivative. In contrast, the C–H fluorination–S_{n}Ar strategy we report allows rapid access to analogues that otherwise require several synthetic steps to prepare.

In a similar manner, analogues of the precursor to pirenzepine (13), a benzodiazepine-based M1-selective antagonist used for the treatment of ulcers, were prepared. The sequence was used to install alkoxy, thio, and arlyoxy substituents at the 2-position in good overall yields. Competing reactions at the electrophilic ethyl carbamate were not observed. The synthesis of the core of 13 requires three steps from 2-chloro-3-aminopyridine.

Relative Rates for the Fluorination of Pyridines and Diazines Having Different Electronic Properties. Because many medicinally important compounds contain multiple heteroaryl rings, it would be valuable if the fluorination was selective for the functionalization of one type of ring system over another. The proposed mechanism \(^{10}\) for the fluorination of pyridines and diazines with AgF\(_{2}\) (eq 1) is initiated by coordination of the basic nitrogen to silver. This coordination could cause a more basic heterocycle to be more reactive than a less basic heterocycle. However, the second step in the proposed mechanism is addition of fluoride to the π system, which would be favored for a more electron-deficient heteroarene. Finally, the third step, a formal oxidation of the heterocycle through hydrogen atom abstraction, would likely be favored for a more electron-rich substrate. Our previous studies of the selectivity between pyridine and pyridine-\(_{d}\) demonstrated that coordination of AgF\(_{2}\) to pyridine is reversible and that cleavage of the C–H bond is irreversible. \(^{10}\)

To determine how the electronic properties of the heteroarene influence the relative rates of fluorination, we conducted a series of competition experiments. In these experiments, AgF\(_{2}\) was allowed to react with a 1:1 mixture of two different pyridines and diazines. Because the yield of the fluorination reactions conducted with a large excess of pyridine, relative to AgF\(_{2}\), is low, reactions containing 1 equiv of each diazine (0.1 mmol each) and 2 equiv of AgF\(_{2}\) (0.2 mmol) were run, and the reactions were quenched after 15 min so that the selectivities were being measured at low conversion (25 ± 2%). Competition experiments between 2-ethyl, 2-methoxy, and 2-chloropyridine were conducted; the steric properties of these substrates are similar to each other, but the basicity of the heterocycles differ incrementally from each other by ~2.6 pK\(_{a}\) units. Competition experiments were also conducted between alkyl-substituted pyridines, pyrimidines, and pyrazines containing two available C–H bonds for fluorination. The results of these competition experiments are shown in Table 5. These data show that more Lewis basic pyridines undergo the C–H fluorination reactions in preference to less Lewis basic pyridines. Moreover, exclusive selectivity for fluorination of a 4-alkylpyridine over two alkyl-substituted diazines was observed; the competition between 2-methylpyrimidine and 2,3-dimethylpyrazine showed that the pyrimidine was the more reactive diazine by a factor of 3.3.

The results of these competition experiments contrast with what would be predicted based only on the relative rates of independent reactions between each substrate and AgF\(_{2}\) 2-Ethylpyridine reacts with 2 equiv of AgF\(_{2}\) to give 38% yield of the 6-fluoropyridine after 15 min. Similarly, 2-methoxypyridine reacts in 36% yield, and 2-chloropyridine reacts in 9% yield after 15 min. Because the rates for fluorination of 2-ethylpyridine and 2-methoxypyridine are comparable, and because AgF\(_{2}\) is present in excess, little selectivity for 2-ethylpyridine over 2-methoxypyridine would be expected based on these data alone. However, AgF\(_{2}\) has negligible solubility in MeCN; therefore, competitive binding of the two substrates to the limited amount of available AgF\(_{2}\) likely results in fluorination of the more basic pyridine.

Table 5. Competition Experiments between Electronically Different Pyridines and Diazines with AgF\(_{2}\)\(^{a}\)

| Substrate pK\(_{a}\) | Yield of independent fluorination reaction: | Fluoroheteroarene product ratio: |
|---------------------|---------------------------------------------|-------------------------------|
| R = Et              | 5.97                                       | >20                           |
| R = OMe             | 3.28                                       | <1                            |
| R = Cl              | 0.72                                       | <1                            |

\(^{a}\) Product ratios were determined by \(^{19}\)F NMR spectroscopy of the crude reaction mixture after quenching with aqueous NaHCO\(_{3}\).
To assess the relative reactivity of multiple pyridines in the context of a medicinally important compound, we conducted the fluorination and $S_N$Ar reaction of etoricoxib (eq 2), a selective COX-2 inhibitor used in the treatment of arthritis. This compound contains two different pyridine rings. The more electron-rich ring contains methyl and 2-pyridyl substituents, and the less electron-rich ring contains chloro, aryl, and 3-pyridyl substituents. This molecule reacted with AgF$_2$ with *complete* selectivity for fluorination of the more basic pyridine system, as predicted from the results in Table 5. No product resulting from fluorination of the 3-chloropyridine was observed. Following this site-selective fluorination, several derivatives of etoricoxib containing pendant alkoxy, amino, cyano, and pyrazolyl units were prepared.

**Site Selectivity for the Fluorination of 3,5-Disubstituted Pyridines.** Many medicinally active pyridines contain two different C–H bonds that could undergo fluorination with AgF$_2$. We previously demonstrated$^{10}$ that several 3-substituted pyridines undergo fluorination with exclusive selectivity to form the 2-fluoro-3-substituted pyridine product. The 3-substituted pyridines that react selectively at the 2-position include those containing 3-halo, alkoxy, cyano, or CF$_3$ groups. 3-Substituted pyridines that give a mixture of 2-fluoroypyridine isomers include those containing 3-alkyl, 3-CO$_2$R, and 3-C(O)NR$_3$ substituents. It was unclear from these results if 3,5-disubstituted pyridines would undergo the fluorination selectively. A set of 3,5-disubstituted pyridines containing phenyl, cyano, benzyloxy, bromo, methyl, and CF$_3$ substituents was prepared. The fluorination of the 15 unsymmetrical pyridines containing these substituents occurred with poor selectivity (from 1:1 up to 6:1), with the exception of the benzyloxy-substituted pyridines. The 3-benzyloxy-substituted pyridines containing various substituents in the 5-position reacted with AgF$_2$ with modest to high selectivity (4:2:1 to 20:1) for fluorination adjacent to the ether substituent (Table 6).

Having shown that an alkoxy group can lead to selective fluorination of a 3,5-disubstituted pyridine, we exploited this selectivity to conduct the late-stage fluorination of a medicinally relevant, 3,5-disubstituted pyridine. The core of crizotinib (eq 3), a drug used for the treatment of metastatic non-small cell lung cancer, contains such a heteroaromatic unit. Reaction of 15 with AgF$_2$ gave products reflecting a 7:2:1 selectivity for fluorination adjacent to oxygen. This selectivity is lower than that observed for the fluorination of 3-bromo-5-benzoxypyridine (Table 6), likely due to the steric hindrance of the arylethoxy substituent. To determine if the lower selectivity of this substrate is due to the greater steric hindrance of the benzoxyl group of 15 than that of a simple benzyloxy substrate, the fluorination reaction was also performed with a 2,6-dimethylphenyl arylethoxy substrate. This compound reacted in 62% yield with similar 5:9:1 selectivity for fluorination adjacent to the ether substituent. Thus, the selectivity is lower for reactions of pyridines containing more hindered benzoxyl groups but is still significant. The steric hindrance of the arylethoxy substrates disfavors both the second and third steps in our proposed mechanism (eq 1) leading to an increase in the relative amount of product from fluorination adjacent to the bromide.

Even though the 2-fluoro-3-benzoxypyridine intermediate is both sterically and electronically deactivated toward $S_N$Ar, several 2-substituted derivatives were prepared under the standard conditions for the $S_N$Ar step shown in Table 1. Even a secondary amine reacted with the 2-fluoropyridine to form the sterically congested product 15c. The isomeric products prepared from 15 after C–H bond fluorination–$S_N$Ar reactions were not separable by standard silica gel chromatography, even though the 2-fluoropyridine isomers could be separated by HPLC and GC.

**Limitations of the C–H Fluorination and $S_N$Ar Reactions.** Although we have demonstrated that the C–H fluorination and $S_N$Ar reactions occur with broad scope and can be conducted on complex molecules, there are some limitations. As we reported previously,$^{10}$ the fluorination reaction is not compatible with free amines or alcohols, carboxylic acids, aldehydes, or electron-rich five-membered heterocycles; however, several protected derivatives of these groups are tolerated by AgF$_2$. In addition, we have found that pyridines or diazines containing multiple electron-withdrawing substituents undergo the fluorination reaction in lower yields than those containing electron-neutral or electron-donating groups. Examples of substrates that reacted with AgF$_2$ in low yields (0–30%) are shown in Table 7. Although the Boc-protected derivative of HG-10-102-01 reacted with AgF$_2$ in low yield, a similar tetra-substituted pyrimidine reacted in high yield for the synthesis of etravirine (vide infra).

We have demonstrated that a simple set of $S_N$Ar reaction conditions can be employed for substitution reactions on a variety of 2-fluoroheteroarenes. However, we did find substrates

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**Table 6. Fluorination of 3,5-Disubstituted Pyridines**

| X   | temp (°C) | concentration (M) | ratio (D/E) | combined yield (%) |
|-----|-----------|-------------------|-------------|-------------------|
| Br  | 50        | 0.050             | 15:1        | 49                |
| Cl  | 50        | 0.025             | 8:1:1       | 64                |
| Me  | 50        | 0.025             | >20:1       | 62                |
| Ph  | 50        | 0.050             | 4:2:1       | 68                |
| CN  | 50        | 0.025             | 12:1        | 67                |
| CF$_3$ | rt       | 0.050             | 20:1        | 85                |
that underwent competing side reactions faster than they underwent $S_N$Ar (Table 7). Fluorinated analogues of tropicamide underwent retro-Michael addition under the basic reaction conditions. Although we demonstrated that tert-butyl esters remain intact during the $S_N$Ar reactions (Table 3, substrate 3), we found that aryl acetates are cleaved faster than substitution of fluoride. This cleavage was observed when attempting $S_N$Ar reactions of bisacodyl. Finally, very electron-rich and sterically hindered pyridines, such as the precursor to Nexium, underwent the $S_N$Ar step in low yields; more forcing conditions resulted in the formation of side products.

Applications of C−H Fluorination and $S_N$Ar for the Synthesis of Medicinal Compounds. Having demonstrated the potential of the C−H fluorination−$S_N$Ar sequence for the late-stage derivatization of medicinally important compounds, we sought to evaluate whether the same strategy could create shorter and higher-yielding synthetic routes to the same types of compounds. Although this chemistry requires stoichiometric silver and is not designed for process-scale chemistry, the strategy of C−H fluorination and $S_N$Ar can be useful in discovery chemistry. One example of a synthesis that could be simplified by the fluorination and substitution process is the synthesis of the simple compound 6-(methylamino)-2-pyridineethanol (Scheme 2, 16). Compound 16 is a precursor to several important compounds, including the integrin inhibitor SB-273005 (Scheme 2C). Although 16 is structurally simple, the two reported syntheses of 16 by medicinal chemists were conducted in five and seven steps from 2-amino-6-methylpyridine (Scheme 2A). We considered that the 2-methylamino group could be installed through C−H bond fluorination and $S_N$Ar from a derivative of 2-pyridineethanol.

Fluorination did not occur on the free alcohol, but it did occur after protecting the alcohol as an ester. An acetyl protecting group was chosen because it could be cleaved in concert with the $S_N$Ar reaction. The fluorination of acetylated 2-pyridineethanol occurred in 88% yield (by $^{19}$F NMR spectroscopy). Treatment of the crude mixture from the fluorination step with aqueous MeNH$_2$ in DMSO led to formation of the methylaminopyridine unit and cleavage of the acetyl group to reveal the free alcohol. This route gave 16 with only two isolations in 64% overall yield, a significantly shorter and higher-yielding approach than the reported syntheses requiring five or seven steps. Although our route requires stoichiometric silver, it is worthy to note that an improved process used to prepare 30 g of 16 still required four steps and occurred in only 39% overall yield.

The combination of C−H bond fluorination and $S_N$Ar also shortened the synthesis of PF-1247324, a potent and selective NaV1.8 inhibitor (Scheme 3). The medicinal chemistry route to this compound comprised six steps and occurred in less than 1% yield; an advanced intermediate was outsourced for the kilogram-scale synthesis of PF-1247324. Our route to this compound began with the fluorination of methyl 5-bromo-
picolinate. The fluoropyridine intermediate contains two electrophilic sites for nucleophilic substitution: a methyl ester and a 2-fluoropyridine. We demonstrated (Tables 3 and 4) that substitution at the fluorine of a 2-fluoropyridine can occur in the presence of auxiliary electrophilic functional groups, including a tert-butyl ester. However, we considered that conditions could be identified to transform the methyl ester to the N-methyl amide without substitution of the fluoride. The reaction between the fluoropyridine methyl ester with aqueous MeNH₂ in THF formed a mixture of products resulting from substitution of both methoxide and fluoride. However, simply changing the reaction solvent from THF to MeOH allowed for the selective transformation of the methyl ester to the N-methyl amide without substitution of the fluoride.

After aqueous workup, the crude reaction mixture was treated with ammonium hydroxide in DMSO to substitute an NH₂ group for the N fluoride. Finally, the 3-bromopyridine was subjected to the reported Suzuki cross-coupling reaction conditions²⁰ to provide the title compound. By our route, the synthesis of PF-1247324 involving C–H fluorination was completed with just three total isolations in 51% overall yield, a major improvement in yield and step count over the published synthesis. Furthermore, the route performed by medicinal chemists required 120 h of total reaction time, while the route we report here required less than 18 h.

Finally, we used our chemistry to prepare the non-nucleoside reverse transcriptase inhibitor Intelence (etravirine, Scheme 4), a compound used in the treatment of HIV. The route to this compound developed by medicinal chemists occurred in five steps and 9% yield from N-(4-cyanophenyl)guanidine hydrochloride.²¹ An alternative route used to prepare etravirine on a kilogram scale required four steps and occurred in 30% yield.²²

Our synthesis of etravirine began with substitution of the 4-chloro substituent in 2,4-dichloro-5-bromopyrimidine with 2,6-dimethyl-4-cyanophenol, from which the solid product was isolated after the addition of water. Next, substitution with 4-amino-2-methylpyrimidine and protection in situ was conducted, and the product was isolated in 88% yield. The installation of a protecting group for the N–H bond was necessary for the subsequent fluorination reaction to proceed. The synthesis of etravirine was then completed by C–H fluorination of the pyrimidine (71% yield by ¹⁹F NMR spectroscopy), substitution with aqueous ammonia, and addition of HCl(aq) to cleave the Boc group. Through this route, etravirine was prepared with three total isolations in 45% overall yield in under 6 h of total reaction time.

**Scheme 4. Synthesis of Intelence (Etravirine) through C–H Fluorination**

| A: Medicinal chemistry synthesis of etravirine |
|---|
| B: Synthesis of etravirine via C–H fluorination/S₉Ar |

**SUMMARY**

In summary, we have developed a broadly applicable strategy for the diverse, site-selective C–H functionalization of pyridines and diazines. The reaction sequence occurs to provide alkoxy-, arlyoxy-, amino-, amido-, heteroaryl-, thio-, and cyano-substituted heterocycles that can be difficult to access through traditional methods. This tandem sequence is attractive for the direct diversification of heteroarenes, due to the exquisite site selectivity for C–H functionalization and the mild conditions for the S₉Ar reaction. In addition, high site selectivity for the fluorination of substrates containing more than one heteroarene or more than one reactive C–H bond is possible using this chemistry. Finally, the process of fluorination and S₉Ar can allow medicinal compounds containing substituted pyridines and diazines to be prepared by short synthetic routes. We anticipate that these reactions will find immediate use for both late-stage functionalization and efficient syntheses of complex molecules.

**ASSOCIATED CONTENT**

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

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**Notes**

The authors declare no competing financial interest.

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